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Chirality Organization of Ferrocenes Bearing Dipeptide Chains of Heterochiral Sequence

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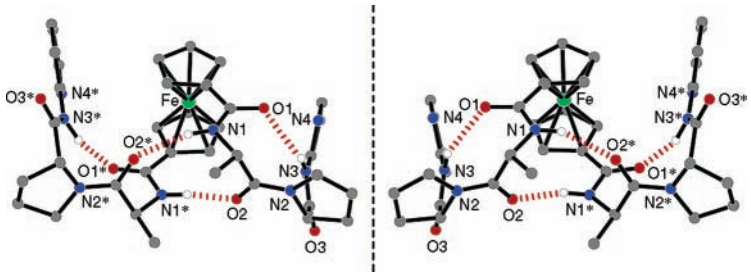
ABSTRACT



The symmetrical introduction of two dipeptide chains of heterochiral sequence (-L-Ala-D-Pro-NHPy) into the ferrocene scaffold as a central reverse-turn unit was demonstrated to induce both antiparallel β-sheet-like and type II β-turn-like structures simultaneously, affording the chirality-organized structure. The ferrocene bearing only one dipeptide chain (-L-Ala-D-Pro-NHPy) exhibited a left-handed helically ordered molecular assembly through a network of intermolecular hydrogen bonds instead of intramolecular hydrogen bonds.

Recently, the field of bioorganometallic chemistry has drawn great attention and undergone rapid development. Considerable effort has been devoted to the design of bioconjugates composed of organometallic compounds and biomolecules such as amino acids and peptides.[1] Ferrocenes have been recognized to be a reliable scaffold for hydrogen bonding to afford the ferrocene-peptide bioconjugates as an artificially regulated system.[2−4] Conformational enantiomerization of the 1,1′-disubstituted ferrocenes has been achieved by the intramolecular interchain hydrogen bonding of the peptide chains, permitting chirality organization.[2h,k,l,3a−e,g−h,4] Chirality choices of amino acids is considered to be a key factor to construct chirality-organized bio-inspired systems with highly ordered structures. Our present design is based on symmetrical introduction of two dipeptide chains of heterochiral sequence (-L-Ala-D-Pro-NHPy) into the ferrocene scaffold as a central reverse-turn unit (Figure 1). The advantage in

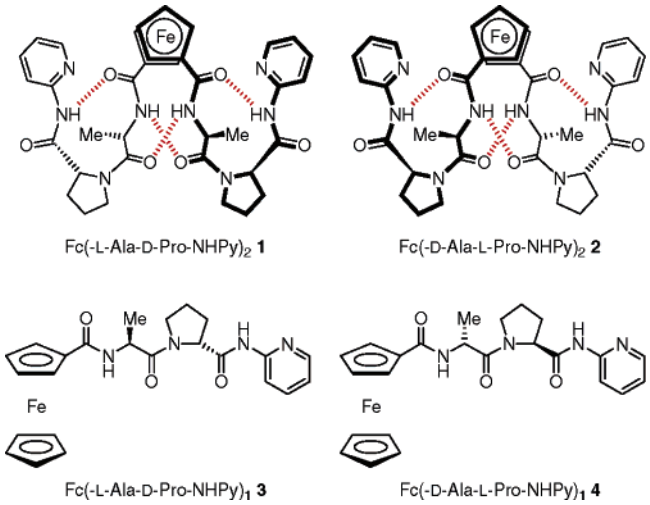


Figure 1. Ferrocenes bearing the dipeptide chains (-Ala-Pro-NHPy).

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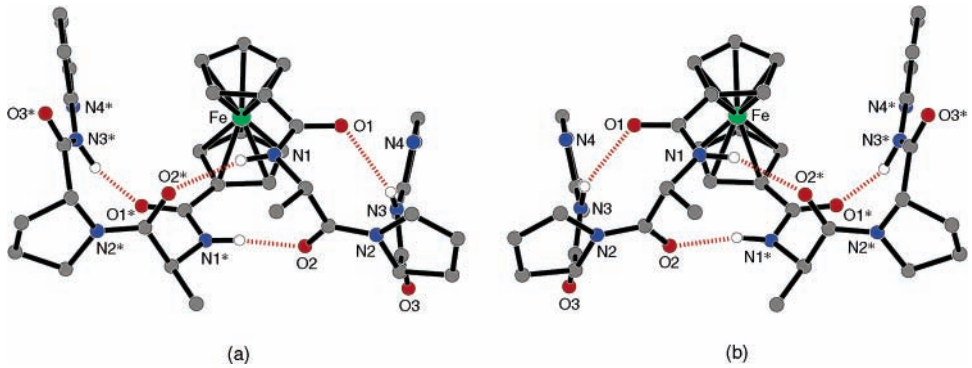

Figure 2. Molecular structure of (a) **1** and (b) **2**.

the use of the -alanyl-proline heterochiral sequence as a dipeptide chain depends on a hydrogen bonding alanyl moiety and a sterically constrained proline as a well-known turn inducer in proteins. Furthermore, the dipeptide chain of heterochiral sequence such as -L-Pro-D-Ala has been employed to enforce a reverse-turn conformation.[5] We herein report the simultaneous formation of antiparallel β-sheet-like and type II β-turn-like structures by using only the dipeptide chains together with the ferrocene scaffold.

The ferrocenes **1** and **2** bearing the dipeptide chains (-L-Ala-D-Pro-NHPy or -D-Ala-L-Pro-NHPy, respectively) were synthesized from 1,1′-bis(chlorocarbonyl)ferrocene and the corresponding dipeptide derivative and were fully characterized by spectral data and elemental analyses. X-ray crystallographic analyses clarified the chirality-organized structure of the ferrocene-peptide bioconjugates **1** and **2**.[6] The single-crystal X-ray structure determination of the ferrocene **1** revealed intramolecular antiparallel β-sheet-like hydrogen bonding between NH (Ala) and CO (Ala of another chain) of each dipeptide chain (N(1)···O(2*), 3.069 Å; N(1*)···O(2), 2.973 Å) to induce the chirality-organized structure (Figure 2a). The *P*-helical arrangement of the ferrocene unit appears to be controlled by the configuration of the alanyl α-carbon atom because a similar type of the chiral molecular conformation is observed in the ferrocene bearing the dipeptide chains (-L-Ala-L-Pro-NHPy).[3e] The helical chirality of the ferrocene unit has also been suggested to be determined by the configuration of the linked amino acid.[2k,l] Conformational enantiomerization through chirality organization was achieved by restriction of the torsional twist based on the intramolecular hydrogen bonds and chiral centers in the peptide chains. Another remarkable feature of the structure is that the NH adjacent to the pyridyl group participates in the intramolecular hydrogen bonding with CO adjacent to the ferrocene unit of the same peptide chain (N(3)···O(1), 3.223 Å; N(3*)···O(1*), 3.153 Å) to nucleate a β-turn-like structure in each dipeptide chain. The torsion angles ϕ_2 ($\phi_2 = -64.5°$ and $\phi_2* = -63.8°$), ψ_2 ($\psi_2 = 134.0°$ and $\psi_2* = 136.0°$), ϕ_3 ($\phi_3 = 68.7°$ and $\phi_3* = 75.1°$), and ψ_3 ($\psi_3 = 19.2°$ and $\psi_3* = 9°$) of **1** indicate a type II β-turn-like structure despite $\phi_2 = -60°$, $\psi_2 = 120°$, $\phi_3 = 80°$, and $\psi_3 = 0°$ for an ideal type II β-turn. The combination of the ferrocene scaffold as a central reverse-turn unit with the

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(6) Crystal data for **1**: $C_{38}H_{42}N_8O_6Fe{\cdot}5CH_2Cl_2$, $M = 1187.31$, orthorhombic, space group $P2_12_12_1$ (No. 19), $a = 10.4525(2)$ Å, $b = 21.2119(4)$ Å, $c = 24.7104(4)$ Å, $V = 5478.7(2)$ Å^3, $Z = 4$, $T = 23.0$ °C, $D_{calc} = 1.439$ g cm^{-3}, μ(Mo Kα) = 8.13 cm^{-1}, Mo Kα radiation ($\lambda = 0.71069$ Å), $R1 = 0.098$, $wR2 = 0.268$. Crystal data for **2**: $C_{38}H_{42}N_8O_6Fe{\cdot}5CH_2Cl_2$, $M = 1187.31$, orthorhombic, space group $P2_12_12_1$ (No. 19), $a = 21.0852(5)$ Å, $b = 24.6133(7)$ Å, $c = 10.4010(2)$ Å, $V = 5397.9(5)$ Å^3, $Z = 4$, $T = 4.0$ °C, $D_{calc} = 1.461$ g cm^{-3}, μ(Mo Kα) = 8.25 cm^{-1}, Mo Kα radiation ($\lambda = 0.71069$ Å), $R1 = 0.096$, $wR2 = 0.264$. Crystal data for **3**: $C_{24}H_{26}N_4O_3Fe{\cdot}0.5H_2O$, $M = 483.35$, monoclinic, space group $P2_1$ (No. 4), $a = 10.9029(2)$ Å, $b = 19.5118(3)$ Å, $c = 12.2690(1)$ Å, $\beta = 94.684(1)°$, $V = 2601.33(6)$ Å^3, $Z = 4$, $T = 4.0$ °C, $D_{calc} = 1.234$ g cm^{-3}, μ(Mo Kα) = 6.11 cm^{-1}, Mo Kα radiation ($\lambda = 0.71069$ Å), $R1 = 0.087$, $wR2 = 0.228$. Crystal data for **4**: $C_{24}H_{26}N_4O_3Fe{\cdot}0.5H_2O$, $M = 483.35$, monoclinic, space group $P2_1$ (No. 4), $a = 10.9323(2)$ Å, $b = 19.5778(4)$ Å, $c = 12.2868(3)$ Å, $\beta = 94.683(2)°$, $V = 2620.97(9)$ Å^3, $Z = 4$, $T = 4.0$ °C, $D_{calc} = 1.225$ g cm^{-3}, μ(Mo Kα) = 6.06 cm^{-1}, Mo Kα radiation ($\lambda = 0.71069$ Å), $R1 = 0.082$, $wR2 = 0.220$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-271990 for **1**, CCDC-271991 for **2**, CCDC-271992 for **3**, and CCDC-271993 for **4**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

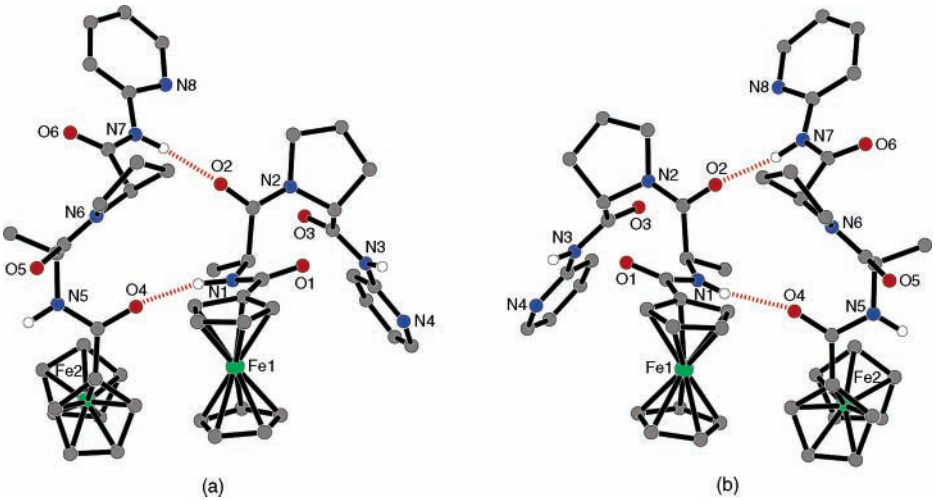

Figure 3. Molecular structure of (a) **3** and (b) **4**. Two independent molecules exist in the asymmetric unit.

dipeptide chains (-L-Ala-D-Pro-NHPy) permits the artificially regulated antiparallel β-sheet-like and type II β-turn-like structures simultaneously.

The molecular structure of **2** composed of the dipeptide chains (-D-Ala-L-Pro-NHPy), in which the *M* helical arrangement of the ferrocene unit is formed, is in a good mirror image relationship with **1**, indicating that **1** and **2** are the conformational enantiomers (Figure 2). The opposite values of the torsion angles of **2** (ϕ_2 ($\phi_2 = 65.0°$ and $\phi_2* = 64.0°$), ψ_2 ($\psi_2 = -134.7°$ and $\psi_2* = -136.3°$), ϕ_3 ($\phi_3 = -67.5°$ and $\phi_3* = -74.7°$), and ψ_3 ($\psi_3 = -18.7°$ and $\psi_3* = -10.5°$)) were observed as compared with those of **1**.

To evaluate the effect of intramolecular antiparallel β-sheet-like hydrogen bonding, the ferrocenes **3** and **4** bearing only one dipeptide chain (-L-Ala-D-Pro-NHPy or -D-Ala-L-Pro-NHPy, respectively) were synthesized similarly as mentioned in **1** and **2**. The ferrocene **3**[6] exhibited an intermolecular hydrogen bonding network instead of the formation of intramolecular hydrogen bonds, wherein two independent molecules exist in the asymmetric unit and are connected alternately through intermolecular hydrogen bonds between the NH (Ala) and CO adjacent to the ferrocene unit (another molecule) (N(1)···O(4), 2.828 Å; N(5a)···O(1), 2.880 Å; N(5)···O(1b), 2.880 Å) and between the NH adjacent to the pyridyl group (another molecule) and CO (Ala) (N(7)···O(2), 2.79 Å; N(3)···O(5a), 2.84 Å; N(3b)···O(5), 2.84 Å) (Figure 3a). Through a hydrogen bonding network, the ferrocene **3** is packed in a left-handed helically ordered arrangement with 19.44 Å pitch height for one turn. The distance between the closest ferrocene units is 6.95 Å (Fe−Fe) (Figure 4a). Noteworthy is that an opposite helically ordered molecular assembly, a right-handed helically ordered arrangement, was observed in the crystal packing of the ferrocene **4** (Figure 4b).[6] The propensity to form the chiral helicity appears to be controlled by the chirality of the dipeptide chains. These results indicate that the intramolecular antiparallel β-sheet-like hydrogen bonds of **1** and **2** play an important role in the creation of the type II β-turn-like structure.

A chirality-organized structure in solution was investigated by ^{1}H NMR, FT-IR, and CD analyses. In the ^{1}H NMR spectra of **1** in $CDCl_3$ (1.0×10^{-2} M), only one kind of the Ala N−H resonance and the NH adjacent to the pyridyl

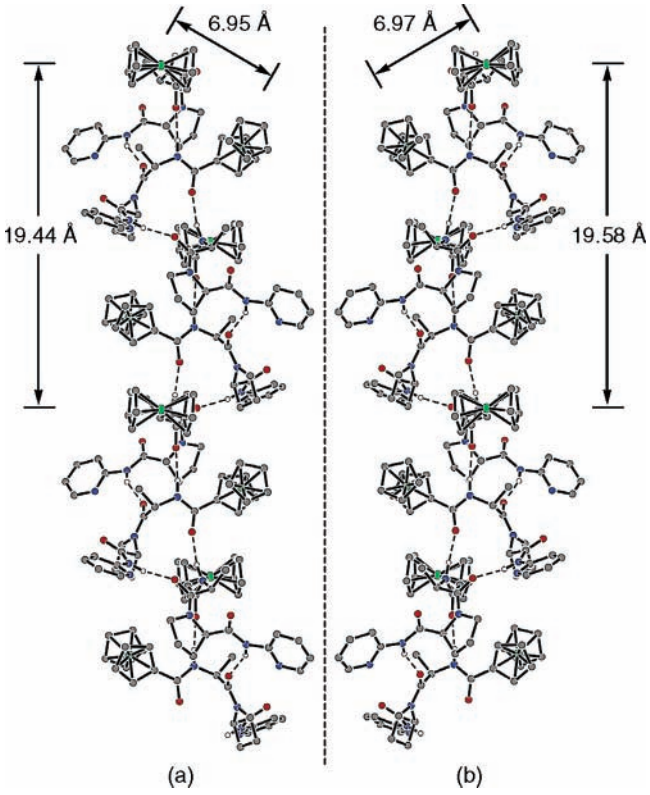

Figure 4. A portion of a layer containing the helically ordered molecular assembly through a network of intermolecular hydrogen bonds in the crystal packing of (a) **3** and (b) **4**.

group were detected at a lower field (8.61 and 9.49 ppm) than those of **3** (2.0×10^{-2} M, 6.54 and 9.34 ppm), respectively. The N−H resonances of **1** were not perturbed by the addition of aliquots of DMSO-d_6 to $CDCl_3$ ($CDCl_3$/DMSO-d_6 (9:1), 8.64 and 9.53 ppm), although a slightly downfield shift was observed with **3** ($CDCl_3$/DMSO-d_6 (9:1), 7.03 and 9.75 ppm). These results indicate that the ferrocene **1** forms symmetrical intramolecular hydrogen bonds even in solution. The FT-IR spectrum of **1** in CH_2Cl_2 (1.0×10^{-2} M) showed only one N−H stretch at 3309 cm^{-1}, which also supports the hydrogen bonding in **1**. The ferrocene **1** exhibited an induced circular dichroism (ICD) at the absorbance region of the ferrocene moiety, which indicates *P*-helical chirality of the ferrocene moiety, although such an ICD was not detected in the case of **3** (Figure 5).

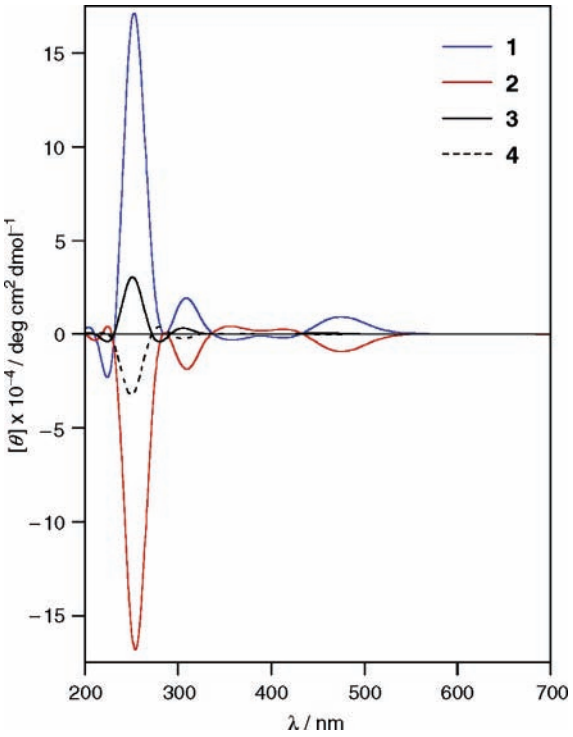

Figure 5. CD spectra of **1**−**4** in dichloromethane (**1** and **2**, 1.0×10^{-4} M; **3** and **4**, 2.0×10^{-4} M).

Furthermore, the mirror-imaged CD signals were obtained in the case of **2**. The chirality-organized structure via intramolecular hydrogen bondings is likely to be present in solution. The protons of the ferrocene moiety of **1** (4.72−4.70, 4.54−4.53, 3.98−3.96, and 3.10−3.09 ppm) were observed in a higher field as compared with **3** (4.76−4.73, 4.67−4.66, 4.33−4.31, and 4.13 ppm) in the ^{1}H NMR probably due to the ring-current effect of the pyridine π-ring, suggesting a type II β-turn-like structure as observed in the crystal structure. Proton magnetic resonance nuclear Overhauser effect (NOE) of **1** in $CDCl_3$ at 25 °C also provided diagnostic evidence for this structure. Irradiation of the Cp proton at the β position enhanced the pyridyl protons (Figure S1, Supporting Information). Irradiation of the Cp proton at the α position also enhanced the Ala NH, NH adjacent to the pyridyl group, and the pyridyl proton at the 3-position (Figure S2, Supporting Information). A type II β-turn-like structure was found to be achieved in solution.

In conclusion, ferrocene-peptide bioconjugates have been constructed to form chirality-organized structures in both solid and solution states. The combination of the ferrocene scaffold as a central reverse-turn unit with the -L-alanyl-D-proline heterochiral sequence as a dipeptide unit was found to induce the antiparallel β-sheet-like and type II β-turn-like structures simultaneously through the intramolecular hydrogen bonds. The ferrocene bearing only one dipeptide chain (-L-Ala-D-Pro-NHPy) exhibited the helically ordered molecular assembly through a network of intermolecular hydrogen bonds. Hydrogen bonds play a crucial role in regulating the three-dimensional structure and function of biological systems, and the highly ordered bio-related molecular assemblies permit the unique functions, as observed in enzymes, receptors, etc. The design and conformational control of foldamers based on virtue of the hydrogen bond's directionality and specificity in synthetic molecules have been also investigated.[7] The present architectural control of dimensional structures utilizing minimum-sized peptide chains possessing chiral centers and hydrogen bonding sites is considered to be a useful approach to artificial highly ordered systems. Studies on the application of the chirality organized ferrocenes for molecular recognition and molecular dynamics are now in progress.

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Supporting Information Available: Experimental details for the syntheses and characterization of **1**−**4**, difference NOE of **1**, and CIF files for **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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