



Pergamon

Solid state and solution conformation of 2-pyridinecarboxylic acid hydrazides: a new structural motif for foldamers

Joachim Garric,^a Jean-Michel Léger,^b Axelle Grelard,^a Masakazu Ohkita^c and Ivan Huc^{a,*}^aInstitut Européen de Chimie et Biologie, 16 av. Pey Berland, 33607 Pessac Cedex, France^bLaboratoire de Pharmacochimie, Université Victor Segalen Bordeaux II, 146 rue Léo Saignat, 33076 Bordeaux, France^cDepartment of Applied Chemistry, Nagoya Institute of Technology, Nagoya 466-8555, Japan

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Abstract—X-Ray crystallography and NMR show a strong preference for *trans* conformers of *N'*-phenyl or *N'*-(2-pyridyl) 2-pyridinecarboxylic acid hydrazides, stabilized by an NH–N_{pyr.} intramolecular hydrogen bond both in the solid state and in solution. This allows us to extrapolate that oligomers of this unit should adopt extended linear conformations. © 2003 Elsevier Science Ltd. All rights reserved.

Peptidomimetics are unnatural oligomers that adopt stable conformations in solution, mimicking the structures and potentially the functions of peptides. Series of aliphatic β-, γ-, and δ-homologues of α-peptides have been reported, comprising various linkages such as amides, sulfonamides, sulfoximines, *N*-oxo-amides, ureas, or hydrazides.^{1,2} Several families of aromatic oligoamides have also been shown to adopt stable linear, bent, and helical conformations stabilized by hydrogen bonds between amide groups and donors or acceptors in the aromatic rings.^{1,3–5} In aromatic oligoamides, unlike in most aliphatic peptidomimetics, hydrogen bonds occur in a non-cooperative fashion *between consecutive units*, which makes the folded structures particularly easy to predict. The conformational behavior of a dimer or trimer can often be extrapolated to longer strands. Aromatic amides can also be incorporated in aliphatic peptidomimetic sequences to template their structures.^{6,7} These oligomers have been based on various aromatic building blocks (e.g. pyridines, pyridine oxides, pyrazines, anthranilic acids, 1,3-dimethoxybenzenes...) but very few cases have made use of a linkage other than the amide group.^{4,7}

We have previously investigated the structures of oligoamides derived from 2-pyridinecarboxylic acids and 2-aminopyridines, and shown that they adopt both single and double helical conformations in the solid state and in solution based on NH–N_{pyr.} hydrogen-bonding to pyridine nitrogens and CO–H hydrogen-

bonding to aromatic protons (Fig. 1(a)).⁵ Zimmerman et al. have shown that 2-pyridyl-ureas exist as two equilibrating *cis* and *trans* forms of the urea involving

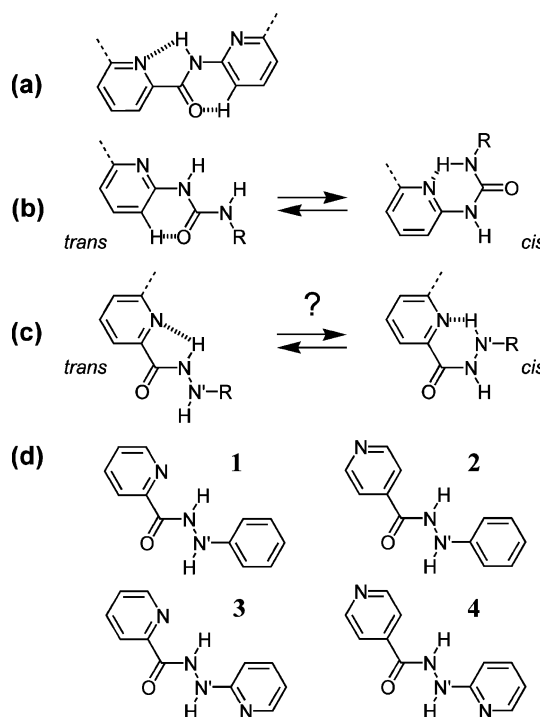


Figure 1. Conformations of 2-pyridinecarboxamides (a) and 2-pyridyl-ureas (b), and possible conformations of 2-pyridinecarboxylic acid hydrazides (c). Structures of 1–4 (d).

* Corresponding author.

either a CO–H or an NH–N_{pyr.} hydrogen bond (Fig. 1(b)).⁴ Here, we present a preliminary study of the conformations of 2-pyridinecarboxylic acid hydrazides in the solid state and in solution, in view of their incorporation into oligomeric strands.

Two intramolecular hydrogen bonds may be foreseen between a pyridine nitrogen and an adjacent hydrazide function, involving either the NH or the N'H proton. Because of a more favorable orientation, the N'H–N_{pyr.} hydrogen bond in the *cis* conformer of the hydrazide is expected to be stronger than the NH–N_{pyr.} hydrogen bond of the more stable *trans* conformer (Fig. 1(c)). However, the hydrazide function is non-planar and N–H and N'–H bonds should define a dihedral angle close to 90°,^{7,8} which might affect hydrogen-bonding with the N'H. The conformations of benzoic acid N'-phenylhydrazides bearing methoxy substituents have been described.⁷ We searched for related compounds in the CCDB but found no structures of 2-pyridinecarboxylic acid hydrazides where the N' nitrogen is neither condensed in a hydrazone, nor acylated. Moreover, although aliphatic hydrazinopeptides have been prepared,⁹ experimental data on their structure are scarce.^{8,10}

Thus, when we started this work, it was not obvious whether a more favorable hydrogen bond would bring upon enough stabilization to favor the a priori less stable *cis* isomer of the hydrazide, as is the case for the urea.

Compounds **1–4** (Fig. 1(d)) were prepared in one step from 2- or 4-pyridinecarboxylic acid chlorides and phenyl hydrazine or 2-hydrazinopyridine, in CH₂Cl₂ in the presence of Et₃N. Phenyl-hydrazide **1** gave crystals suitable for X-ray analysis from CHCl₃/*n*-hexane which revealed a *trans* conformation of the hydrazide (Fig. 2(a)).¹¹ The NH–N_{pyr.} (2.74 Å, 97.6°)¹² intramolecular hydrogen bond is far from being linear and similar to those observed in amides.⁵ The NH–N'H torsion angle is 131.5°, a value close to that reported by Aubry et

al.,¹⁰ which differs substantially from the expected 90°.^{7,8} The N' nitrogen of the hydrazide is distorted pyramidal (defining three angles at 114.1, 110.3, and 115.8°). In the crystal lattice, the molecules are arranged in linear tapes held by intermolecular hydrogen bonds involving both NH and N'H proton donors (N'H–N_{pyr.}: 3.32 Å, 141.9°; NH–O: 2.62 Å, 138.8°).¹²

Compound **3** was prepared with the idea that its additional pyridine nitrogen could be involved in intramolecular hydrogen bonds with the NH or N'H protons in the *cis* or the *trans* form and alter the balance between them. Crystals were again grown from CHCl₃/*n*-hexane and yielded the structure in Figure 3, which also shows a *trans* conformer of the hydrazide.¹³ The crystal parameters are very similar to those of **1** (same space group and unit cell dimensions)^{11,13} and the two structures are practically superimposable. Linear arrays of molecules are also found in the lattice involving intermolecular hydrogen bonds between the same donors and acceptors as in the structure of **1**. However, the relative orientations of the molecules are different which leads to different hydrogen bond distances and angles (N'H–N_{pyr.}: 3.07 Å, 169.6°; NH–O: 2.76 Å, 149.6°).¹²

Thus, **1** and **3** follow different packing modes in the crystal. But the additional pyridine nitrogen in **3** does not participate in any intra- or intermolecular hydrogen bond, and does not even alter the torsion angles within the molecule, suggesting a strong preference for that particular conformer.

The conformations of **1** and **3** were also studied by NMR in CDCl₃ solutions. Both **1** and **3** feature a strongly deshielded hydrazide proton (at 9.54 and 9.88 ppm, respectively) and a less deshielded hydrazide proton (at 6.25 and 6.87 ppm, respectively). Their assignment was made according to long range C/H correlations in HMBC experiments. The more deshielded proton correlates with the carbonyl carbon

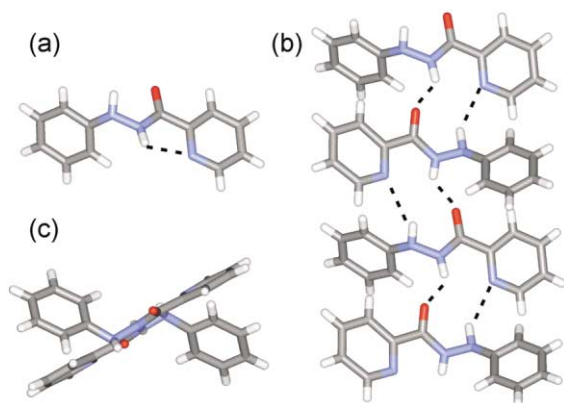


Figure 2. (a) X-Ray crystal structure of **1** showing the *trans* form of the hydrazide and the NH–N intramolecular hydrogen bond; (b) linear array of molecules in the crystal involving N'H–N_{pyr.} and NH–O intermolecular hydrogen bonds; (c) top view of the linear array.

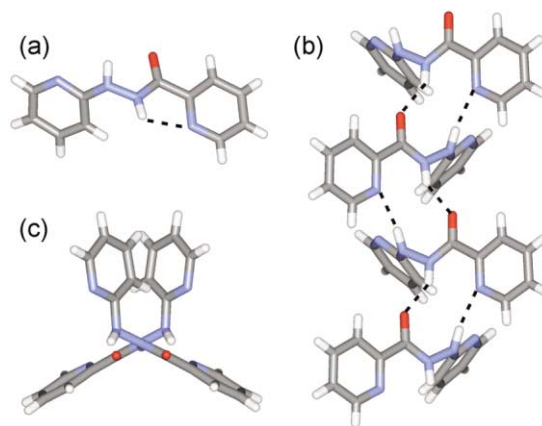


Figure 3. (a) X-Ray crystal structure of **3** showing the *trans* form of the hydrazide and the NH–N_{pyr.} intramolecular hydrogen bond; (b) linear array of molecules in the crystal involving N'H–N_{pyr.} and NH–O intermolecular hydrogen bonds; (c) top view of the linear array.

and was assigned to the NH , the less deshielded proton correlates with the vicinal carbon of the phenyl or 2-pyridyl substituent and was assigned to the $\text{N}'\text{H}$ (Fig. 4(a)). The large chemical shift difference between the two protons ($\Delta\delta=3.3$ and 3.0 ppm for **1** and **3**, respectively) cannot be explained on the sole basis of electron withdrawing effects of acyl versus aryl substituents and suggests that the NH proton is involved in an intramolecular hydrogen bond with the pyridine nitrogen as is found in the solid. However, this could not be demonstrated by studying **1** and **3** directly. For example, NOE-diff experiments on **1** show correlations of NH and of $\text{N}'\text{H}$ with protons of the phenyl ring (Fig. 5), but this is expected both in the *trans* and the *cis* form of the hydrazide (Fig. 4(b)). That the NH protons of **1** and **3** are indeed involved in an intramolecular hydrogen bond is supported by the low dependence of their chemical shift ($\Delta\delta < 0.05$ ppm) upon addition of a hydrogen bonding solvent (20% D_6 -DMSO) to the CDCl_3 solution, and upon increasing concentration or decreasing temperature. On the other hand, the NH' protons show a high chemical shift variation under these conditions ($\Delta\delta > 0.72$ ppm). Moreover, when the nitrogen of the pyridinecarbonyl group is moved from position 2 (in **1** and **3**) to position 4 (in **2** and **4**), the chemical shift of $\text{N}'\text{H}$ is almost unaffected ($\Delta\delta < 0.1$ ppm), whilst the chemical shift of the NH is strongly shifted upfield ($\Delta\delta > 1.38$ ppm). The 4-pyridinecarbonyl group has an electron withdrawing strength similar to that of the 2-pyridinecarbonyl moiety, but it cannot form an intramolecular hydrogen bond involving the NH or the $\text{N}'\text{H}$ proton.

Finally, NOE-diff experiments revealed that in **3**, the CH proton in position 3 of the 2-pyridyl group correlates with the NH but not with $\text{N}'\text{H}$. This is consistent with the conformation of **3** observed in the crystal, and shows that it also prevails in solution (Fig. 5).

In summary, both **1** and **3** show a strong preference for a *trans* conformation in the solid and in solution and no contribution of the *cis* conformer could be detected. Assuming the preferred conformation of **3**, a molecular model of an oligohydrazide of 6-hydrazino-2-pyridine-

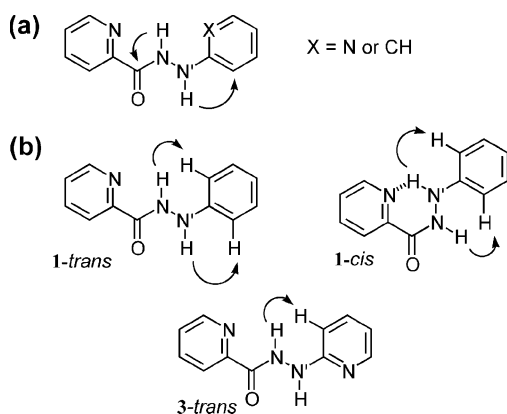


Figure 4. Relevant C/H correlations (a), and NOE correlations (b), observed by NMR in **1** and **3**.

carboxylic acid was built (Fig. 6). Its structure is that of an extended linear strand, the successive N–N linkages being parallel and almost coaxial. The relative positions of the pyridine rings is determined by the NH – $\text{N}'\text{H}$ torsion angles. In the structure shown in Fig. 6, these

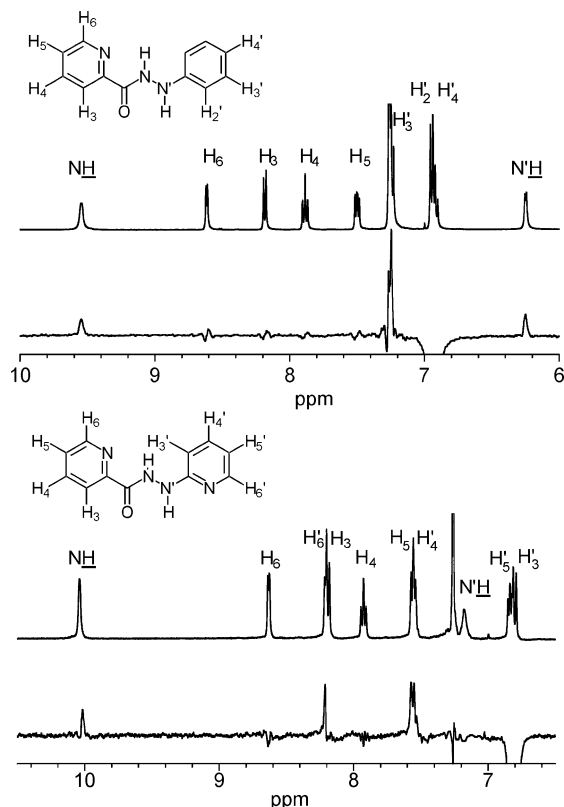


Figure 5. Part of the 400 MHz ^1H NMR spectra of **1** and **3** in CDCl_3 . Top: spectrum of **1** and NOE-diff experiment at 25°C showing the signals of NH , $\text{N}'\text{H}$ and H_3 after saturation of the signal of H_2 . Bottom: spectrum of **3** and NOE-diff experiment at -45°C showing the signals of NH , H'_6 , and H'_4 after saturation of the signal of H'_3 , and concomitantly of that of H'_5 . For compound **3**, NOEs are overcast by rapid exchange between NH and $\text{N}'\text{H}$ at higher temperatures.

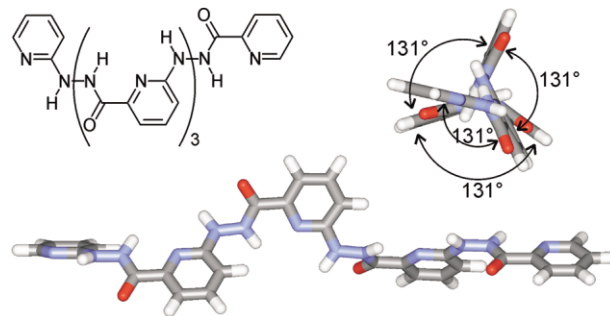


Figure 6. Structure, top view and side view of a molecular model of an oligohydrazide of 6-hydrazino-2-pyridinecarboxylic acid, built by interconnecting three units of **3** as found in the solid state. The NH – $\text{N}'\text{H}$ torsion angles were manually set at 131° (the parameters of most force fields are defined to reach an energy minimum when this angle is 90°).

angles are set at 131° and are arbitrarily chosen with the same sign, which results in an helical arrangement of the pyridyl groups. The synthesis and incorporation of these pyridine hydrazide units in oligomers containing pyridine–amide monomers will be explored in the sequel.

Acknowledgements

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References

- For reviews, see: (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173; (b) Hill, D. J.; Mio, M. J.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893.
- For recent examples: (a) Woll, M. G.; Lai, J. R.; Guzei, I. A.; Taylor, S. J. C.; Smith, M. E. B.; Gellman, S. H. *J. Am. Chem. Soc.* **2001**, *123*, 11077; (b) Semetey, V.; Rognan, D.; Hemmerlin, C.; Graff, R.; Briand, J.-P.; Marraud, M.; Guichard, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1893; (c) Etezady-Esfarjani, T.; Hilty, C.; Wüthrich, K.; Rueping, M.; Schreiber, J.; Seebach, D. *Helv. Chim. Acta* **2002**, *85*, 1197.
- Selected example: (a) Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1997**, *119*, 10587; (b) Delnoye, D. A. P.; Sijbesma, R. P.; Vekemans, J. A. J. M.; Meijer, E. W. *J. Am. Chem. Soc.* **1996**, *118*, 8717; (c) Gong, B. *Chem. Eur. J.* **2001**, *7*, 4337 and references cited therein.
- (a) Corbin, P. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2000**, *122*, 3779; (b) Corbin, P. S.; Zimmerman, S. C.; Thiessen, P. A.; Hawryluk, N. A.; Murray, T. J. *J. Am. Chem. Soc.* **2002**, *124*, 10475.
- (a) Berl, V.; Huc, I.; Khoury, R.; Krische, M. J.; Lehn, J.-M. *Nature* **2000**, *407*, 720; (b) Berl, V.; Huc, I.; Khoury, R.; Lehn, J.-M. *Chem. Eur. J.* **2001**, *7*, 2798; (c) Berl, V.; Huc, I.; Khoury, R.; Lehn, J.-M. *Chem. Eur. J.* **2001**, *7*, 2810; (d) Huc, I.; Maurizot, V.; Gornitzka, H.; Léger, J.-M. *Chem. Commun.* **2002**, 578.
- (a) Nowick, J. S.; Lam, K. S.; Khasanova, T. V.; Kemnitzer, W. E.; Maitra, S.; Mee, H. T.; Lui, R. *J. Am. Chem. Soc.* **2002**, *124*, 4972 and references cited therein; (b) Zeng, H.; Yang, X.; Flowers, R. A.; Gong, B. *J. Am. Chem. Soc.* **2002**, *124*, 2903.
- Nowick, J. S.; Pairish, M.; Quen Lee, I.; Holmes, D. L.; Ziller, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 5413.
- For computational studies, see: Günter, R.; Hofman, H.-J. *J. Am. Chem. Soc.* **2001**, *123*, 247 and references cited therein.
- Guy, L.; Vidal, J.; Collet, A.; Amour, A.; Reboud-Ravaux, M. *J. Med. Chem.* **1998**, *41*, 4833.
- Aubry, A.; Bayeul, D.; Mangeot, J.-P.; Vidal, J.; Stérin, S.; Collet, A.; Lecoq, A.; Marraud, M. *Biopolymers* **1991**, *31*, 793.
- Crystal data for **1**: C₁₂H₁₁N₃O, *M* = 213.24, monoclinic, *a* = 8.090(2), *b* = 15.099(3), *c* = 8.985(5) Å, β = 100.14(3)°, *V* = 1080.4(7) Å³, *T* = 296(2) K, space group *P*2₁/*c*, *Z* = 4, μ(Cu-Kα) = 0.707 mm⁻¹, 1837 reflections measured, 1837 unique. The final *R* indices were *R*₁ (*I* > 2σ(*I*)) = 0.0437, *wR*₂ (all data) = 0.1192. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Database as supplementary publication no. CCDC 193207.
- The distance is between the two heavy atoms, and the angle is the N–H–(N/O) angle.
- Crystal data for **3**: C₁₁H₁₀N₄O, *M* = 213.23, monoclinic, *a* = 8.087(1), *b* = 15.079(1), *c* = 8.822(1) Å, β = 99.20(1)°, *V* = 1061.95(19) Å³, *T* = 296(2) K, space group *P*2₁/*c*, *Z* = 4, μ(Cu-Kα) = 0.750 mm⁻¹, 1780 reflections measured, 1780 unique. The final *R* indices were *R*₁ (*I* > 2σ(*I*)) = 0.0467, *wR*₂ (all data) = 0.1323. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Database as supplementary publication no. CCDC 193206.