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Conformational Control in Metallofoldamers: Design, Synthesis and Structural Properties

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Metallofoldamers are sequence-specific oligomers, which are designed to fold into three-dimensional architectures upon metal coordination. Their folding can involve additional noncovalent interactions and results in new chiral secondary structures, enhanced stabilization of existing secondary structures, or unique materials for specific applications. This microreview highlights recent advances in the field.

Introduction

Conformational control is essential in the design of biomimetic materials with unique functions. Therefore, a variety of strategies have been employed to stabilize well-defined conformations of abiotic oligomers in solution.[1] Among these is the use of specific noncovalent forces, such as hydrogen bonding, donor-acceptor complexation, aromatic π-stacking and metal–ligand interactions, as well as nonspecific van der Waals interactions and solvophobic effects. This microreview will focus on recent work aimed at the synthesis and study of "metallofoldamers" – oligomers that fold into three-dimensional structures in a controlled manner upon metal ion coordination.

Metal ions often play an important role in the structure and function of natural biopolymers. For example, the catalytic activity of many enzymes and ribozymes depends upon specific coordination of metal species. The geometry of a metal complex depends on the size of the metal, the identity of the ligands and the related electronic interactions. For example, d-block metals with the intermediate coordination numbers four, five, or six can adopt tetrahedral or square-planar, pyramidal, or octahedral geometries, respectively. Larger atoms or ions, particularly those of the f-block (e.g. lanthanides), tend to form complexes with higher coordination numbers leading to high-order geometries such as dodecahedral. The established relationship between metal geometry, secondary structure, and function has inspired the design and investigation of a unique class of foldamers,[1–4] sequence-specific oligomers that fold into three-dimensional architectures upon metal coordination. There are mainly two groups of foldamers: single-stranded (peptidomimetics and their abiotic analogues) and self-assembled multiple-stranded (nucleotidomimetics and their abiotic analogues). Mimics of oligonucleotides that bind metal ions have been studied extensively[5] and will not be discussed in this review.

Coordination of metal ions to single-stranded oligomers can either template a helical structure or nucleate its formation (Figure 1).[6] "Helicates", molecules that template an abiotic helix, have been broadly investigated and reviewed.[1,7] This field includes short single-stranded oligopyridines, oligo(*m*-phenyleneethynylene) and zinc bilinones, all fold into helices upon coordination to metal ions. In addition, long chains of oligopyridines are capable of adopting double-helical conformations, because the system maximizes coordination bonds and aromatic π-stacking while minimizing the number of components in the assembly.[8] In the context of helicates, it is important to note that the folding reaction of the oligomeric backbones is coupled to the assembly-disassembly process of metal coordination. In many cases, this process is not specific and

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might be difficult to control (for example, racemic mixtures of left and right helices are usually formed, leading to achiral foldamer products). In this microreview, the term "metallofoldamers" represents peptidomimetic and abiotic oligomers that fold into secondary structures, in a controlled manner, upon coordination to metal ions. Emphasis will be placed on linear as well as cyclic systems, in which absolute helicity can be achieved or enhanced through a rational design of metallofoldamers. In addition, examples of metallofoldamers that were designed for specific applications will be presented and discussed.

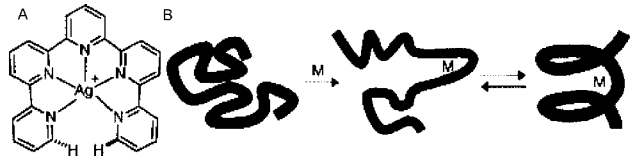

Figure 1. Classification of metallofoldamers: (A) templated helix-like structures and (B) nucleated secondary structures. Reprinted with permission from ref.[6] (Fox's group). Copyright 2005 American Chemical Society.

Folded Oligomers in Which Metal Coordination Templates or Nucleates the Formation of an Abiotic Single-Stranded Helix

Folding of Linear Oligomers

As shown in natural systems, ordered structure in biopolymers depends upon a combination of different physicochemical interactions.[4] Based on this notion, scientists began to develop abiotic oligomers in which metal coordination promotes various nonlocal interactions, leading to a controlled folded structure. The first example of an abiotic oligomer, whose structure in solution has been designed to involve both nonspecific (solvophobic[9]) and specific (metal-coordination) interactions, was reported by the group of Moore in 1999.[10] The solution behavior of a *meta*-connected oligomer, whose backbone consists of twelve nonpolar phenylacetylene units, was tested in the context of metal binding. This oligomer contains six cyano groups located on alternating aromatic rings that are available for metal coordination (oligomer **A**, Figure 2).

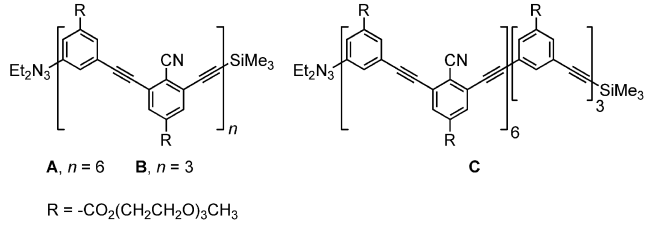

Figure 2. Abiotic oligomers for the examination of solvophobic and coordination interaction.

In the helical conformation, this sequence places the six cyano groups into the interior of the tubular cavity, creating two trigonal planar coordination sites (Figure 3). The solvent of choice for metal-binding experiments was tetrahydrofuran, which does not cause a solvophobically driven helical structure in this system.[11] The metal selected was silver triflate (AgO_3SCF_3) because it can adopt a trigonal-planar coordination geometry.[12] Changes in UV/Vis spectra upon metal binding were indicative of a *cisoid* conformation of the diphenylacetylene units, consistent with a helical structure,[11] which was further confirmed by ^1H NMR spectroscopy. In addition, the UV titration spectra did not change after two equivalents of AgO_3SCF_3 were added, indicating that two Ag^+ ions were bound to each oligomer. The association constant of the overall reaction (K_1K_2) was estimated to be greater than 10^{12} M^{-2}. In order to further investigate the binding reaction, oligomers **B** and **C** (Figure 2), anticipated to bind one equivalent of AgO_3SCF_3, were synthesized and tested for metal coordination. UV/Vis, ^1H NMR, and ESI-MS spectra confirmed that only oligomer **C** binds to silver triflate, with an association constant of $K_1 = 2 \times 10^4$ M^{-1}. These results suggest that the binding of two equivalents of AgO_3SCF_3 in oligomer **A** is a cooperative process with $K_2 >> K_1$ (Figure 3). Overall, this work demonstrates that folding is driven by a combination of solvophobic interactions that favor the helical structure and metal–ligand interactions. Hence, the oligomer can be modified to selectively bind metal ions in the internal cavity of a helical structure, and consequently nucleates the formation of a nonbiological single-stranded helix.

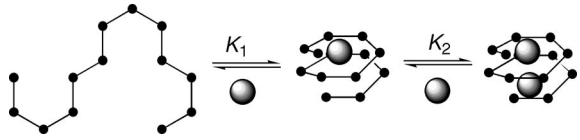

Figure 3. Representation of the metal-induced formation of helical structures as reported by the group of Moore. The metal ions (Ag^+) are shown as spheres.

This idea was further demonstrated by the group of Fox[6] using abiotic molecules based on salophen and salen ligands. Although these molecules do not adopt helical structures in the absence of metal ions, they were shown to fold into single-stranded helices in the presence of Ni^{2+} or Cu^{2+} (Figure 4). The design of these ligands for the formation of single-stranded helical foldamers relies on the hypothesis that a combination between square planar metal complexes and a series of aromatic π-stacking interactions may result in a stable helix.[13] Ligand **1** was obtained in a five-step synthesis,[14,15] with the advantage that the building block compounds can be prepared in multigram quantities and that the amide bond-forming reactions are straightforward. Metal complexes with Ni^{2+} and Cu^{2+} were prepared in good yields by mixing of **1** with metal acetate precursors. These materials form helical structures in the solid state, as shown by X-ray diffraction studies, and are conserved in solution, as evident from NMR spectroscopy.

Circular dichroism (CD) analysis and optical rotation measurements revealed that the resolved crystalline metal complexes **2a** and **2b** (Figure 4) racemize quickly when dissolved at 5 °C. This observation implies that the secondary

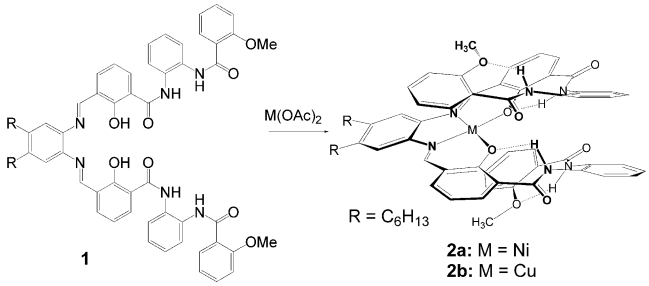

Figure 4. Abiotic oligomers for the examination of hydrogen bonding and coordination interaction. Reprinted with permission from ref.[6] (Fox's group). Copyright 2005 American Chemical Society.

structure can reorganize easily and could potentially be used as a template for responsive materials. The secondary structure can also be altered as a consequence of an induced change in the coordination environment of the metallofoldamers. Indeed, electrochemical experiments have shown that structural reorganization occurs upon metal-centered reduction of Cu^{2+}-containing foldamers. When the reduction is carried out in the presence of coordinating ligands, it is proposed that apical binding of those ligands gives square pyramidal complexes. Semiempirical (AM1) calculations support the idea that the helical structure can be disrupted by the reduction of Cu^{2+} to Cu^{+} with concomitant reorganization to the square pyramidal complex. This work is the first example of abiotic materials, in which the metal coordination sphere is not inherently chiral, but instead causes a series of cooperative, noncovalent interactions that ultimately result in a folded structure. The helical structure is therefore induced by metal coordination, which is required for folding and further reinforced by aromatic π-stacking interactions.

An alternative way to control the chiral environment of a metallofoldamer is via secondary sphere chirality,[16] through which remote stereocenters control the asymmetric environment about the metal.[17] In a subsequent study from the same lab,[18] an enantiomerically pure oligomeric ligand **3** (Figure 5) was synthesized with the anticipation that it would fold into a discrete conformation upon metal binding as the methyl groups positioned on the peripheral benzofuran rings would point to the outside of the helix.[19] A Ni^{2+} complex was prepared accordingly, crystallized, and analyzed by X-ray diffraction to show that the helical structure is indeed controlled by the stereocenters at the periphery; however, the peripheral carbonyls point to the interior of the helix. Solution NMR experiments in variant temperatures (23 to –40 °C) revealed the existence of two species that undergo chemical exchange with a barrier of ca. 13 kcal/mol. Further analysis by CD indicated that the complex is a mixture of helices **4(*P*)** and **4(*M*)** with opposite handedness (indicated by the spectrum of **4**, Figure 5).

In attempts to control the absolute helicity of the metallofoldamer, a different salophen (oligomeric ligand **6**, Figure 5) was designed to stabilize the (*M*)-helix by a three-center hydrogen bond[20] while destabilizing the (*P*)-helix through steric interference of the amide carbonyl, by additional ester functions. Accordingly, ligand **6** was synthesized and mixed with $Ni(OAc)_2$ to obtain the corresponding Ni complex (oligomer **5**, Figure 5). As predicted, X-ray diffraction analysis determines the folding of crystalline **5** into the "carbonyl-in" (*M*)-helix conformation (Figure 6). Evidence that the solution structure of **5** is helical was provided by CD and ^1H NMR measurements. Based on the results,

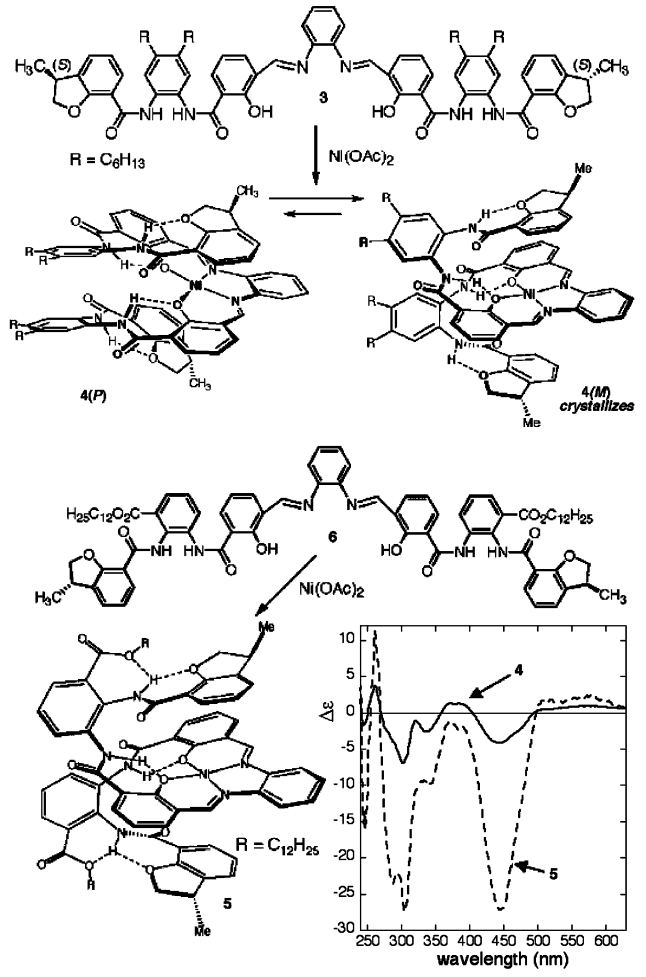

Figure 5. Synthesis and chiroptical properties of chiral foldamers, as reported by the group of Fox. Reprinted with permission from ref.[18] (Fox's group). Copyright 2006 American Chemical Society.

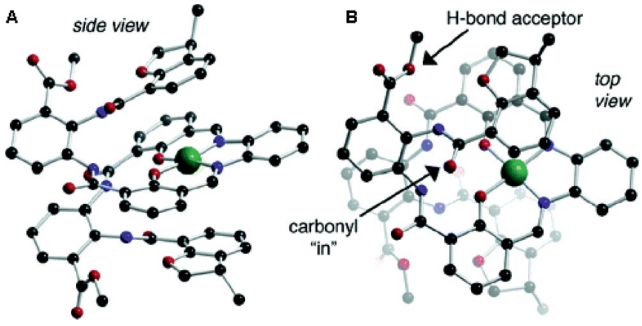

Figure 6. Molecular structures of a chiral foldamer from crystallographic coordinates. Reprinted with permission from ref.[18] (Fox's group). Copyright 2006 American Chemical Society.

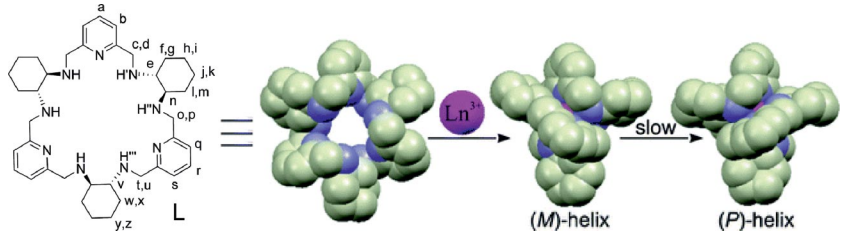

Figure 7. Schematic representation of macrocycle **L** (left), helix formation upon binding to a lanthanide ion and helix inversion, as demonstrated by the groups of Muller and Lisowski. Reprinted with permission from ref.[25] (Muller's and Lisowski's groups). Copyright 2008 American Chemical Society.

the authors point out that either **5(*M*)** is the major conformation or the undetermined conformer also has *M*-helicity. Overall, this work demonstrates that control over the absolute sense of helicity can be effectively achieved by a combination of hydrogen bonding and steric interference arising from peripheral stereocenters in a metal coordination derived foldamer.

Folding of Cyclic Oligomers

While the above examples involve linear oligomers, large macrocycles also can form helical complexes upon metal binding. Coordination to a metal ion forces the macrocycle to adopt a twisted conformation,[21] in which its two halves create a double helical system. In rare cases, two diastereomeric structures of opposite helicity can be obtained for one compound by a thermodynamic inversion process. While helix inversion[22,23] between well-defined and well-characterized diastereomers is a biological phenomenon[24] found in natural systems, a similar process is not common in artificial systems. Following the idea that enantiomerically pure ligands will lead to metallofoldamers with single handed helical structure, Muller and Lisowski have reported a chiral nonaazamacrocycle amine, which coordinates Ln^{3+} ions to form enantiopure helical complexes (Figure 7).[25] Moreover, helix inversion between the kinetic and thermodynamic binding products in the Yb^{3+} complexes was also demonstrated. The nonaaza macrocycle **L** was prepared by the condensation of 2,6-diformylpyridine and *trans*-1,2-diaminocyclohexane,[23a] leading to a 3+3 macrocyclic Schiff base, which was then easily converted into the corresponding macrocyclic amine. The chiral macrocycle **L** was obtained in the enantiopure forms $\mathbf{L}_{RRRRRR}$ and $\mathbf{L}_{SSSSSS}$, corresponding to all-*R* or all-*S* configuration of the diaminocyclohexane carbon atoms, respectively.[26] Mixing of ligand **L** with Ln^{3+} precursors (Ln = Eu, Tb, Yb) resulted in the formation of metal complexes, as indicated by ^{1}H NMR spectroscopy, which were further isolated as enantiopurenitrate salts. The X-ray crystal structure of (*M*)-$[Ln\mathbf{L}_{RRRRRR}]^{3+}$ complexes revealed that they all adopt a unique type of geometry.

Because the cavity radius of the "open" form of the ligand is too large to accommodate a single Ln ion, the macrocycle wraps around the cation in a helical fashion, leading to the generation a left-handed M double helix. The ^{1}H NMR spectra of the (*M*) $[Ln\mathbf{L}_{RRRRRR}]$ complexes reflect their relatively high stability in solution. For instance, the ^{1}H NMR spectrum of a water solution of (*M*)-$[Eu\mathbf{L}_{RRRRRR}]^{3+}$ shows only traces of the (*P*) complex after three weeks. The (*M*)-$[Yb\mathbf{L}_{RRRRRR}]^{3+}$ complex, however, is somewhat less stable, as in water it gradually converts into the (*P*) paramagnetic complex. After refluxing for 15 h, equilibrium is reached, with 95% conversion into the (*P*)-$[Yb\mathbf{L}_{RRRRRR}]^{3+}$ complex. The process can also be observed by CD spectroscopy, which reveals profound differences between the two forms. The inversion in helicity is explained by the notion that the less stable (*M*)-$[Yb\mathbf{L}_{RRRRRR}]^{3+}$ isomer is a kinetic product of the complexation of the free ligand (100% *ee*), while the (*P*)-$[Yb\mathbf{L}_{RRRRRR}]^{3+}$ isomer is a thermodynamic product (90% *ee*). In addition to the thermodynamic control over the absolute helicity, the inversion process is also dependent on the size of the Ln^{3+} ion, e.g. it is observed for solutions of the $[Tb\mathbf{L}]^{3+}$ complex, but not for $[Eu\mathbf{L}]^{3+}$.

Folded Oligomers in Which Metal Coordination Enhances Secondary Structure and Leads to Higher-Order Architectures

One of the long-term goals in the development of functional folded materials is the creation of stable structures with protein-like properties. Despite recent advances in the stabilization of secondary structures upon metal coordination, the design of a sequence that can fold into a well-defined tertiary structure in solution is still challenging. The focus of ongoing studies aiming at the generation of folded architectures by metal coordination is threefold: (*i*) enhanced stabilization of an existing secondary structure (e.g. helix), (*ii*) generation of higher order architectures such as a two-helix bundle or (*iii*) both. Illustrative examples of these approaches are discussed in the following sections.

Metal Coordination in Folded Aromatic Amide Oligomers

Recently, hydrogen bonding interactions have been used in combination with the aromatic π-stacking interactions to induce folding in oligomer systems.[1] A common motif throughout this research is the use of aryl amides.[3,27] These foldamers form stable secondary structures in solu-

tion and in the solid state; therefore, the incorporation of metal ions is anticipated to further stabilize and/or generate higher-ordered structures. The group of Parquette studied the impact of metal coordination on the conformational properties of dendrimers by using small foldamers.[28] Their first efforts were to coordinate multiple Cu^{2+} centers to pyridine-2,6-dicarboxamide dendrons that adopt compact helical conformations due to the *syn-syn* conformational preference of the pyridine-2,6-dicarboxamide repeat unit.[29] In these systems, the helical antipodes experience a highly dynamic equilibrium that interconverts the *M* and the *P* conformations rapidly with kinetic barriers too small to be measured by NMR spectroscopy. Coordination of Cu^{2+}, however, produced a kinetically stable, nondynamic conformational state at room temperature. In a more recent work,[30] this group reported the structural consequences of coordinating a different foldamer, 2,6-bis{2-[(4*S*)-4,5-dihydro-1,3-oxazol-2-yl]phenyl}carbamoylpyridines (**7**), with divalent metal ions such as Cu^{2+}, Ni^{2+}, and Zn^{2+} (Figure 8). As shown by X-ray crystallography analysis, a *P*-helical conformational preference was exhibited by all three of the complexes, identical to the preference observed for the parent (metal free) dendron. Moreover, ^{1}H NMR peak analysis indicates that metal coordination increases the helical interconversion barrier and thus the dynamic helicity of the dendron, making it conformationally "locked".

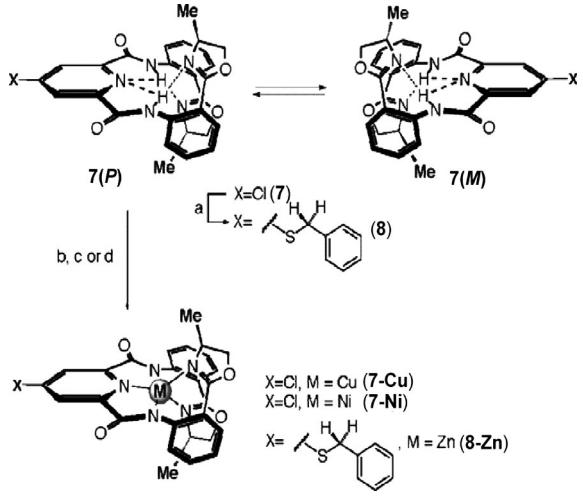

Figure 8. Synthesis of aromatic aryl amide foldamers and their metal complexation (reported by the Parquette group). (a) NaH, $PhCH_2SH$, THF, 72%; (b) $Ni(OAc)_2$, CH_2Cl_2/MeOH (9:1), $(C_2H_5)_3N$, 69% (for 7-Cu); (c) $Cu(OTf)_2$, CH_2Cl_2/MeOH (9:1), $(C_2H_5)_3N$, 87% (for 7-Ni); (d) $(C_2H_5)Zn$, toluene, (for 8-Zn). Reprinted with permission from ref.[30] (Parquette's group). Copyright 2006 American Chemical Society.

Nitschke and Huc reported the use of metal complexes as dynamic connection elements between oligomeric helical segments.[31] Specifically, Cu^+ and Fe^{2+} complexes were applied to link and define the relative orientation of two helices mimicking a turn structure in proteins, but at an unconventional angle. This work focused on the aromatic oligoamides of 8-amino-2-quinoline carboxylic acid, which adopt particularly stable helical conformations in the solid state and in a wide variety of solvents.[32] Amine-functionalized tetramer **9** (Figure 9) adopts a helical conformation that spans over one-and-a-half turns. The reaction of **9** with 6-methyl-2-formylpyridine and $CuBF_4$ produced a pseudo-tetrahedral Cu^+ complex **10**, as characterized by mass spectrometry, ^{1}H NMR spectroscopy, and X-ray crystallography. The conformation of **10** 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[33] of the metal complex. ^{1}H NMR spectroscopy indicates a high degree of influence on the handedness of each helix by the configuration of the neighboring metal. Crystallographic investigations allowed the characterization of four out of the six possible forms of **10**. As expected, the two 2-iminopyridine moieties formed a tetrahedral complex with Cu^+. This geometry dictated an unusual, perpendicular, orientation between the two helices (Figure 10). The unconventional 90° angle between two helices in **10** constitutes a unique motif that hints at the prospect of assembling large square structures comprising helical oligomer "edges" bearing amine functions at both extremities linked by metal complexes at each "corner".

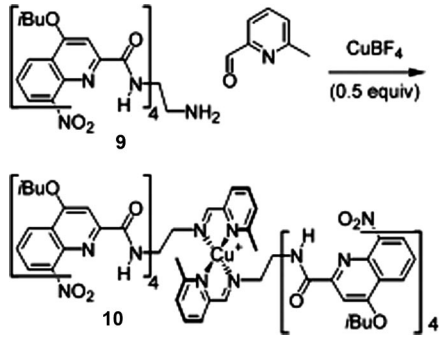

Figure 9. Equilibrium between **9** and tetrahedral Cu^+ complex **10**. Reprinted with permission from ref.[31] (Nitschke's and Huc's groups). Copyright 2008 Wiley-VCH Verlag GmbH & Co.

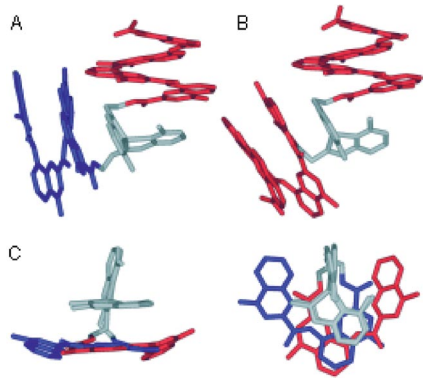

Figure 10. Crystal structures showing (A) the *PΔM* **10** and (B) *MΛM* **10**. (C) Top and side views of the overlay of fragments of the above complexes showing two Δ Cu^{+1} complexes (in gray) and the first two quinoline residues of an *M* helix (in red) and of a *P* helix (in blue), as reported by the groups of Nitschke and Huc. Side chains, BF_4^- ions, and included solvent molecules are omitted for clarity. Reprinted with permission from ref.[31] (Nitschke's and Huc's groups). Copyright 2008 Wiley-VCH Verlag GmbH & Co.

Mixing **1** with 2-formylpyridine and $Fe(BF_4)_2$ in acetonitrile resulted in a mixture of compounds, but only one gave suitable crystals for crystallography. X-ray diffraction analysis provided the structure of a racemic *MΔM*/*PΛP* Fe^{2+} complex bearing only two helix-iminopyridine ligands as well as two hydroxide counterions bound directly to the metal center. In this case, the relative orientation of the two helices imparted by the octahedral geometry of Fe^{2+} is almost parallel. The two hydroxide ligands that are connected to Fe^{2+} appear to play a role in this orientation, as they seem to prevent the helices from folding back on the iminopyridine moieties. The structure of the complex formed upon binding to an Fe^{2+} ion further validates metal-directed dynamic assembly as an efficient approach to generate helically folded, aromatic–amide oligomers and to precisely set their relative orientation.

Metal Coordination in Peptidomimetic Foldamers

Examples of metallo-peptidomimetics involve two types of oligomers: β-peptides and "peptoids" -a class of α-peptides. The secondary structure of both types has been well characterized,[34] therefore metal coordination is anticipated to induce further stabilization and/or create higher-ordered structures. One advantage of these peptidomimetics is their facile preparation achieved by efficient solid-phase synthesis.[35] This method can be automated, enabling the generation of several compounds in parallel. Moreover, it allows ambient temperatures, (typically 25 °C), faster synthesis, and fewer purification steps.

β-Peptides are well-characterized nonnatural oligomers, which have been developed within the last decade.[34a] Systematic studies on β-peptides were conducted in solution and in the solid state, revealing their potential to adopt well-defined ordered conformations.[34b,36] Recently, Seebach[37] has investigated the ability of Zn^{2+} complexation to fortify and enforce β-peptide secondary structure towards the generation of artificial β-peptidic zinc fingers, a mimic of a natural motif found in proteins.[38] To achieve this aim, a β-decapeptide, four β-octapeptides, and a β-hexadecapeptide have been designed and synthesized. For the first five β-peptides, the design was such that the peptides would (*i*) fold to a *14*-helix (a helical secondary structure defined by 14-membered ring hydrogen bonds),[36c] a hairpin turn, or neither, and (*ii*) incorporate the cysteine and histidine side chains in strategic positions to allow binding of Zn^{2+} in order to stabilize or destabilize the intrinsic secondary structure of the peptide. The β-hexadecapeptide was designed to (*i*) fold into a turn, to which a *14*-helix is attached through a β-dipeptide spacer, and (*ii*) contain two cysteine and two histidine side chains for Zn^{2+} complexation in order to mimic a Zn-finger motif. β-Peptides were generated by manual solid-phase synthesis.[39] After cleavage from the resin, the β-peptides were purified by preparative HPLC, and characterized by analytical HPLC, MS, NMR, and CD measurements. Dramatic changes of the CD pattern were observed when $ZnCl_2$ was added to aqueous solutions of the β-peptides, buffered at pH>7 (pK_a of histidine = 6.04). Although the CD spectra demonstrated that there are interactions between the β-peptides and Zn^{2+} ions in solution, they did not provide any structural information for further qualitative assignments. Some CD spectra suggested the formation of 1:1 complexes, an observation that was further confirmed by electrospray mass spectrometry. ^1H NMR analysis, in the absence or presence of $ZnCl_2$, indicated that the β-peptide, which is present as a *14*-helix in methanol, is forced to a hairpin-turn structure by Zn binding in water. In addition, the β-peptide, having cysteine and histidine residues positioned far apart from each other, adopts a distorted turn structure in the presence of Zn^{2+}.

An alternative approach for mimicking natural metal-binding motifs is the use of "peptoids" – *N*-substituted glycine oligomers. Peptoids have emerged as intriguing mimics of polypeptides,[40] particularly with respect to their ability to form well-defined folded architectures.[34b] Moreover, many peptoid sequences exhibit a remarkable propensity for folding even at small oligomer chain lengths.[41] Peptoid oligomers can be synthesized efficiently by solid-phase methods, allowing the introduction of a variety of side chains (Figure 11),[35] therefore enabling the coordinated display of multiple chemical functionalities, which can potentially emulate active sites of proteins (e.g. metal binding sites).

The group of Zuckermann has described the introduction of a high-affinity zinc-binding function into a peptoid, which consists of two helices bound together by a short peptide coil, and demonstrated its folding into a two-helix bundle upon binding of a zinc ion (Figure 12).[42] Each helix was designed to contain a bulky chiral side chain in two-thirds of the monomer positions, since these side chains are known to enforce helicity.[41a] The side chains that were used – (*S*)-*N*-(1-phenylethyl)glycine (Nspe) and (*S*)-*N*-(1-carboxylethyl)glycine (Nsce) – impose steric hindrance on the backbone, generating a polyproline type I-like helix with three residues per turn. The chosen motif for the loop region was Gly-Pro-Gly-Gly, which has a propensity to form type II β-turns in proteins.[43] Borrowing from the well-understood zinc-binding motif, Cys_2His_2,[38a,38b] thiol, and imidazole moieties were positioned within the peptoid such that both helices had to align in close proximity to

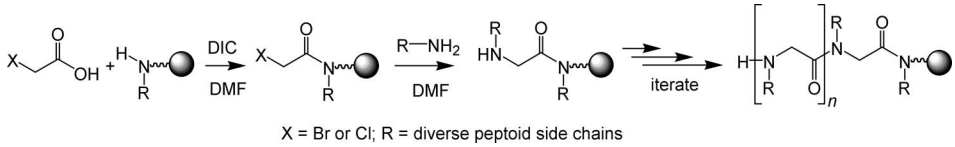

Figure 11. Two-step solid-phase synthesis of peptoids.

form a binding site. In order to measure the change in the distance between the two helical segments and to probe the binding of zinc, fluorescence resonance energy transfer (FRET) reporter groups were used.[44] Thus, a fluorescence donor (anthranilamide) was incorporated at one end of the peptoid and a quencher (nitrophenol) at the other end. FRET efficiencies were used to determine the folding of the peptoids, and the affinity and selectivity of the zinc binding peptoids. The first observation was that zinc binding increases the FRET efficiency in acetonitrile, indicating that zinc stabilizes the two-helix bundle by holding the two helical segments together. Moreover, in mixtures of two different peptoids, there was no change in the intermolecular FRET efficiencies upon addition of zinc, proving that the two helix-bundles are stabilized without inducing self-association. CD spectroscopy revealed no significant changes in the far-UV region upon zinc binding, indicating that the secondary structure of the individual peptoid helixes is unchanged. In addition, the position and number of zinc-binding residues, as well as the sequence and size of the loop that connects the two helices were systematically varied, followed by FRET efficiency measurements. The results suggest, for example, that a higher zinc-binding affinity was due to a longer loop region in the peptoid, probably because longer flexible linkers accommodate optimal zinc coordination geometry. In addition, among various divalent metal ions, e.g. Ca^{2+}, Mg^{2+}, and Cu^{2+}, the most significant change in the FRET efficiency was achieved by Zn^{2+}, with a binding affinity an order of magnitude higher then the other metal ions, a kind of selectivity that is also found in biological systems. This work is a prominent example of a tertiary structure formation governed by the docking of preorganized helices.

Maayan et al. have designed and synthesized helical peptoids bearing one or two multidentate ligands. Upon metal coordination, an enhancement of the secondary structure was demonstrated, either by stabilization of an existing helix or by the formation of a helical duplex. Moreover, the helical secondary structure environment induces chirality about the metal center and enforces the creation of a chiral metal complex from ligands that are not inherently chiral.[45]

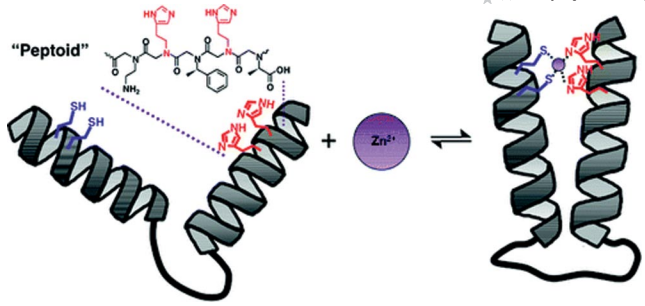

Figure 12. Schematic representation of peptoid two-helix bundle forming upon Zn^{2+} binding. Reprinted with permission from ref.[42] (Zuckermann's group). Copyright 2008 American Chemical Society.

The introduction of multidentate metal-binding ligands as pendant groups in nonhelical peptoid sequences was first demonstrated, and presented in an earlier study from the same group.[46] For example, 8-hydroxy-2-quinolinemethylamine was prepared from the commercially available 8-hydroxy-2-quinolinecarbonitrile by a one step hydrogenation procedure and incorporated within different peptoids without need for protection of the hydroxy group. In order to explore the influence of metal binding on the conformation of chiral helical peptoids, hydroxyquinoline ligands were incorporated to their scaffolds. These peptoid ligands were expected to bind divalent metal ions, producing tetracoordinated metal species.[47] Specifically, **$H_1$5** and **$H_2$6** (Figure 13) were synthesized as model systems for comparison of inter- and intramolecular metal complex formation, respectively.

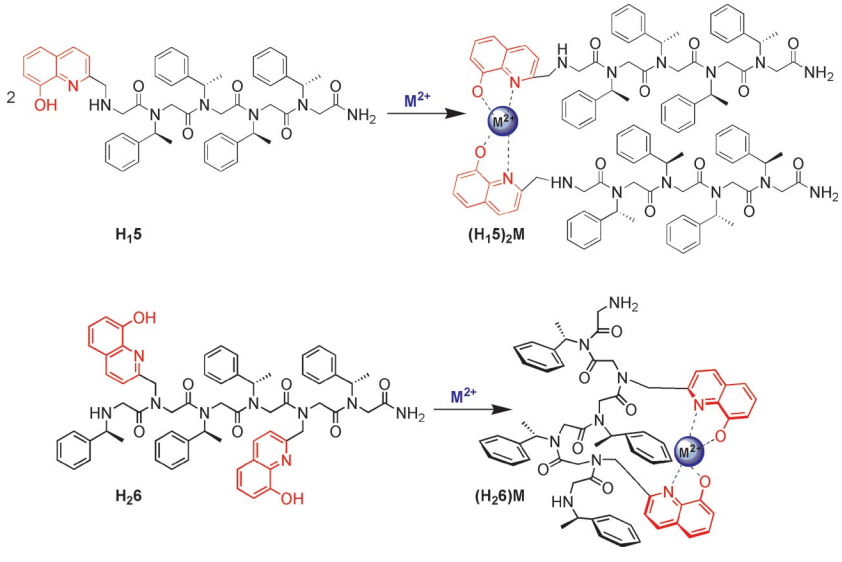

Figure 13. Schematic representations of the peptoids **$H_1$5** and **$H_2$6** and their metal complexes.[45]

The pentamer **H$_1$5**, with one hydroxyquinoline site at the N-terminus, was expected to form a peptoid duplex upon metal binding (2:1 peptoid/metal). The hexamer **H$_2$6** contains two hydroxyquinoline ligands, endowing this oligomer with the capacity to form an intramolecular 1:1 peptoid/metal complex (Figure 13). Positioning the ligands at *i* and *i* + 3 in the sequence matches the pitch of the helix and was designed to orient these groups in proximity on the same face of the scaffold, separated by one helical turn.

Oligomers **H$_1$5** and **H$_2$6** were synthesized in good yields,[45] and their ability to bind metal ions was evaluated by UV/Vis spectroscopy (Figure 14, A and C). Job plots constructed from UV titration of the peptoids with either Cu^{2+}or Co^{2+} were consistent with a 2:1 (**H$_1$5**)$_2$M (M = Cu^{2+} or Co^{2+}) duplex and a 1:1 (**H$_2$6**)M intramolecular complex. The peptoid-to-metal ratio was corroborated further by mass spectrometry analysis. CD measurements revealed substantial changes upon metal complex formation (Figure 14, B and D). Solutions of the metal complexes exhibited increases in the magnitude of the CD signals near 200 nm and 220 nm, relative to the metal-free peptoids. In the case of (**H$_1$5**)$_2$M, this suggests an increase in conformational order, as the magnitude of the signal reflects the degree of helicity. The increase in the CD signal was more dramatic for (**H$_2$6**)M, consistent with greater conformational constraint and enhanced secondary structure content due to intramolecular metal complexation. Metal binding to **H$_1$5** and **H$_2$6** also produced new CD peaks between 240 and 280 nm, the region corresponding to the 8-hydroxyquinoline π–π* transition, which reflects the transmission of the stereogenic character of the peptoid scaffold to the metal center. These results indicate the reciprocating effects of metal binding – the chirality of the peptoid backbone establishes an asymmetric environment about the metal center while metal complexation enhances the helical character of the backbone.[48] This synergistic interaction between helices and metal complexes, which has not been observed before in artificial folded oligomers, holds potential for applications in asymmetric catalysis and material science.

The last example of metallopeptoids involves *N*-benzyloxyethyl cyclic oligomers of various sizes that bind alkali metal ions, a study conducted in the groups of Izzo and De Riccardis.[49] The synthesis of the linear *N*-benzyloxyethyl glycine oligomers was accomplished both in solution[50] and through solid-phase methods. Head-to-tail macrocyclizations of the linear compounds were achieved in the presence of different condensing agents, producing three cyclic peptoids – trimer, tetramer, and hexamer (Figure 15). The peptoids were characterized in solution, by NMR spectroscopy, and in the solid state by X-ray crystallography. The spectroscopic data of the cyclic trimer revealed C_3-symmetric all-*cis* "crown" conformation. In the case of the cyclic tetramer, a single-crystal X-ray analysis demonstrated a *ctct* "chair" tetralactam core geometry.[51] The cyclic hexamer, on the other hand, showed conformational disorder in solution, an observation that prompted metal complexation studies with this peptoid. Indeed, stepwise addition of sodium picrate induced the formation of a new chemical species with a remarkably simplified NMR spectrum, suggesting the presence of an S_6-symmetry axis

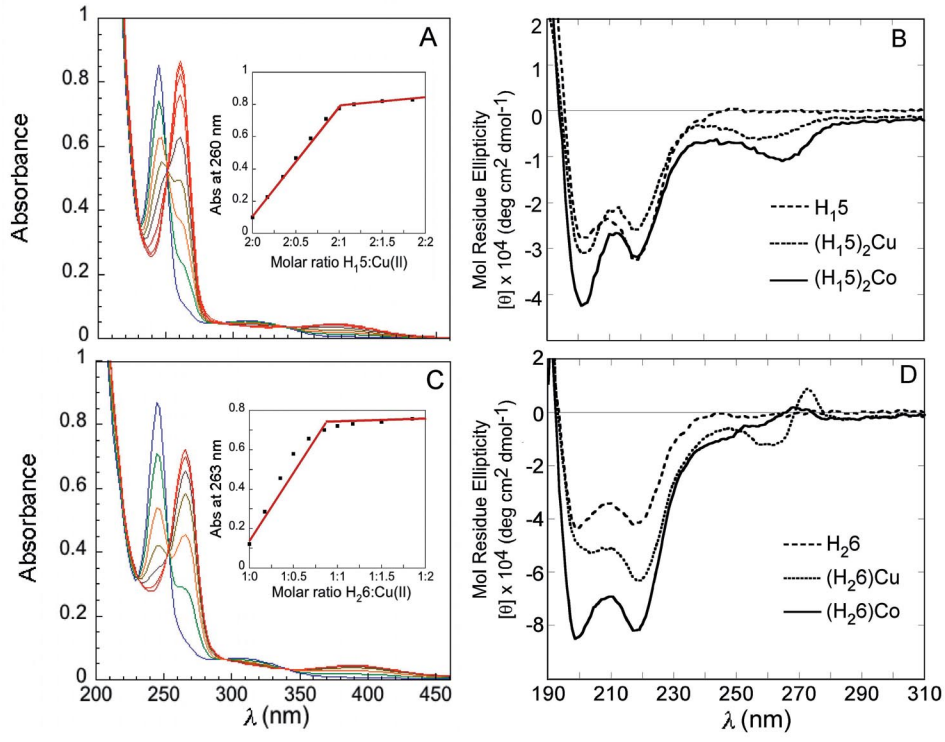

Figure 14. UV/Vis spectra and job plot for titration of (A) $H_1$5 with Cu^{2+} and (C) $H_2$6 with Cu^{2+}. CD spectra for (B) $H_1$5, $(H_1)_2$Cu, and $(H_1)_2$Co, and (D) $H_2$6, (H_2)Cu, and (H_2)Co. UV/Vis spectra: (A) 54 μM peptoid in MeOH/H_2O (4:1) solution, (C) 40 μM peptoid in MeOH/H_2O (4:1) solution, blue = free ligand, red = metal complex. CD spectra: 100 μM MeOH/H_2O (4:1) solutions.[45]

passing through the inner cavity of the sodium cation. Moreover, equilibrium NMR spectroscopic studies indicated that the electrostatic (ion-dipole) interactions stabilize this conformation in solution. The authors reported one successful attempt in which needlelike crystals, suitable for X-ray structure analysis, of the cyclic hexamer as a 2:3 complex with strontium picrate were obtained (Figure 16).

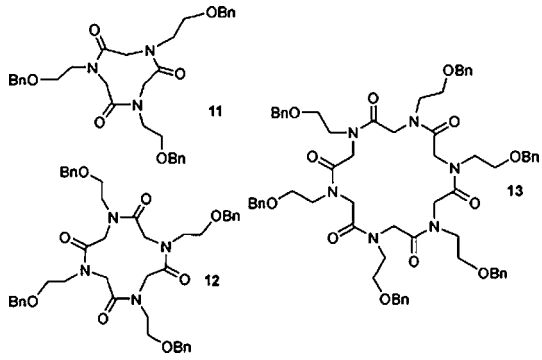

Figure 15. Izzo and De Riccardis's cyclic peptoids. Reprinted with permission from ref.[49] (Izzo's and De Riccardis's groups). Copyright 2008 Royal Society of Chemistry.

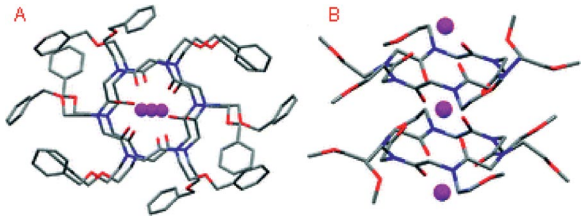

Figure 16. X-ray crystal structure of complex 13_2·[Sr(Picr)$_2$]$_3$: (A) top view (B) side view. Hydrogen atoms and picrates have been omitted for clarity. Reprinted with permission from ref.[49] (Izzo's and De Riccardis's groups). Copyright 2008 Royal Society of Chemistry.

The analysis showed a unique peptoid bond configuration with the carbonyl groups alternately pointing toward the strontium cations and forcing the *N*-linked side chains to assume an alternate pseudo-equatorial arrangement. Although the authors do not discuss conformational control in cyclic peptoids upon metal coordination, this work was found to be interesting in the context of this microreview because to date, it reports the first and only example of a metallopeptoid structure to be solved. Moreover, in a follow-up study, these groups reported cation transport carried by cyclic peptoids across a phospholipid membrane.[52] Two additional cyclic peptoids, an octamer and a decamer, were synthesized and characterized, and their size-dependent selectivity for first group alkali metal cation transport was demonstrated.

Toward the Generation of Functional Materials

The examples discussed above demonstrate different strategies by which conformational control in synthetic oligomers could be achieved via metal coordination. Many efforts in this area of research, however, are aimed at mimicking properties and function of natural biopolymers towards the generation of superior materials. Despite years of study, the use of metallofoldamers for desirable applications such as selective catalysis and molecular recognition (as in sensors) is in its infancy. The few examples of functional metallofoldamers and their potential use will be presented next.

Foldamers as Sensors for Metal Ions

Chemosensors are molecules that are able to selectively detect one specific analyte from a mixture of different components. Applications of chemosensores are broad and can be found in the areas of chemistry, environmental chemistry, and biology.[53] For example, selective detection of metal ions is important because many physiological processes are triggered, regulated or influenced by these cations.[54] Highly specific calcium sensors based on foldamers were introduced by the groups of Ajayaghosh and Daub. In a series of studies,[55] these groups investigated the binding affinity of different squaraine bichromophoric podands for alkaline earth metal cations and demonstrated a high selectivity towards the Ca^{2+} ion even in the presence of other metal ions, such as K^+, Na^+, and Mg^{2+} (Figure 17). In these systems, metal coordination induces folding of squaraine pedants, and the resultant exciton coupling between the squaraine chromophores signals the binding event. The foldamers were prepared by a two-step synthesis involving basic conditions and relatively high temperatures (70–90 °C), in overall yields of about 10%.[56] The bichromophore showed a strong absorption maximum around 630 nm in acetonitrile; however, in DMSO/H_2O mixtures of different compositions these foldamers showed a blueshifted absorption band at 586 nm attributed to a characteristic aggregation of an intramolecular folding of the bichromophoric

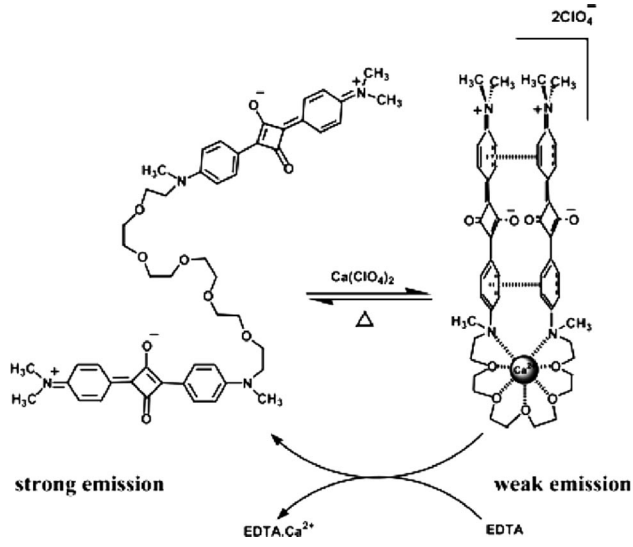

Figure 17. Illustration of a squaraine bichromophore folding upon coordination to the Ca^{2+} ion. Reprinted with permission from ref.[55c] (Ajayaghosh's group). Copyright 2005 American Chemical Society.

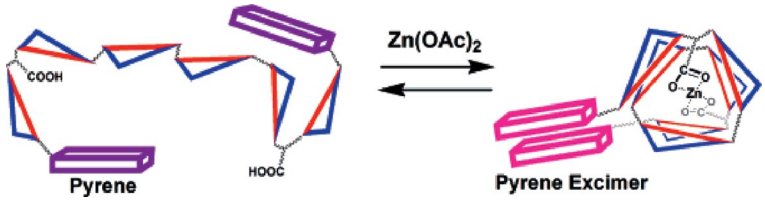

Figure 18. Detection of Zn^{2+} ion by Zhong and Zhao's hybrid foldamer. Reprinted with permission from ref.[59] (Zhao's group). Copyright 2007 American Chemical Society.

pedants. In the case of Ca^{2+}, the solvent-induced aggregation resulted in a visual color change from light blue to purple-blue, indicating a strong chromophoric interaction. Alkali metal ion binding experiments in acetonitrile revealed a similar visible color change in the presence of calcium perchlorate, which was intense and specific to Ca^{2+}.

In a related work, Zhao et al. reported a tunable mercury sensor based on the principle that the binding affinity of a foldamer can be adjusted by its folding conditions.[57] For this purpose, a cholate foldamer connected by amide groups and functionalized by amino acids, whose folding is driven completely by solvophobic interactions, was prepared.[58] Fluorescence titration revealed a binding stoichiometry of 1:1 for the metal/foldamer ratio, as confirmed by the Job plot. As shown in the fluorescence spectra, this foldamer could easily detect 20 nM Hg^{2+} in a solvent mixture of 5% methanol/(hexane/ethyl acetate, 2:1) (Figure 18). Nonlinear least-squares fitting gave association constants ranging from 1.5×10^7 to 5.5×10^3 M^{-1} depending on the solvent system in which the metal complexation takes place. This observation can be explained on the basis of the assumption that the two sulfur groups, which are separated by two cholate units, cannot chelate mercury in the unfolded state. The folded mercury-binding conformer has a hydrophobic exterior, which makes it incompatible with highly polar solvents. Therefore, mercury sensing can be tuned simply by changing the solvent system. Following this concept, a detector for Zn^{2+} was further developed by the same group.[59] A hybrid foldamer containing six cholate units and two glutamic acids was labeled with two pyrene groups at the chain ends. Addition of Zn^{2+} resulted in an enhanced emission of the pyrene excimer, indicating folding of the hybrid compound upon metal binding. Its specificity for Zn^{2+} is mostly evident from other divalent metal ions that bind with the foldamer less strongly and/or interact with the pyrene labels in different fashions. Because the foldamer senses the metal ion by going from the unfolded to the folded conformation, the most sensitive detection of Zn^{2+} happens in 15% methanol/ethyl acetate. The sensitivity of the detection depended on the relative population of the folded and unfolded conformers, being highest when about 90% of the foldamer was in the unfolded state.

Metallofoldamers as Molecular Actuators

A mechanical molecular actuator is a molecule that can switch between different conformational states under external control.[60–63] This conformational transition may result in a change in size and shape of the molecular actuator.[64] Such architectural rearrangements can be used to construct nanoscale bioactive devices, for example, a molecular valve for applications in delivery of small molecules and catalysis.

Taking the peptidomimetic approach, Schafmeister et al. have synthesized a bis(peptide)-based molecular actuator.[65] This compound was generated by using solid-phase methods and consists of two molecular rods, each approximately 24 Å[66] long, containing four bis(amino acid)[67] monomers. The two rods are connected by a flexible hinge that consists of an ornithine residue, which allows the ends to come together and form a metal-binding site. The shape change was designed to be controlled by metal exchange, placing two 5-carboxymethyl-8-hydroxyquinoline (Q) groups at the two ends of the molecule for the binding of a Cu^{2+} ion (Figure 19). Titration of this bis(peptide) with Cu^{2+} shows spectral changes consistent with the formation of a $[CuQ_2]$ complex. Addition of three equivalents of ethylenediaminetetraacetic acid (EDTA) to the metal-bound oligomer causes the spectrum to return to that of the metal-free species, which indicates that the switch is reversible. To

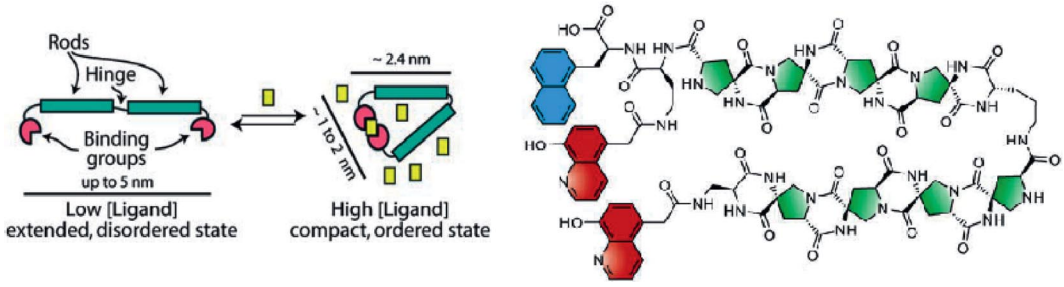

Figure 19. Operation (left) and structure (right) of Schafmeister's molecular actuator. Reprinted with permission from ref.[65] (Schafmeister's group). Copyright 2008 Wiley-VCH Verlag GmbH & Co.

determine the shape, size, and aggregation state of the oligomer in the metal-free and metal-bound states, sedimentation equilibrium and velocity experiments were carried out. The analysis of the sedimentation equilibrium data indicates that both the oligomer and its copper complex are monomeric under the experimental conditions. The sedimentation coefficient for the copper complex is 18% larger than that of the unbound oligomer, which is consistent with the observation that the metal-free species is more extended relative to the metal-bound species and sediments slower as a result of increased hydrodynamic friction. Size exclusion chromatography further confirmed that this bis(peptide) undergoes contraction and expansion controlled by the addition and removal of Cu^{2+} ion.

Concluding Remarks

The selected examples of metallofoldamers discussed here illustrate the significant progress made in the design of foldamers that adopt well-defined secondary structures solely upon metal–ligand coordination interactions or in combination with a variety of other interactions, such as hydrogen bonding, aromatic π-stacking, and solvophobic effects. Although the scope of applications still needs to be enlarged, metallofoldamers have shown an impressive ability to form single-handed helical structures and other chiral architectures. Moreover, several metallofoldamers have been applied as sensors due to their selective folding when binding to a specific metal ion, while others show promise for applications as responsive materials on the basis of their ability to fold and unfold upon changes in the oxidation state of the coordinated metal ion. Finally, the synergistic interaction between helices and metal complexes in metallopeptoids demonstrates transfer of chiral information from a folded scaffold to an embedded metal center and hence holds potential for applications in asymmetric catalysis.

Acknowledgments

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