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COMMUNICATION

Z-Formamidoximes in molecular folding and macrocycles†‡

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The formamidoxime configurational *Z* isomer coupled with the pyridylbiscarboxamide conformational codon were used to fold planar, curved structures. When embedded into macrocycles, this folded motif promotes dimerization through π–π stacking and hydrogen-bonding and the formation of tubules akin to molecular channels in the solid state.

Inspired by the importance of molecular folding in nature and its consequences on biological functions[1] and pathologies,[2] chemists have been very active at creating new folding motifs coding for particular structures ('folding codons').[3] As in peptide secondary structures, hydrogen-bonding has played a significant role in these developments.[4] Surprisingly, despite their significance in biological targeting,[5] self-assembly,[6] and coordination chemistry,[7] amidines and formamidines have found few applications in molecular folding, although they offer very rich H-bonding patterns and conformational/configurational control.[8] More specifically, formamidines derived from alkoxyamines ('formamidoximes', Scheme 1) have, to our knowledge, never been applied to molecular folding prior to our work. This is quite intriguing, as their *Z*-isomer has been consistently characterized in the solid state as locked in a 5-membered H-bonded ring.[9] In the present communication is reported the first instance of folded structures based on *Z*-formamidoxime subunits that are conjugated to the well-known pyridylbiscarboxamide[4a,10] and form planar segments prone to dimerization through π–π stacking. Molecular folding based on this conjugate motif is illustrated on an open-structure (*ZZ*-open) as well as 18-atom and 54-atom macrocycles (*ZZ*-M and Tri(*ZZ*-M)) respectively, Scheme 1) and was studied by ^{1}H NMR spectroscopy and crystallography.

The syntheses of *ZZ*-open, *ZZ*-M and Tri(*ZZ*-M) are described in the supporting information‡ (and will be discussed in a separate publication specifically examining the strategies of condensation and cyclization involving formamidoximes).[11] The present article focuses on the folding, molecular structure and resulting self-assembly of the *Z*-Formamidoxime-Pyridyl-biscarboxamide-*Z*-Formamidoxime (FPF) triad, where the amide hydrogen atoms were anticipated to organize the three consecutive units into a U-shape overall segment (Scheme 1).

Solution-state studies

In solution, the ^{1}H NMR signals of the three molecules reflect similar electronic environments. The pyridyl 3Py(A) protons (see Scheme 1 for numbering) are deshielded by the proximity of the carboxyl oxygen (δ(3Py(A)) ~8.5 ppm), while the formamidine Hf proton appears as a sharp doublet with a large, *trans*, coupling constant (^3J = 10 Hz) to the NH proton at a chemical shift which is typical for *Z*-*N*-acylformamidoxime motifs (δ(Hf) ~7.8 ppm), and very different from their *E* counterpart.[11b] The NH group coupled to Hf appears as a doublet with the same large coupling constant, and at a chemical shift consistent with H-bonding to both the pyridine nitrogen and the formamidoxime oxygen[11] (δ(NH) ~9.7 ppm in pyridylbisaryl-carboxamides with H-bonding to the central pyridine nitrogen only[10a]). Based on chemical shifts, it appears as though the intramolecular H-bond is stronger in the more rigid *ZZ*-M (Fig. 1, middle spectrum).

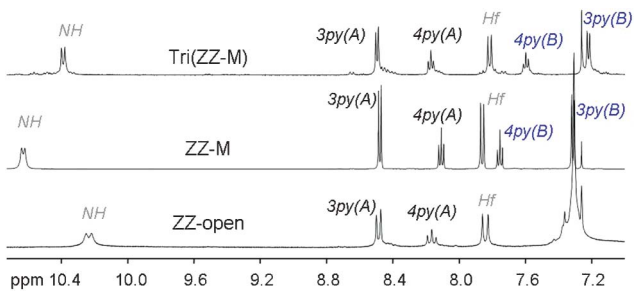

Fig. 1 ^{1}H NMR of *ZZ*-open (300 MHz), *ZZ*-M (500 MHz), and Tri(*ZZ*-M) (500 MHz), from bottom to top, in $CDCl_3$, 25 °C (see Scheme 1 for molecule formula and proton numbering).

Interestingly, chemical shifts in *ZZ*-M are about the same in $CDCl_3$ and in CD_3OD (except for the NH signal which disappears in CD_3OD).‡ In particular Hf remains at 7.9 ppm suggesting that the *Z*-configuration of the C=N double bond is retained in a competing H-bonding solvent.§

Solid-state studies

X-ray diffraction analysis of *ZZ*-M crystals grown by slow diffusion of diethyl ether into a dichloromethane solution confirmed

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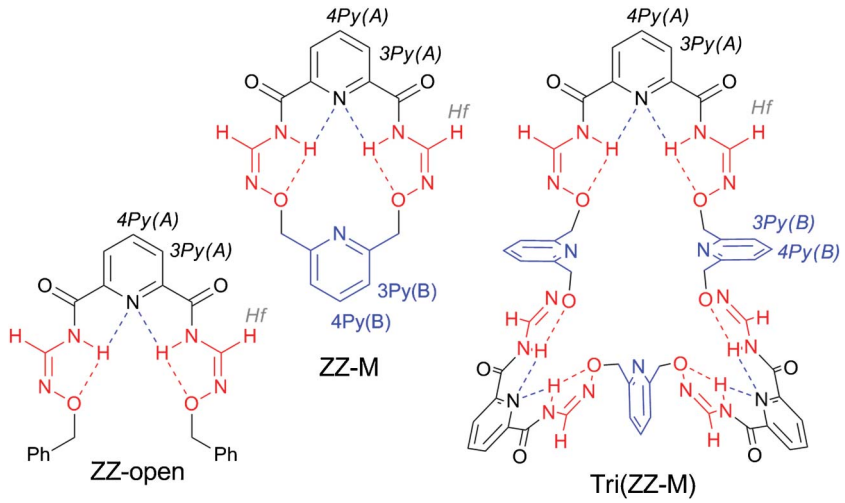
‡ Electronic supplementary information (ESI) available: Synthetic procedures and characterizations of formamidoxime macrocycles and open structure. Stacked plot for ^{1}H NMR spectra of *ZZ*-open, *ZZ*-M and Tri(*ZZ*-M). CCDC reference numbers 828090 (monoformamidoxime PyFBn), 837812 (*ZZ*-M) and 837813 (Tri(*ZZ*-M)). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob06378b



Scheme 1 Open and macrocyclic structures with proton numbering. Highlighted in red are the *Z*-formamidoxime subunits.

the anticipated planar U-shape organized by the H-bond relay through the NH group within the FPF triad (Fig. 2).

Bond lengths for the pyridine N···H(N) in *ZZ*-M are longer than in known pyridyldicarboxamide-based open-ended foldamers (2.38–2.40 Å *vs.* 2.20–2.22 Å[10a]). However, such effect may mostly reflect steric constrains associated with macrocyclization, as observed before.[12] Indeed, in a mono pyridylamide-*Z*-formamidoxime diad, the pyridine N···H(N) H-bond is shorter (2.238 Å).[11b,‡] Similarly, H-bonds within the formamidoxime units of the *ZZ*-M macrocycle are slightly longer than in the model diad (2.29–2.35 Å *vs.* 2.243 Å).

ZZ-M macrocycles dimerize in the solid state through a combination of π–π stacking of their planar FPF segments and water mediated H-bonding involving the nitrogen atoms of the extra pyridine rings (noted B in Scheme 1) which are not intramolecularly H-bonded, and offer an opening akin to a mouth (Fig. 2a,b). Highlighting the propensity for the FPF motif to stack, two such dimers further dimerize in an antiparallel manner to form a quartet channel (Fig. 2c).

A similar behaviour is observed in the solid state for Tri(*ZZ*-M). Due to its sheer size, the 54-atom macrocycle is a very intriguing member of the FPF family, full of information about local folding, overall compaction (Fig. 3) and self-assembly in the solid state (Fig. 4 and 5). Although the molecular structure of Tri(*ZZ*-M) may be expected to adopt a 3-fold symmetry based on its chemical formula (Scheme 1) and symmetrical ^{1}H NMR (Fig. 1), its crystal structure differentiates one curved FPF motif (1-loop unit, Fig. 3) from the other two which stack on top of one another (stacked 2-loop unit, Fig. 3). Such a stacking effect within a bispyridylcarboxamide-derived macrocycle has precedent.[12h]

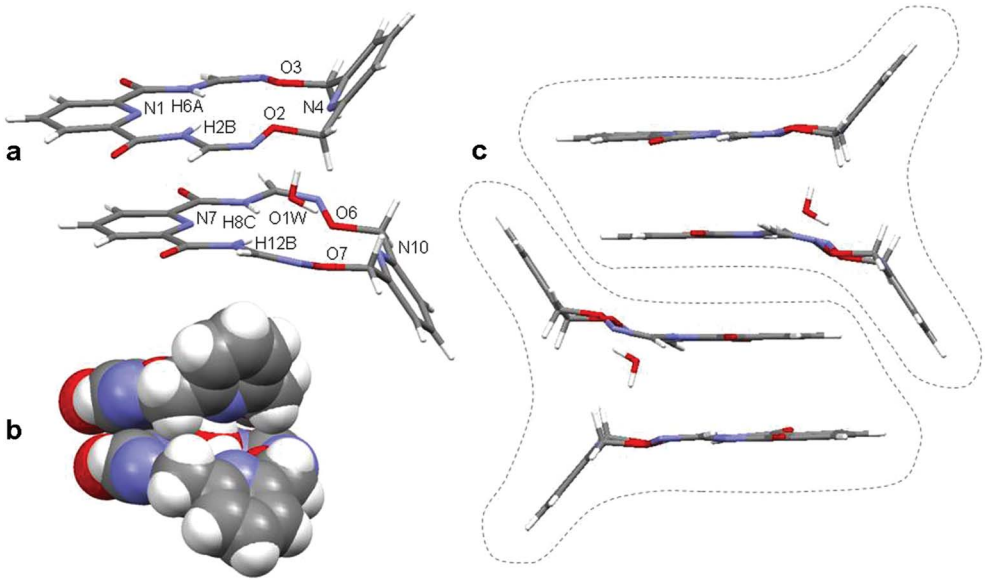


Fig. 2 Crystal structure of *ZZ*-M; a) side view of the water-mediated dimer, b) focused on the pyridine–water–pyridine H-bonded mouth; c) self-assembly into a dimer of dimers by π–π stacking. Selected bond distances (Å): N1···H6A: 2.406, N1···H2B: 2.397, H6A···O3: 2.294, H2B···O2: 2.325, N7···H8C: 2.386, N7···H12B: 2.381, H8C···O6: 2.351, H12B···O7: 2.344, O1W···N4: 2.893, O1W···N10: 2.976.¶

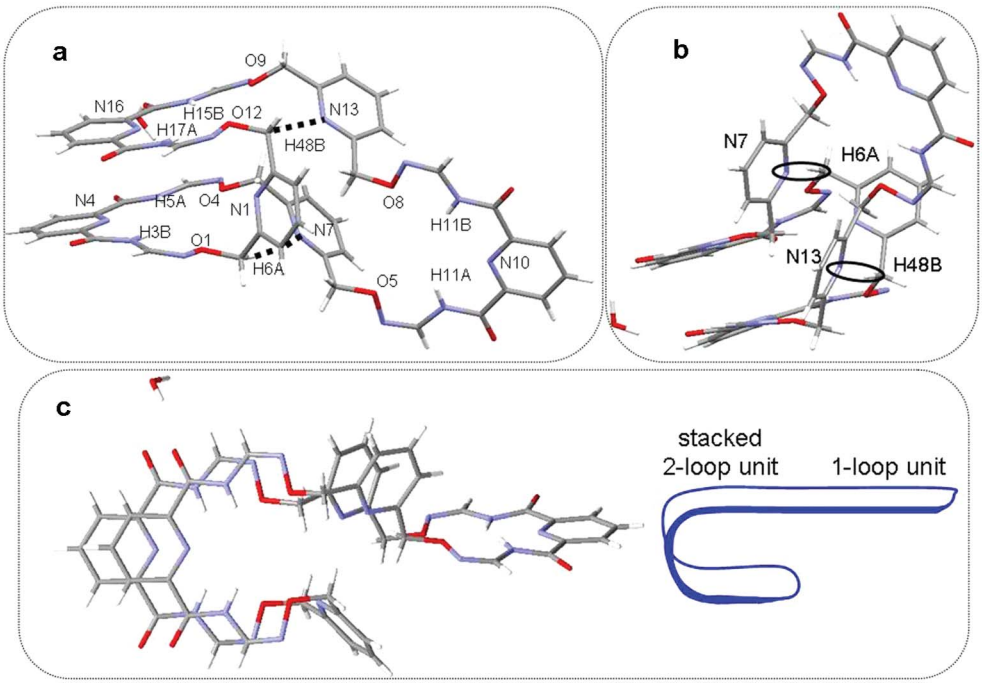


Fig. 3 Crystal structure of Tri(*ZZ*-M); a) molecular structure seen from the side showing the stacked 2-loop unit, b) view highlighting the folding mode of the pyridylmethylene hinges; c) molecular structure seen from the top and simplified cartoon‖

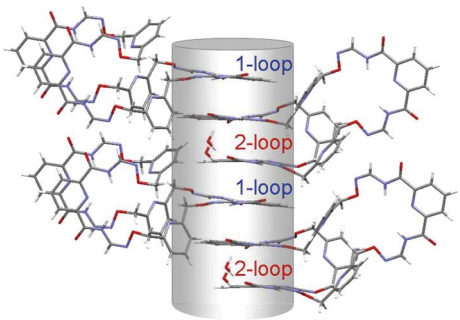


Fig. 4 Self-assembly of Tri(*ZZ*-M) into alternating 2-loop/1-loop tubular stacks in the solid state.

Within each of the three planar loop structures, the same H-bonded relay is observed as in the *ZZ*-M macrocycle, however with shorter N···H(N) distances, ranging from 2.29 to 2.36 Å. Within the formamidoxime as well, the length of the (N)H···O H-bond is decreased in Tri(*ZZ*-M) (2.17–2.26 Å) compared to *ZZ*-M, probably due to the larger flexibility of Tri(*ZZ*-M) and its resulting ability to adjust its structure to optimize interactions.

When analyzing the folding pattern within Tri(*ZZ*-M), it is interesting to note that the two stacked FPF units are not only held through π–π interactions as in *ZZ*-M, but also through two mutual H-bonds between the benzyl-like protons and pyridine nitrogen atoms of two bridging pyridyl-methylene segments ((C)–H···N(Py) 2.42 and 2.48 Å; highlighted in black in Fig. 3a,b). As in *ZZ*-M where they bind a water molecule, the pyridine units constituting the hinge between the rigid segments therefore play a significant role in the self-organization of these species. These interactions are, however, probably only expressed in the solid state, as the ^{1}H NMR signature of Tri(Z-MM) points to three equivalent FPF motifs (Fig. 1) and CH_2 groups electronically similar to the flexible *ZZ*-open analog in $CDCl_3$.‡

The planar curved segments of Tri(*ZZ*-M) and its 2-loop/1-loop structural pattern (Fig. 3c) allow its self-assembly in the solid state into a very interesting tubular network. Indeed, infinite 1 D tubules result from the stacking of alternating 1-loop and 2-loop units (Fig. 4).

Simultaneously, while the 1-loop subunit of one Tri(*ZZ*-M) molecule is included in a 1 D tubule in one direction, its corresponding 2-loop fragment is involved in another stack in a perpendicular direction. In other words, each Tri(*ZZ*-M) molecule is involved in two 1 D tubules growing in perpendicular directions (Fig. 5). The overall result is a self-assembled structure into a compact, crosslinked network of orthogonal linear tubules (Fig. 5).

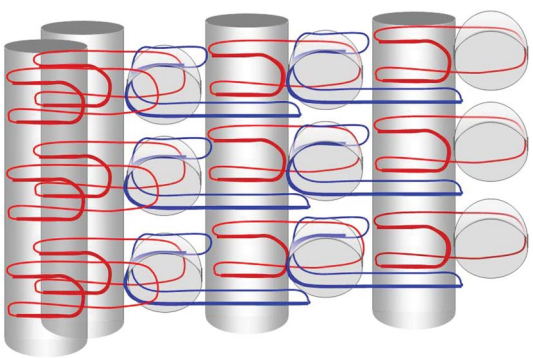


Fig. 5 Cartoon representation of the Tri(*ZZ*-M) network of tubules extending in two orthogonal directions in the crystal.

In conclusion, the conjugation of the pyridylbiscarboxamide conformational codon with the *Z*-formamidoxime configurational isomer (FPF triad) allows the folding of a curved, planar motif through a relay of H-bonds. In the present article, this new triad was applied to the folding of an open-ended structure (*ZZ*-open) and two macrocycles (*ZZ*-M and Tri(*ZZ*-M)). The curved FPF motif is planar and prone to π–π stacking, as exemplified in the solid-state structures of *ZZ*-M and Tri(*ZZ*-M). In both cases, extensive π–π stacking interactions are expressed to form tubular structures. In this context, the 3 D structure of Tri(Z-MM) crystals is particularly striking. Because each molecule is involved in two orthogonal infinite stacks, the solid is composed of a compact, crosslinked infinite network of tubular substructures. Although the cavity defined by the curved FPF motif is probably too small to offer guest inclusion, its organization into uncapped tubules is inspiring in the perspective of gas storage. Several enlarged analogs of the pyridyl-biscarboxamide codon have been used to expand the cavity of folded helices.[4a] They may similarly be used in conjunction with the formamidoxime subunit in order to expand the cavity of the tubular channels reported herein, and allow significant gas/guest loading, while the orthogonal self-assembled tubules (assuming they are maintained) should promote fast exchange in and out of the crystal.

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Notes and references

§ This observation is consistent with what we observed at room temperature in DMSO-d_6 on open structures such as *ZZ*-open.
¶ These crystals were grown in the presence of the dimethylammonium triflate condensation by-product and triflate. Although they were both incorporated into the crystal,‡ they are omitted in Fig. 2 for clarity.
‖ Selected bond distances for Tri(*ZZ*-M) (Å): N16···H15B: 2.364, H15B···O9: 2.209, N16···H17A: 2.306, H17A···O12: 2.169, N4···H5A: 2.293, H5A···O4: 2.196, N4···H3B: 2.295, H3B···O1: 2.220, N10···H11B: 2.339, H11B···O8: 2.242, N10···H11A: 2.326, H11A···O5: 2.260.

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