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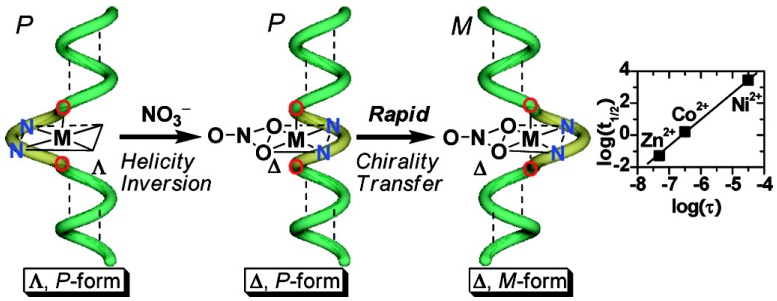

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Time-Programmed Peptide Helix Inversion of a Synthetic Metal Complex Triggered by an Achiral NO_3^- Anion

Hiroyuki Miyake,* Hiroshi Kamon, Ikuko Miyahara, Hideki Sugimoto, and Hiroshi Tsukube

Department of Chemistry, Graduate School of Science, Osaka City University, Sugimoto, Sumiyoshi-ku, Osaka 558-8585, Japan

Received September 10, 2007; E-mail: miyake@sci.osaka-cu.ac.jp

The inversion and transfer of chirality information of supramolecular helices are ubiquitous phenomena in nature. Biological DNA and proteins often alter their helix sense in response to particular external stimuli and switch biologically important events on.[1] For example, right-handed DNA converts to the left-handed Z form upon partial flipping over of base pairs. Polyproline controls its overall helical direction via *cis-trans* interconversion of its peptide bonds. Such biological processes are well controlled in characteristic time scales and relayed to the sophisticated events. Although several artificial molecules were reported to alter their helix directions[2] and molecular motions[3] upon metal cation and other environmental stimuli, we show here dynamic peptide helix inversion of a synthetic peptide−metal complex, in which the metal center acts as a time-tuning device (Figure 1). The metal complex used is composed of a chiral hexacoordinated metal center and two achiral pentapeptide chains (see L2 in Figure 1). We previously reported that the parent L1−$Co(ClO_4)_2$ complex dynamically converted a left-handed Λ *cis*-α structure to a right-handed Δ *cis*-α one upon addition of NO_3^- anion.[4] When the chirality-switchable metal complex is combined with pentapeptide chains, the helix inversion of the peptide chains of the L2 can be followed by helicity inversion of the octahedral metal center upon addition of NO_3^- anion stimulus (Figure 1). Since the inversion rate of complex helicity is tuned based on the substitution lability of the metal center, the present metallo−peptide complex offers time-tunable peptide helix inversion which has a time scale from milliseconds to hours.

The new peptide ligand L2, which contains racemic pentapeptide chains, was synthesized by condensation of *N*,*N*′-ethylenebis[*N*-methyl-(*S*)-alanine] and H-(Aib-ΔPhe)$_2$-Aib-OCH_3.[5a] As demonstrated by Inai and his co-workers,[5] the peptide ligand L2 itself exhibited a reversed *S*-shape CD signal in the styrene group absorption range (around 270 nm in CH_3CN, Figure S1). Its pentapeptide moieties had no chiral center, but the introduced chiral alanine (Ala) moiety predominantly induced the right-handed *P* 3_{10} peptide helix.[5a,6]

A CH_3CN solution of L2−$Co(ClO_4)_2$ exhibited large positive CD signals due to a peptide chromophores (∼270 nm) and Co(II) complex d−d transition (∼530 nm) (Figure 2, black line). As established for the L1−$Co(ClO_4)_2$ complex,[4b] the positive CD signal observed around 530 nm indicates that the helicity around the Co(II) center is in a left-handed Λ *cis*-α form. Although free L2 peptide itself exhibited a small CD signal at 270 nm, this CD signal was amplified (almost doubled) by Co(II) complexation. Thus, the *P* 3_{10} helical content of the two pentapeptide chains was significantly enhanced by the connected Co(II) complex moiety.

Figure 2 indicates that both CD signals of the L2−$Co(ClO_4)_2$ complex around 270 and 530 nm were dynamically inverted upon addition of NO_3^- anion. Titration experiments showed that 1 equiv of NO_3^- anion was required for both inversion processes involving the Co(II) center and the peptide helix. Because addition of NO_3^- anion rarely changed the CD signal of L2 itself, coordination of an NO_3^- anion to the Co(II) center caused inversion of the helicity of the metal center (from Λ form to Δ form; see Figure 1) and further induced the inversion of the peptide helical structure (from *P* form to *M* form). In addition to the Co(II) complex, Zn(II) and Ni(II) complexes with L2 showed similar inversion of their peptide helices upon addition of NO_3^- anion but offered different time scales for the helix inversion.

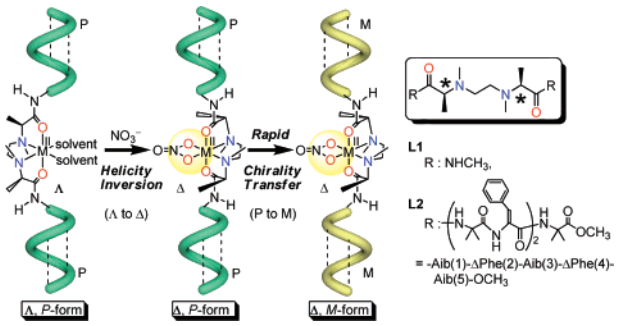

Figure 1. Helicity inversion around a metal center and sequential chirality transfer to peptide helices. Helical tubes indicate the pentapeptide moiety (-Aib-ΔPhe-Aib-ΔPhe-Aib-OCH_3) of ligand L2. Green and gold colored tubes indicate right-handed and left-handed 3_{10} helical structures (*P* form and *M* form), respectively.

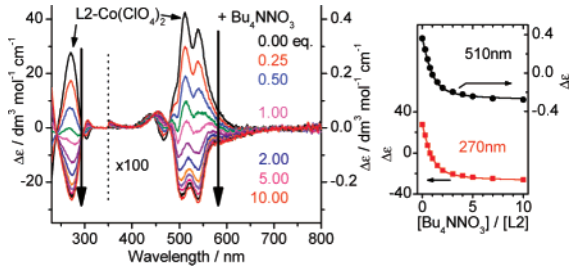

Figure 2. CD spectral changes of the L2−$Co(ClO_4)_2$ complex upon addition of Bu_4NNO_3 in CH_3CN at room temperature, and titration profiles of the CD amplitudes at 270 and 510 nm. [L2] = [$Co(ClO_4)_2 \cdot 6H_2O$] = 1.5×10^{-3} mol dm^{-3}; 0.1 mm cuvette for <350 nm, 10 mm cuvette for >350 nm; Δε values were calculated per ligand concentration.

The X-ray crystal structure of the complex [Zn(L2)$(H_2O)_2$]$(ClO_4)_2$ showed that the Zn(II) cation was coordinated by two amide oxygen, two amine nitrogen, and two water oxygen atoms to give the Λ form (Figure 3a). The attached pentapeptide chains formed *P*-helical structures with two intramolecular hydrogen bonds [C═$O_{Aib(1)}$···$HN_{\Delta Phe(4)}$ and C═$O_{\Delta Phe(2)}$···$HN_{Aib(5)}$], although one peptide, A-chain, included typical torsion angles for the 3_{10} helical structure [147.8° for ψ in Aib(1), −49.3 and −32.8° for φ and ψ in ΔPhe-(2) moieties], and the B-chain exhibited a somewhat different structure [−50.8° for ψ in Aib(1), 44.0 and −126.4° for φ and ψ in ΔPhe(2) moieties; Table S1]. In contrast, the X-ray crystal structure of the complex [Zn(L2)(NO_3)](NO_3) showed *M* 3_{10} peptide

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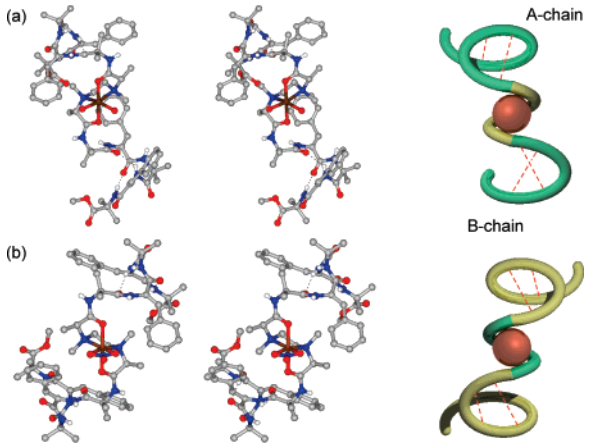

Figure 3. Stereoviews and schematic illustrations of crystal structures of $[Zn(L2)(H_2O)_2](ClO_4)_2 \cdot (CH_3CN)_{0.5} \cdot (H_2O)_{10}$ (a) and $[Zn(L2)(NO_3)](NO_3) \cdot (CH_3CN) \cdot (CHCl_3)_5$ (b). The minor component in $[Zn(L2)(H_2O)_2]^{2+}$, most hydrogen atoms and solvent molecules are omitted for simplification.

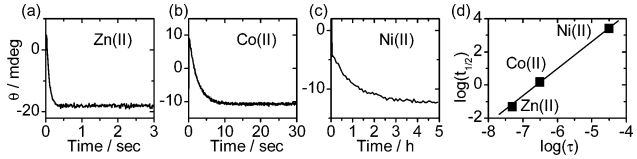

Figure 4. Relaxation traces (270 nm) of the L2−$M(ClO_4)_2$ complex by mixing 50 equiv of Bu_4NNO_3 in CH_3CN at room temperature measured by stopped-flow CD apparatus [M = Zn (a), Co (b), Ni (c)]; [L2] = 0.3×10^{-3} mol dm^{-3}, $[M(ClO_4)_2 \cdot 6H_2O] = 0.6 \times 10^{-3}$ mol dm^{-3}, $[Bu_4NNO_3] = 15 \times 10^{-3}$ mol dm^{-3}; 0.5 mm cuvette. Relationship between half-lifetime ($t_{1/2}$) of helicity inversion and water exchange lifetime (τ/s) on each metal cation (d).

helical structures and a Δ form Zn(II) center with one bidentate NO_3^- anion (Figure 3b). In these complexes, the pentapeptide chains were stabilized by a hydrophobic interaction and weak CH−π interactions between the NCH_3 and ΔPhe(2) moieties.[7] The ^{1}H NMR spectra of the L2−$Zn(ClO_4)_2$ and L2−$Zn(NO_3)_2$ complexes exhibited C_2-symmetric patterns, indicating that intramolecular hydrogen bonds formed by two types of NH groups (Figures S6 and S8). Marked NOESY cross-peaks between N_iH and $N_{i+1}H$ signals in the segment between ΔPhe(4) and Aib(5) (Figures S7 and S9) support the idea that both complexes have similar 3_{10} peptide helical structures observed in the crystal state.

The time course of the peptide helix inversion was analyzed using stopped-flow CD measurements (Figure 4a−c). When 50 equiv of NO_3^- anion was added to a CH_3CN solution of the L2−$Co(ClO_4)_2$ complex, two positive CD signals at 270 and 510 nm were rapidly inverted to negative signals in same time scale. The half-lifetime values ($t_{1/2}$) were estimated by exponential decay curve fitting as 1.5 s for peptide helix inversion and 1.8 s for Co(II) complex helicity inversion. Thus, inversion of the peptide helices immediately followed the inversion of Co(II) complex helicity, as illustrated in Figure 1. The L2−$Ni(ClO_4)_2$ complex exhibited positive CD signals at ∼270 and ∼1000 nm, both of which were slowly inverted upon addition of 50 equiv of NO_3^- anion (half-lifetime of 44 min for inversion of both peptide and complex helicities), while the L2−$Zn(ClO_4)_2$ complex showed a much shorter half-lifetime of 49 ms for peptide inversion. The estimated half-lifetime (log $t_{1/2}$) of these metallo−peptide complexes determined at 270 nm show a linear correlation with the water exchange lifetime of aqueous metal cations (Figure 4d).[8,9] Thus, the time course of the peptide helix inversion was well programmed by the nature of the metal center. Since L1−$M(ClO_4)_2$ complexes have a much longer helicity inversion lifetimes than the corresponding L2 complexes ($t_{1/2}$ for M = Co: 25 s, $t_{1/2}$ for M = Ni: 4.7 h), the two helical peptide chains further communicated to promote helix inversion of the other peptide chain in the L2−metal complex systems.

As observed with protein folding,[10a] the rotation of a F1-ATPase motor,[10b] and other biological machinery systems, the present metallo−peptide complex has the time-controlled helicity induction around a metal center, anion-triggered helicity inversion, and helicity transfer to peptide units. Such molecular-based time programming systems provide new insight on how natural biopolymers produce highly organized supramolecular structures and dynamically sophisticated functions.

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Supporting Information Available: Synthetic procedures of L2, and crystal structures and NOESY spectra of Zn(II) complexes. CD and ESI-MS spectra of metal complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) The ^{1}H NMR spectrum of L2 in CD_3CN exhibited a C_2-symmetric pattern which was largely changed by addition of DMSO-d_6 or increasing temperature (Figures S2 and S3). Since NOESY cross-peaks were observed between the N_iH and $N_{i+1}H$ signals in the segment from Aib(3) to Aib(5) (Figure S4), three types of NH groups were involved in intramolecular hydrogen bonding to build up the 3_{10} peptide helices.

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(8) Helicity inversion of the L2−$Cu(ClO_4)_2$ complex occurred too fast to be detected by our measurement ($t_{1/2}$ = <10 ms).

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