Metallo-Foldamers

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Metallo-Foldamers with Backbone-Coordinative Oxime Peptides: Control of Secondary Structures**

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Metal coordination is a powerful tool for constructing biologically relevant structural motifs found in nucleic acids, proteins, and polysaccharides. Pioneering work in the modeling of natural helices started from helicates,[1,2] in which linear synthetic ligands complex with several metal ions and form single- or multi-stranded helical structures. As part of this approach, DNA analogues featuring metal base pairs have also been developed as semi-natural helicates.[3] In these artificial helical complexes, replacement of hydrogen bonds in natural helices with metal coordination bonds is a key design concept to construct more stable, diverse, dynamic, and functional helicates based on the unique structures and functions of metal ions.

To date, a variety of excellent peptide-based synthetic foldable molecules "foldamers"[4–6] have been designed and applied not only to vital related functions,[7] but also to structure-dependent chemical functions.[8] Thus, metal–peptide conjugates[9] have great potential in terms of diverse conformation libraries, dynamic features, and metal-based functions. Herein, we report a novel type of metallo-foldamer formed from a peptide mimic containing up to four synthetic oxime amino acids (Figure 1). We envisaged that the incorporation of a metal-coordinative oxime group into an amino acid mimic would provide a peptide mimic with multiple metal binding sites possibly leading to metal-mediated secondary structures such as helices, hairpins, turns, and sheets. In this study, we have demonstrated that oxime–peptide complexes with up to two Pd^{II} ions form folded structures such as helices, hairpins, and double-hairpins, as revealed by NMR and XRD analyses. Furthermore, we found that they show conformation changes because of the linkage isomerization upon addition of acids or bases.

Our design concept is to incorporate an additional metal binding site into the backbone of a synthetic amino acid as a minimal structure of foldamers. A structurally robust oxime group[2j,10] is the essential part of amino acid **1** as a metal binding site, and both C- and N-terminal parts have an α-methylene group where one or two side chains may be introduced as needed. The peptides can be synthesized according to general liquid-phase methods without protecting the oxime groups. In this study, we prepared two dipeptides **2** and **3**[11] and one tetrapeptide **4** from monomeric **1** (Figure 1b and Scheme S1 in the Supporting Information). It was expected that the oxime nitrogen atoms and the O or N (as N^-) atoms of amide groups would take part in metal coordination to provide some secondary folded structures depending on the kind of metal ions and complexation conditions. In view of the high Lewis acidity and greater coordination space of square-planar coordination geometry, Pd^{II} was selected as the first choice.

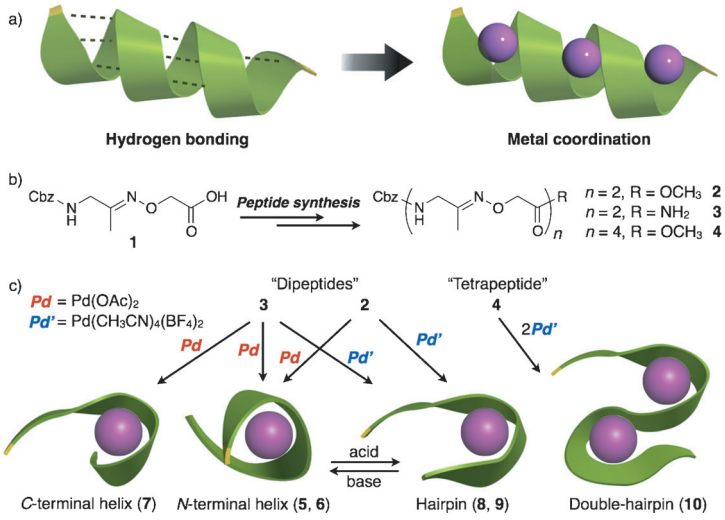

Figure 1. a) A conceptual scheme of this study. b) Syntheses of dipeptides, **2** and **3**, and a tetrapeptide **4** from a protected oxime amino acid **1**, and c) the formation of mononuclear helical complexes, **5**–**7**, and hairpin complexes, **8** and **9**, and a dinuclear double-hairpin complex **10**.

Upon complexation of the C-terminal, ester-protected dipeptide **2** and $Pd(OAc)_2$ in CD_3CN, the formation of a single product was confirmed by ^1H NMR spectroscopy (see Figure S27 in the Supporting Information). The disappearance of two N-H signals suggests the complexation of both carbamate and amide N-H moieties with deprotonation. The large up-field shift of CH_2 protons of the Cbz (benzyloxycarbonyl) group at the N-terminal, which is probably because of the electronic influence from the neighboring O=C-N-Pd moiety, also supports the complexation at the carbamate moiety. The formation of a mononuclear complex was confirmed by electrospray ionization time-of-flight (ESI-TOF) mass spectrometry (*m*/*z* 549.06 $[Pd(H_{-2}\mathbf{2})\cdot Na]^+$). The

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product was obtained as yellow crystals in 86% yield by recrystallization from $CHCl_3$/toluene. The single-crystal X-ray analysis revealed the molecular structure of a neutral, mononuclear complex Pd(H$_{-2}$**2**) (**5**) as shown in Figure 2a.

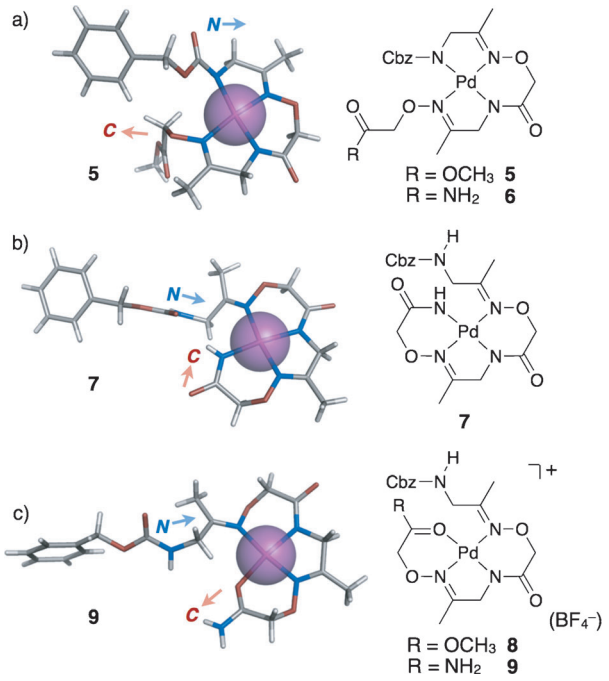


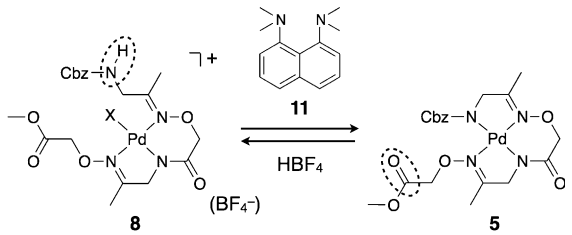
Figure 2. Chemical structures of **5**–**9** and crystal structures of a) N-terminal helix **5**, b) C-terminal helix **7**, and c) hairpin **9**.[17] Disordered atoms in **5**, one acetic acid molecule in **7**, and disordered atoms and one BF_4^- anion in **9** are omitted for clarity.

The obtained structure contains one square-planar Pd^{II} ion bound by two oxime and two deprotonated amide nitrogen atoms as expected from its solution-phase ^{1}H NMR spectra. Notably, complex **5** has a one-roll helical structure because of the overlap of both N- and C-terminals, leading to the existence of enantiomeric pairs of *P* and *M* helices in the crystal. Interconversion of both helical enantiomers in solution appears to be fast on a ^{1}H NMR timescale at room temperature because of an absence of diastereotopic splitting of the methylene protons of **5**. The fast racemization of **5** is consistent with the results of recent metallo-foldamers reported by Fox and co-workers.[2m]

In contrast to **2**, the C-terminal, amide-protected dipeptide **3** afforded two different mononuclear species through complexation with $Pd(OAc)_2$ in CD_3CN as confirmed by ^{1}H NMR spectroscopy (a ratio of about 2.5:1, see Figure S34 in the Supporting Information) and ESI-TOF mass spectrometry (*m*/*z* 534.06 [Pd(H$_{-2}$**3**)·Na]$^+$). The major product, with upfield shifted CH_2 protons of the Cbz group, was assigned to **6**, similarly to **5**. In the minor product, complex **7**, little shifting of the CH_2 of the Cbz group was observed and therefore the most likely structure is that where the deprotonated C-terminal amide nitrogen binds to the Pd^{II} ion (Figure 2b, right). Fortunately, complex **7** was crystallized from CH_3CN in 24% yield. As expected, the resulting structure was a neutral, mononuclear complex Pd(H$_{-2}$**3**) (**7**) as determined by X-ray analysis (Figure 2b, left). In this structure, two oxime nitrogen atoms and two deprotonated amide nitrogen atoms at the C-terminal bind to a Pd^{II} ion to form an N_4 plane with two six-membered chelate rings, which is different from metal complexes of natural peptide chains forming only five-membered chelate rings. As the Pd^{II} ions in **6** and **7** are bound by the N-terminal and C-terminal of **3**, respectively, **6** and **7** have an isomeric relationship.

In the helical complexes **5**–**7**, formed from **2** or **3**, two deprotonated N-H groups bind to the Pd^{II} centers as the *trans* ligands. Coordination structures of such complexes are often controllable by addition of acid and base.[9a,d] Indeed, complexation of dipeptides **2** and **3** with $Pd(CH_3CN)_4(BF_4)_2$ containing BF_4^- anions instead of basic AcO^- anions in $Pd(OAc)_2$ afforded alternative mononuclear complexes as confirmed by ^{1}H NMR spectroscopy (see Figures S27, S43 in the Supporting Information) and ESI-TOF mass spectrometry (*m*/*z* 527.07 [Pd(H$_{-1}$**2**)]$^+$ for **8** and 512.08 [Pd(H$_{-1}$**3**)]$^+$ for **9**). The molecular structure of **9** was determined by the X-ray crystal analysis of [Pd(H$_{-1}$**3**)]BF_4 which was isolated in 81% yield (Figure 2c). In contrast to the helical complexes **5**–**7**, one carbonyl oxygen atom of the C-terminal of **9** binds to a Pd^{II} ion to form a monocationic, square-planar complex, which is regarded as a hairpin rather than a helix. Overall, the common coordination structure of complexes **5**–**9** is an N-N$^-$-N tridentate coordination with two oxime nitrogen atoms and one deprotonated amide nitrogen atom to form a helix or a hairpin structure, in which the fourth intramolecular coordination is influenced by the basicity of the counter anions.

The reversible structural conversion between helix **5** and hairpin **8** through intramolecular ligand exchange has been clearly established upon treatment of acid or base (Scheme 1).[12] When 2.6 equivalents of *N*,*N*,*N*′,*N*′-tetra-



Scheme 1. Acid–base control of the fourth intramolecular coordination with reversible interconversion between mononuclear complexes, **8** and **5**.

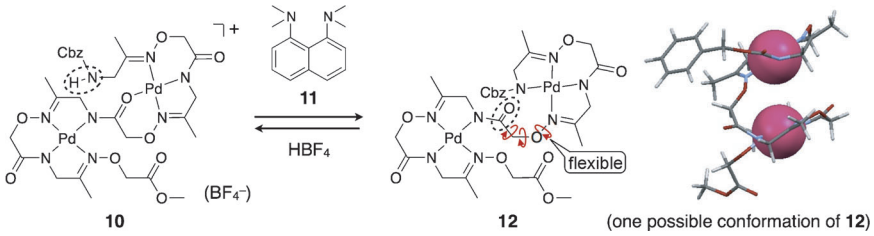
methyl-1,8-naphthalenediamine (**11**) was added as a base to a solution of cationic hairpin **8** in CD_3CN, quantitative formation of helix **5** was confirmed by ^{1}H NMR spectroscopy. This indicates that the N-terminal carbamate nitrogen atom binds to the Pd^{II} ion with simultaneous deprotonation. Conversely, addition of HBF_4 to the solution of **5** resulted in quantitative reverse conversion to hairpin **8** (see Figure S27 in the Supporting Information). This reversible conversion between **5** and **8** was found to be repeatable by ^{1}H NMR measurements in which **11** and HBF_4 were alternately added

to the regenerated **8** to achieve quantitative spectral transformation (see Figure S62 in the Supporting Information). This result demonstrates that the structural conversion of Pd^{II}-mediated foldamers depends on the Lewis acidity of the Pd^{II} ions used and the acid–base balance. Recently, helicity inversion of mononuclear acyclic metal complexes through acid–base control or anion addition have been reported by Miyake and co-workers.[9k,13] In contrast, our approach would lead to direct control of the secondary structure itself because our metallo-foldamers can be elongated with multiple metal ions that are structure-determining components.

For multinuclear higher-order structures, complexation of a longer tetrapeptide **4** was subsequently examined. Upon addition of three equivalents of $Pd(CH_3CN)_4(BF_4)_2$ to a solution of **4** in [D_6]DMSO, a single product was found to form as shown by ^{1}H NMR spectroscopy (see Figure S51). The unchanged signals of the N-terminal carbamate N-H protons suggest that this moiety does not bind to Pd^{II} as observed with cationic hairpins **8** and **9**. ESI-TOF mass spectrometric measurement supports the formation of the dinuclear complex (*m*/*z* 889.09 $[Pd_2(H_{-3}\mathbf{4})]^+$). The folded structure was eventually determined by single-crystal X-ray analysis although the data quality was not very high (Figure 3a).[14] As expected, the resulting structure was a dinuclear, cationic complex $[Pd_2(H_{-3}\mathbf{4})]BF_4$ (**10**) with a Pd^{II}-Pd^{II} distance of 5.98 Å bridged by a deprotonated amide bond (O and N^-). While the N-terminal Pd^{II}-centered structure with oxime-amide-oxime-carbonyl coordination is similar to cationic hairpin **8**, the C-terminal structure with amide-oxime-amide-oxime coordination is almost identical to neutral helix **5**. As a result, complex **10** adopts a double hairpin structure.[15]

To confirm the solution structure of **10**, ^{1}H and ^{13}C NMR spectra of **10** in [D_6]DMSO were fully assigned with the aid of ^{1}H-^{1}H COSY, NOESY, ^{1}H-^{13}C HSQC, and HMBC measurements. In the NOESY spectrum, several long-range, interstrand NOEs (nuclear Overhauser effects) such as H^d-H^l, H^c-H^l, and H^j-H^q were observed besides short-range, intrastrand NOEs. This result suggests that a double-hairpin structure is formed in solution (Figure 3b).[12] On the other hand, other long-range NOE signals (H^b-H^f) observed here are not consistent with the distance observed in the X-ray structure (8.4 Å), indicating that the conformation of the Cbz part of the N-terminal is flexible.

The structure of double hairpin **10** can be regarded as a mixture of the structure of hairpin **8** and helix (therefore chiral) **5** as mentioned above. If the N-H moiety of the N-terminal carbamate in **10** is deprotonated and thereby binds to Pd^{II} by replacing the middle amide carbonyl oxygen donor, a repeating structure of a kind of two consecutive helices **5** would be formed (Scheme 2). Indeed, the addition of base **11** to a solution of **10** in [D_6]DMSO gave rise to a new species **12** in which the N-H moiety of the N-terminal carbamate



Scheme 2. Acid–base control of the intramolecular coordination with reversible interconversion between dinuclear complexes **10** and **12**.

appears to be deprotonated to bind Pd^{II} as suggested from the large upfield shift of the CH_2 signal of the Cbz group. This behavior is comparable to the conversion from cationic hairpin **8** to neutral helix **5**. Similarly, species **12** was quantitatively and reversibly converted to the initial structure **10** by adding HBF_4 (see Figure S63 in the Supporting Information). The double hairpin **10** has a rigid structure due to the two Pd^{II} centers being bridged by the middle amide group. However, the resulting deprotonated **12**, after intramolecular ligand exchange, most likely can adopt a few, more flexible conformational isomers such as a helix, sheet, or intramolecularly stacked Pd^{II} complex (see Figures S66 and S67).

In summary, a new series of square-planar Pd^{II}-mediated foldamers with mononuclear and dinuclear helix or (double) hairpin structures were constructed by novel backbone-coordinative oxime peptides. Some of these metallo-foldamers allow significant structural interconversion between two distinct structures through intramolecular ligand exchange based on the acid–base balance. Metals with different Lewis acidity and coordination geometry would modulate alternative, dynamically folded structures such as homo- and hetero-multinuclear helices, hairpins, sheets, and their mixed ternary structures thus leading to metal-based sensing functions. Additionally, water-soluble oxime peptides without protecting groups at both terminals[16] would provide their metallo-foldamers with biological and bio-inspired functions such as catalytic activities[9f,g] and specific binding to biopolymers.[2-d,e,9c]

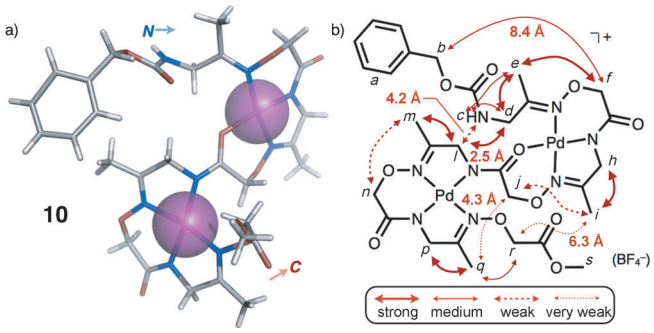


Figure 3. a) Crystal structure of the dinuclear double-hairpin complex **10**.[17] Disordered atoms and one BF_4^- anion are omitted for clarity. b) Observed NOE signals for **10** in NOESY measurement (500 MHz, [D_6]DMSO, 293 K) with distances calculated from the X-ray structure.

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[11] The single-crystal X-ray structural analysis of dipeptide **3** revealed the *E* form structure of the oxime bond and its 18-helix conformation through hydrogen bonding in the solid state (Figure S19).

[12] Although the carbonyl groups bind to Pd^{II} ions in the crystal structure of **9**, this carbonyl-bound structure appears not to be the main species in the CD_3CN solution because the chemical shift of this carbonyl group of **9** in the ^{13}C NMR spectrum was almost the same as that of **5**. Therefore, it is most likely that one solvent molecule binds to Pd^{II} instead in the solution as shown in Scheme 1. In contrast, the carbonyl-bound structure for **10** which is shown in the crystal structure appears to be maintained as a predominant conformation even in the $[D_6]$DMSO solution as judged from the results of NOESY analysis (Figure 3b) and ^{13}C NMR measurements (see Figure S52).

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[14] The origin of the low data quality of the diffraction data of **10** may come from the low quality of the crystal, which is a non-merohedral twin. In the structural refinement, some restraints

for thermal parameters were used for several atoms in the main residue. However, the NOESY measurement strongly supports this folded structure.

[15] a) H. L. Schenck, S. H. Gellman, *J. Am. Chem. Soc.* **1998**, *120*, 4869 – 4870; b) H. Rapaport, G. Möller, C. M. Knobler, T. R. Jensen, K. Kjaer, L. Leiserowitz, D. A. Tirrell, *J. Am. Chem. Soc.* **2002**, *124*, 9342 – 9343.

[16] We have preliminarily synthesized water-soluble oxime peptides and their metal complexes not only with Pd^{II} but also with other transition-metal ions such as Rh^{III}, Cu^{II}, and Ni^{II}. The details will be reported elsewhere.

[17] CCDC 891133 (**3**), 891134 (**5**), 891135 (**7**), 891136 (**9**), and 891137 (**10**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.