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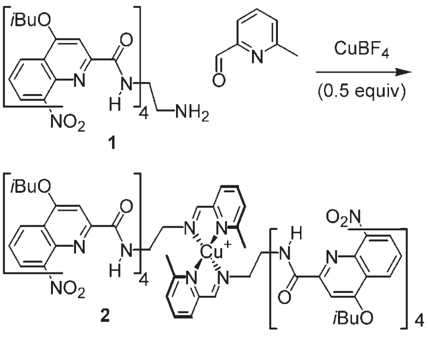
Metal-Directed Dynamic Formation of Tertiary Structure in Foldamer Assemblies: Orienting Helices at an Angle

Nicolas Delsuc,[a] Marie Hutin,[c] Victoria E. Campbell,[b] Brice Kauffmann,[a] Jonathan R. Nitschke,*[b] and Ivan Huc*[a]

A number of non-natural folding oligomers—or foldamers—have been shown to adopt well-defined helical or extended conformations resembling the secondary structures of biopolymers.[1] Interest in foldamers stems from the prospect that if the forms of biopolymers can be mimicked, their functions may be mimicked as well and even be further expanded, thereby opening the perspective of countless applications. Thus, one major line of development in foldamer chemistry is the investigation of function; for example, biological activity[2,3] and molecular-recognition properties.[4,5] However, even in nature, isolated secondary structures achieve little function relative to tertiary or quaternary structures. Another line of foldamer development and a major challenge in synthetic chemistry is thus to elaborate strategies to design, produce, and characterize artificial, folded objects composed of several non-natural secondary elements. Key steps recently taken in this direction have allowed the first characterizations of artificial "tertiary" or "quaternary" folded motifs in the solid state.[6] In this endeavor, the objective is not simply to reproduce natural patterns using non-natural scaffolds, but also to explore patterns that do not exist in nature. Here we report on the use of metal complexes as dynamic connection elements between oligomeric helical segments. Specifically, a metal complex was used to connect and define the relative orientation of two helices, as does a turn structure in proteins, but at an unconventional angle. A tetrahedral Cu^I ion was shown to impart a roughly perpendicular orientation between two helices, whilst an octahedral Fe^{II} center oriented two helices in an almost parallel fashion.

Aromatic oligoamides (AOA's) of 8-amino-2-quinoline carboxylic acid adopt particularly stable helical conformations in the solid state and in a wide variety of solvents.[7] They provide a firm foundation upon which to build in modular fashion towards large multi-helical, folded architectures. Several reports describe the irreversible covalent attachment of AOA's.[6a,8] Alternatively, dynamic linkages that let the system self-organize facilitate synthesis and allow one to use thermodynamic equilibration to probe a given system's intrinsic preferences.[9] We thus set out to explore the use of reversible linkages based on metal complexes to connect AOA's. The dynamic formation of imine–Cu^I complexes from amines, 6-methyl-2-formylpyridine and Cu^I (Scheme 1)[10] was well-suited for this purpose, because it is simple to implement and because the two levels of reversi-



Scheme 1. Equilibrium between **1** and tetrahedral Cu^I complex **2**. Helical chirality (*P*/*M*) and chirality at the metal center (Λ/Δ) result in a mixture of three racemic pairs of diastereomers for **2**: *P*Λ*P*/*M*Δ*M* (**2a**), *P*Δ*P*/*M*Λ*M* (**2b**), and *P*Λ*M*/*P*Δ*M* (**2c**).

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[a] Dr. N. Delsuc, Dr. B. Kauffmann, Dr. I. Huc
Institut Européen de Chimie et Biologie
Université de Bordeaux—CNRS UMR5248 and UMS3033
2 rue Robert Escarpit, 33607 Pessac (France)
Fax: (+33) 540002215
E-mail: i.huc@iecb.u-bordeaux.fr

[b] V. E. Campbell, Dr. J. R. Nitschke
Department of Chemistry, University of Cambridge
Lensfield Road, Cambridge CB2 1EW (UK)
Fax: (+44) 1223-336017
E-mail: jrn34@cam.ac.uk

[c] Dr. M. Hutin
Département de chimie organique
Université de Genève—Sciences II
30 quai Ernest-Ansermet, 1211 Genève 4 (Switzerland)

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ble bonding that it involves—imine formation and metal coordination—provide many possibilities to fine-tune the system.[11]

Amine-functionalized tetramer **1** (Scheme 1) adopts a helical conformation that spans over one-and-a-half turns. The reaction of **1** with 6-methyl-2-formylpyridine and Cu^{I}BF$_4$ (0.5 equiv) produced pseudotetrahedral Cu^{I} complex **2** quantitatively, as characterized by mass spectrometry, ^{1}H NMR spectroscopy, and X-ray crystallography. The conformation of **2** features several intrinsically chiral elements that are all expected to undergo dynamic exchange: the right (*P*) or left (*M*) handedness of the two helical segments, and the Λ or Δ configuration[12] of the metal complex. The latter undergoes racemization through dissociation of at least one nitrogen atom from the metal; the former may undergo racemization through ligand exchange or through helix-handedness inversion. A total of six species, three enantiomeric pairs of diastereomers, is thus expected: two pairs in which both helices have the same handedness *P*Λ*P*/*M*Δ*M* (**2a**) and *P*Δ*P*/*M*Λ*M* (**2b**) and one pair in which the two helices have opposite handedness *P*Λ*M*/*P*Δ*M* (**2c**). The proportions between these species are expected to reflect the balance of attractive and repulsive intramolecular interactions between the various chiral components within each configuration. In the theoretical case in which the handedness of a given helix may be equally *P* or *M* regardless of the Λ or Δ configuration of the Cu^{I} complex and regardless of the *P* or *M* handedness of the other helix, the proportions of **2a**, **2b**, and **2c**, would be 25, 25, and 50%, respectively, **2c** being twice as abundant as the other two, because it may be constructed in two degenerate ways.

The conformational preferences of **2** were first assessed by ^{1}H NMR spectroscopy. Depending on whether metal ligand exchange and helix handedness inversion are fast or slow processes on the NMR timescale, **2a**–**2c** may give rise to distinct or average signals. In the slow exchange regime, different patterns are expected according to the symmetry of the molecules: the two helical segments are equivalent in **2a** and **2b**, whereas they are inequivalent (diastereomeric with respect to the metal complex) in **2c**. Twice as many signals are thus expected for **2c** than for **2a** and **2b**.

In an initial attempt, a derivative of **2** was prepared not from 6-methyl-2-formylpyridine but from 2-formylpyridine. The mass spectra revealed complete formation of the expected product, but the NMR spectra were broad, which we interpreted as resulting from fast racemization at the Cu^{I} stereocenter (Figure 1c). A methyl group in the 6-position of the pyridine ring is expected to slow this process[13] and indeed, the spectra of **2** in CD$_2$Cl$_2$ were sharp (Figure 1b). Three new sets of peaks can be distinguished according to their relative intensity (7%, 44% and 49%). Only minor variations of these proportions occurred upon cooling to 213 K or upon using CD$_3$CN as a solvent. The multiplicity of the signals allowed us to assign unambiguously the species of intermediate abundance as **2c**. The major and minor species thus correspond to either **2a** or **2b**. Similar proportions and a more pronounced separation of the signals were observed when 6-methyl-2-formylpyridine was replaced by 2-quinoline carboxaldehyde (Figure 1a). These results indicated a high degree of communication between the handedness of each helix and the configuration of the neighboring metal center. Additionally, the proportions observed experimentally fit a model in which **2c** is statistically favored over **2a** and **2b** by a factor of 2, thus allowing us to rule out a direct influence of the handedness of one helix over the other.[14] Such an influence could create a bias in favor of homohelical species (**2a**, **2b**) or heterohelical species (**2c**). The mechanism by which chiral communication takes place between each helix and the metal complex cannot be deciphered from solution studies, but it may be pointed out that the signals of the major species all appear upfield from those of the minor species, suggesting stronger π–π stacking and associated ring current effects in the former.

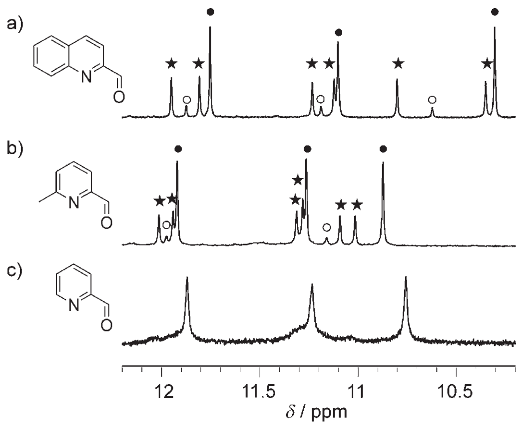

Figure 1. Part of the 500 MHz ^{1}H NMR spectra of **2** (b) and of analogues derived from 2-formylpyridine (c) and 2-quinolinecarboxaldehyde (a). Spectra were recorded at 253 K in CD$_2$Cl$_2$. The selected window shows all aryl–amide resonances. In a) and b), signals belonging to the *P*Λ*M*/*P*Δ*M* isomer are marked with stars, and signals belonging to the *P*Λ*P*/*M*Δ*M* and *P*Δ*P*/*M*Λ*M* isomers with white and black circles, respectively.

Crystallographic investigations proved particularly successful as they allowed the characterization of four out of the six possible forms of **2** (Figure 2, see also Supporting Information). The heterohelical species **2c** and the homohelical species **2a** crystallized as racemates from MeOH and benzene, respectively. The selection during crystallization of a single diastereomeric pair of enantiomers from among the three pairs present in solution thus entailed a sorting of the dynamic library of diastereomers.[15]

In both structures, each 2-iminopyridine moiety is perpendicular to the terminal quinoline ring of the helix to which it belongs due to the gauche conformation of the ethylene spacer. As expected, the two 2-iminopyridine moieties formed a tetrahedral complex with Cu^{I}. This geometry thus dictated an unusual, roughly perpendicular, orientation between the two helices. Helix orientation is additionally stabilized by the stacking of each helix's 2-iminopyridine moiety upon the terminal quinoline residues of the other helix. This would appear to account for the slow inversion of the helix handedness of **2** on the NMR timescale, as illustrated by

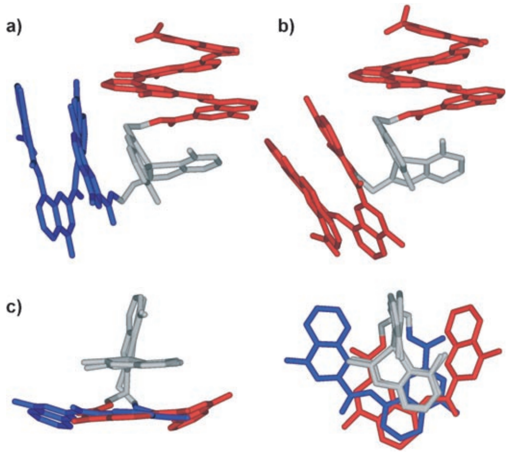

Figure 2. Crystal structures showing a) the *P*Δ*M* **2c** and b) *M*Δ*M* **2a** conformations of **2**. c) Top and side views of the overlay of fragments of the above complexes showing two Δ Cu^I complexes (in grey) and the first two quinoline residues of an *M* helix (in red) and of a *P* helix (in blue). Side chains, BF_4^- ions, and included solvent molecules are omitted for clarity.

diastereotopic ^1H NMR signals of its OCH_2 groups (not shown), whereas this process occurs quickly on the NMR timescale in **1**. The structures of **2a** and **2c** differ little overall, except in the π–π stacking mentioned above. Indeed, the handedness inversion of one helix that converts **2a** into **2c** involves a 180° flip of the terminal quinoline residue with respect to the 2-formylpyridine moiety of the other helix (Figure 2c).

In addition to Cu^I, imine bonds may also be readily templated by using Fe^{II}.[16] Up to three helix–pyridylimine ligands might be expected to coordinate to an iron(II) center, potentially resulting in a large number of *P*/*M*, Λ/Δ, and *fac*/*mer* stereoisomers. Mixing **1** with 2-formylpyridine and $Fe^{II}[BF_4]_2$ (0.33 equiv) in acetonitrile rapidly gave a dark purple solution. Mass spectra indicated the presence of three distinct species in solution: free **1**, an Fe^{II} complex containing two helix–pyridylimine ligands and two hydroxide ligands (**3**), and a second Fe^{II} complex bearing three helix–pyridylimine ligands (**4**). NMR spectra of this mixture were complex (see the Supporting Information), consistent with the presence of numerous stereoisomers. Employing a 60 kHz ^1H sweep width we did not observe paramagnetic NMR resonances that could be attributed to **3**, which suggested that low-spin Fe^{II} might be present, with ^1H resonances hidden among those attributable to the $[Fe_2L_3]^+$ complex, or that the metal might be in equilibrium between both spin states, with no observable ^1H resonances.[17]

Crystallization experiments gave a purple solid of noncrystalline appearance mixed with green single crystals. X-ray diffraction carried out upon the latter provided the crystal structure of **3** (Figure 3): a racemic *M*Δ*M*/*P*Λ*P* Fe^{II} complex bearing only two helix–iminopyridine ligands as well as two hydroxide counterions bound directly to the metal center. The mixture of constitutionally distinct Fe^{II} complexes **3** and **4** is thus sorted during crystallization, with **3** forming well-ordered crystals, but **4** presumably forming less crystalline material, as might be expected given the apparently large number of stereoisomers of **4** present. Complex **3** differs from **2** in several important respects. The relative orientation of the two helices imparted by the octahedral geometry of Fe^{II} is almost parallel. The two hydroxide ligands of Fe^{II} appear to play a role in this orientation as they seem to prevent the helices from folding back on the iminopyridine moieties.

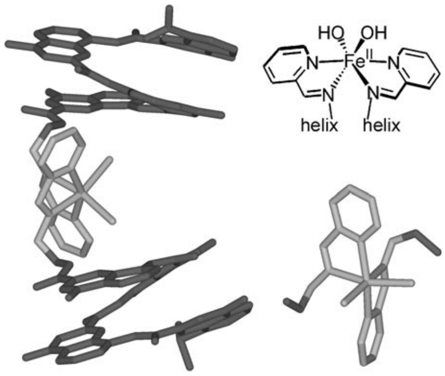

Figure 3. Formula and crystal structure of **3**. Left-handed helices are shown in dark grey and the metal complex in light grey. A separate view of the metal complex is shown in the bottom right. Side chains, hydrogen atoms and included solvent molecules are omitted for clarity.

Though less extensively characterized than **2**, the structure of complex **3** further validates metal-directed dynamic assembly as an efficient approach to assemble helically folded, aromatic–amide oligomers and to set precisely their relative orientation. The unconventional 90° angle between two helices in **2** constitutes a novel motif that hints at the prospect of assembling large square structures comprised of helical oligomer "edges" bearing amine functions at both extremities linked by metal complexes at each "corner". In these processes, mixtures of diastereomers are expected to self-sort as allowed by the dynamic nature of the linkages. Alternatively, absolute helical handedness may be controlled in AOA's by means of chiral residues.[18] Research along these lines is currently in progress.

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Keywords: chirality · helical structures · structure elucidation · supramolecular chemistry · X-ray diffraction

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