Structural Characterization of Chirality-Organized Ferrocene-Dipeptide Conjugates that Contain Pyridine *N*-Oxide Moieties

Toshiyuki Moriuchi, Hao Wu, Yoshiki Tayano, Toshikazu Hirao

Citation	Asian Journal of Organic Chemistry, 6(9): 1250-1256
Issue Date	2017-09
Type	Journal Article
Textversion	Author
Rights	This is the peer reviewed version of the following article: MORIUCHI T., WU H., TAYANO Y., & HIRAO T. (2017). Structural Characterization of Chirality-Organized Ferrocene-Dipeptide Conjugates that Contain Pyridine N-Oxide Moieties. Asian Journal of Organic Chemistry. 6, 1250-1256. , which has been published in final form at https://doi.org/10.1002/ajoc.201700145 . This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.
DOI	10.1002/ajoc.201700145

MORIUCHI T., WU H., TAYANO Y., & HIRAO T. (2017). Structural Characterization of Chirality-Organized Ferrocene-Dipeptide Conjugates that Contain Pyridine N-Oxide Moieties. *Asian Journal of Organic Chemistry.* 6, 1250-1256. https://doi.org/10.1002/ajoc.201700145

Structural Characterization of Chirality-Organized Ferrocene-Dipeptide Conjugates Having Pyridine *N*-Oxide Moieties

Toshiyuki Moriuchi,*[a] Hao Wu,[a] Yoshiki Tayano,[a] and Toshikazu Hirao*[a]

Abstract: Ferrocene-dipeptide conjugates, Fc(-L-Ala-L-Pro-PyO)$_2$ (**2**) and Fc(-L-Ala-L-Pro-PyO)$_1$ (**3**), were synthesized by the introduction of the L-Ala-L-Pro dipeptide having the C-terminal pyridine *N*-oxide moiety into the ferrocene organometallic scaffold. The single-crystal X-ray structure determination of the ferrocene-dipeptide conjugate **2** composed of two dipeptide chains confirmed the formation of intramolecular antiparallel β-sheet-like hydrogen bonds between CO (Ala) and NH (Ala of another chain) to induce the chirality-organized structure, wherein the ferrocenoyl moiety adopts a *P*-helical chirality. In the crystal packing of **2**, the right-handed molecular arrangement of peptide chains through hydrogen bonding was observed. On the contrary, the ferrocene-dipeptide conjugate **3** composed of only one dipeptide chain showed the self-assembled tetramer structure through the formation of intermolecular hydrogen bonds and π-π interactions between pyridine *N*-oxide moieties.

Introduction

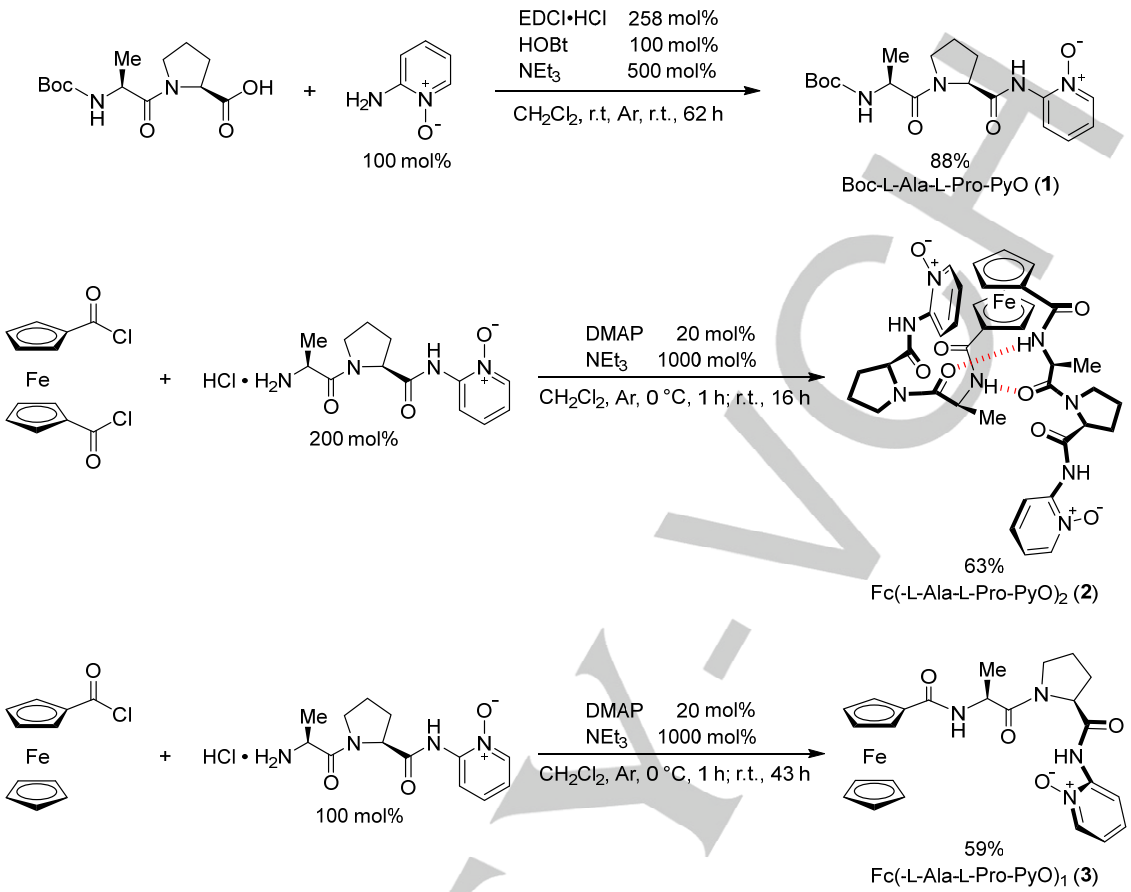
Structurally defined molecular arrangement is of importance for the design of functional materials,[1] wherein the chemical and/or physical properties depend on the molecular arrangement of component molecules. The directionality and specificity of hydrogen bond have been demonstrated to play a crucial role in the construction of supramolecular assemblies.[2] Complementary intra- and intermolecular hydrogen bonds between amino acids are formed in secondary structures of proteins, resulting in the highly-organized structures to fulfill the unique functions. The utilization of chirality organization properties of amino acids based on chiral centers and hydrogen bonding sites is considered to be a convenient strategy to design a chirality-organized molecular self-assembly system. Generally, molecular scaffolds are employed to control the arrangement of amino acids and regulate the direction of hydrogen bonding sites.[3] Ferrocene,[4] which is a stable organometallic compound with two rotatory coplanar cyclopentadienyl rings, is regarded as a reliable central reverse-turn unit because of that the inter-ring spacing of ferrocene is appropriate for hydrogen bonding of the introduced peptide chains. From the view point of bioorganometallic chemistry,[5] considerable efforts have been devoted to investigate the hydrogen bonding abilities of the introduced amino acid moieties in ferrocene-amino acid conjugates to induce secondary structures of proteins.[6] We have also demonstrated the design of a variety of chirality-organized ferrocene-dipeptide conjugates by control of the sequence and chirality of amino acids.[7] On the other hand, pyridine *N*-oxide derivatives have been used as asymmetric catalysts[8] and building units in supramolecular chemistry based on the coordination and hydrogen bonding abilities.[9] The introduction of pyridine *N*-oxide derivatives into peptides is envisioned to afford additional functional properties. In this context, we embarked upon the conjugation of the L-Ala-L-Pro dipeptide having the C-terminal pyridine *N*-oxide moiety and the ferrocene organometallic scaffold as a central reverse-turn unit to induce the chirality-organized assemblies.

[a] Dr. T. Moriuchi, H. Wu, Y. Tayano, Prof. Dr. T. Hirao
Department of Applied Chemistry, Graduate School of Engineering
Osaka University
Yamada-oka, Suita, 565-0871
E-mail: moriuchi@chem.eng.osaka-u.ac.jp
hirao@chem.eng.osaka-u.ac.jp
Supporting information for this article is available on the WWW under http://dx.doi.org/

Results and Discussion

The L-Ala-L-Pro dipeptide was focused on as a dipeptide chain because of a hydrogen bonding moiety of alanine and a sterically constrained moiety of proline as a well-known turn inducer in proteins. The L-Ala-L-Pro dipeptide having the C-terminal pyridine *N*-oxide moiety Boc-L-Ala-L-Pro-PyO (**1**) was obtained by the reaction of Boc-L-Ala-L-Pro-OH with 2-aminopyridine *N*-oxide in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI•HCl), 1-hydroxybenzotriazole (HOBt), and triethyamine in dichloromethane as shown in Scheme 1. The reaction of 1,1'-bis(chlorocarbonyl)ferrocene with H-L-Ala-L-Pro-PyO hydrochloride, which was obtained by the *N*-Boc deprotection of **1**, in the presence of dimethylaminopyridine and triethylamine in dichloromethane was found to afford the ferrocene-dipeptide conjugate Fc(-L-Ala-L-Pro-PyO)$_2$ (**2**) The ferrocene-dipeptide conjugate Fc(-L-Ala-L-Pro-PyO)$_1$ (**3**) was synthesized by the reaction of (chlorocarbonyl)ferrocene with H-L-Ala-L-Pro-PyO hydrochloride.

X-ray crystallographic analyses were performed in order to clarify the chirality-organized structures and the self-assembly properties of the dipeptide derivative and the ferrocene-dipeptide conjugates (Table 1). Single crystals with diffraction-quality of the dipeptide derivative Boc-L-Ala-L-Pro-PyO (**1**) were grown by diffusion of hexane into dichloromethane solution of **1**. The molecular structure of **1**, in which the formation of intramolecular hydrogen bonds was not observed, is depicted in Figure 1a. In the crystal packing, the dipeptide derivative **1** showed intermolecular hydrogen bonding network to induce the head-to-tail molecular arrangement, wherein each molecule is connected through intermolecular hydrogen bonds between NH (Ala) and PyO (pyridine *N*-oxide of another molecule) (N(1)···O(3)$^{[c]}$, 2.848(4) Å) and between the NH adjacent to the pyridine *N*-oxide



Scheme 1. Synthesis of the dipeptide derivative Boc-L-Ala-L-Pro-PyO (**1**), the ferrocene-dipeptide conjugate Fc(-L-Ala-L-Pro-PyO)$_2$ (**2**), and the ferrocene-dipeptide conjugate Fc(-L-Ala-L-Pro-PyO)$_1$ (**3**).

Table 1. Crystallographic date for **1**, **2**, **and 3**

	1	**2**	**3**
Empirical formula	$C_{18}H_{26}N_4O_5$	$C_{38}H_{42}N_8O_8Fe_1 \cdot 0.5CH_2Cl_2$	$C_{24}H_{26}N_4O_4Fe_1$
Formula weight	378.43	837.11	490.34
Crystal system	orthorhombic	triclinic	hexagonal
Space group	$P2_12_12_1$ (No. 19)	$P1$ (No. 1)	$P6_2$ (No. 171)
a (Å)	6.37447(12)	10.7661(5)	28.900(7)
b (Å)	14.6943(3)	12.1152(7)	13.246(4)
c (Å)	20.4766(4)	14.7427(6)	
α (°)		82.5442(17)	
β (°)		86.5434(11)	
γ (°)		89.5831(18)	
V (Å^3)	1918.01(6)	1903.22(16)	9581(4)
Z	4	2	12
D_{calcd} (g cm^{-3})	1.310	1.461	1.020
μ (Cu Kα) (cm^{-1})	8.041		
μ (Mo Kα) (cm^{-1})		5.306	4.994
T (°C)	-150.0	-170.0	4.0
λ (Cu Kα) (Å)	1.54187		
λ (Mo Kα) (Å)		0.71075	0.71075
$R1$ [a]	0.0473	0.0488	0.0793
$wR2$ [b]	0.1178	0.1379	0.2500

[a] $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$.

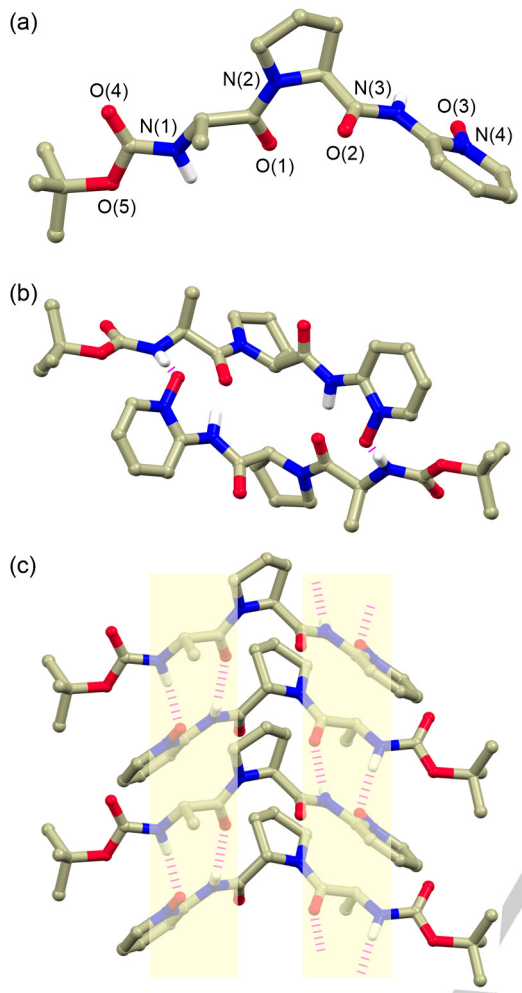


Figure 1. (a) Molecular structure of **1**, (b) top, and (c) side view of the intermolecular hydrogen bonding network in the crystal packing of **1**. The pale yellow colored sheets show the hydrogen bonding network. (hydrogen atoms, which are not involved in hydrogen bonding, are omitted for clarity).

Table 2. Hydrogen Bonds for **1**, **2**, **and 3**

Compound	type [a]	Donor	Acceptor	D • • • A (Å)	D-H • • • A (°)
1	inter	N(1)	O(3) [c]	2.848(4)	170(3)
	inter	N(3)	O(1) [d]	3.170(4)	152(3)
2 [b]	intra	N(1)	O(22)	2.873(6)	165(6)
	intra	N(21)	O(2)	2.956(6)	161(6)
	inter	N(23)	O(71) [e]	2.788(6)	144(4)
	intra	N(51)	O(72)	3.028(6)	159(5)
	inter	N(53)	O(1) [f]	2.876(6)	139(5)
	intra	N(71)	O(52)	2.899(6)	158(5)
3 [b]	inter	N(1)	O(51)	2.874(19)	163(6)
	intra	N(3)	N(2)	2.671(17)	113(7)
	intra	N(53)	N(52)	2.785(17)	118(6)
	inter	N(51)	O(54) [g]	3.139(17)	165(6)

[a] inter: intermolecular, intra: intramolecular. [b] Two independent molecules exist in the asymmetric unit. [c] X+1/2, -Y+1/2, -Z+2. [d] X+1/2-1, -Y+1/2, -Z+2. [e] X-1, Y-1, Z. [f] X+1, Y, Z. [g] –X+1, -Y+1, Z

group and CO (Ala of another molecule) (N(3)···O(1)[d], 3.170(4) Å) to form 10-membered intermolecularly hydrogen-bonded ring as shown in Figures 1b and 1c. The D···A distances and D-H···A angles of hydrogen bonds are shown in Table 2.

Diffusion of hexane into dichloromethane solution of the ferrocene-dipeptide conjugate Fc(-L-Ala-L-Pro-PyO)$_2$ (**2**) afforded single crystals with diffraction-quality of **2**. The ferrocene-dipeptide conjugate **2** crystallized in the space group *P*1 with two independent molecules in the asymmetric unit (Table 1). The molecular structure of **2** composed of two dipeptide chains revealed the formation of intramolecular antiparallel β-sheet-like hydrogen bonds between NH (Ala) and CO (Ala of another chain) of each dipeptide chain (N(1)···O(22), 2.873(6) Å; N(21)···O(2), 2.956(6) Å; N(51)···O(72), 3.028(6) Å; N(71)···O(52), 2.899(6) Å) to induce the chirality-organized structure, resulting in the *P*-helical chirality of the ferrocenoyl moiety as depicted in Figure 2a. The introduction of dipeptide chains into the ferrocene organometallic scaffold was found to induce conformational enantiomerization by restriction of the torsional twist about the Cp(centroid)-Fe-Cp(centroid) axis based on intramolecular hydrogen bondings as observed in the previous reported ferrocene-dipeptide conjugates.[7] Two independent molecules are connected alternately through π-π interactions between the pyridine *N*-oxide moieties (Figure 2b). Introduced pyridine *N*-oxide moieties were found to play an important role in the molecular assemblies through π-π interactions instead of the formation of hydrogen bonds. Furthermore, intermolecular hydrogen bonds between the NH adjacent to the pyridine *N*-oxide group and CO adjacent to the ferrocene unit (another molecule) (N(23)···O(71)[e], 2.788(6) Å; N(53)···O(1)[f], 2.876(6) Å) were formed to connect two independent molecules alternately to form hydrogen-bonded assembly as shown in Figure 2c. In the hydrogen-bonded assembly, the right-handed molecular arrangement of peptide chains through hydrogen bonding was observed (Figure 2d). The self-assembled structure of **2** through the formation of hydrogen bonds and π-π interactions is displayed in Figure 2e, wherein each hydrogen-bonded assembly is fastened by π-π interactions between the pyridine *N*-oxide moieties.

The ferrocene-dipeptide conjugate Fc(-L-Ala-L-Pro-PyO)$_1$ (**3**) was structurally elucidated by single-crystal X-ray structure determination. Single crystals with diffraction-quality of **3** were grown by diffusion of hexane into dichloromethane solution of **3**. The ferrocene-dipeptide conjugate **3** crystallized in the space group *P*6$_2$ with two independent molecules in the asymmetric unit (Table 1). In contrast to the molecular structure of the *N*-Boc protected dipeptide derivative **1**, the molecular structure of the ferrocene-dipeptide conjugate **3** composed of only one dipeptide chain confirmed the formation of intramolecular hydrogen bond of N-H•••N pattern between the NH adjacent to the pyridine *N*-oxide group and the nitrogen of Pro moiety (N(3)···N(2), 2.671(17) Å; N(53)···N(52), 2.785(17) Å) as shown in Figure 3a (Table 2). Two independent molecules are connected through intermolecular hydrogen bonding between NH (Ala) and CO adjacent to the ferrocene unit (another molecule) (N(1)···O(51), 2.874(19) Å) (Figure 3b). One molecule of two independent molecules was found to form the homodimer through the formation of the

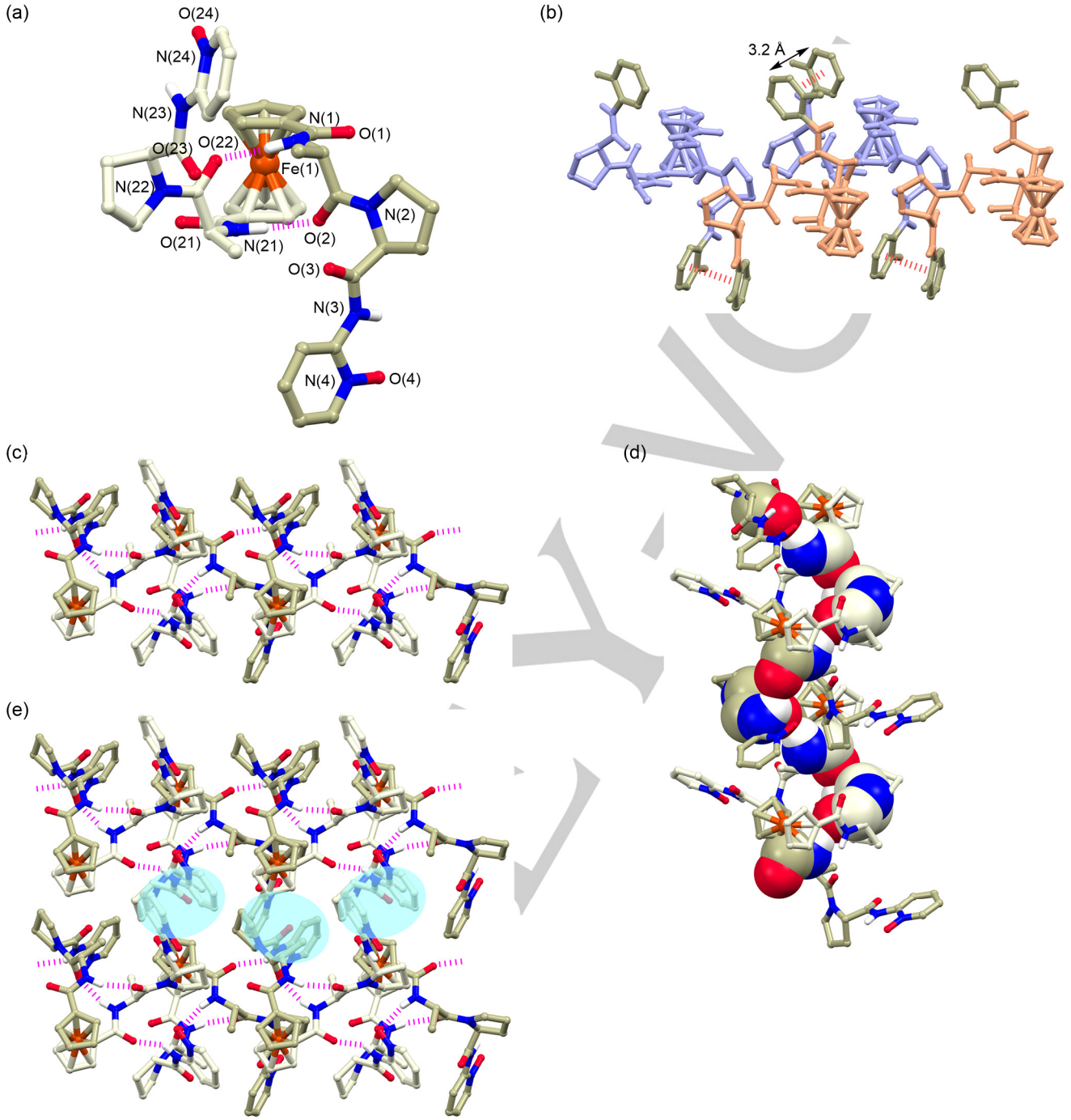


Figure 2. (a) Molecular structure of **2**, (b) a portion of the molecular assembly through π-π interactions between the pyridine *N*-oxide moieties of two independent molecules, (c) a portion of the hydrogen-bonded molecular assembly, (d) a portion of the right-handed molecular arrangement of peptide chains through hydrogen bonding, (e) a portion of the self-assembled structure through the formation of hydrogen bonds and π-π interactions in the crystal packing of **2**. The pale blue colored rounds show the π-π interactions (hydrogen atoms, which are not involved in hydrogen bonding, are omitted for clarity).

22-membered intermolecularly hydrogen-bonded ring between NH (Ala) and PyO (pyridine *N*-oxide of another molecule) (N(51)···O(54)[g], 3.139(17) Å) and π-π interaction between the pyridine *N*-oxide moieties as displayed in Figure 3c. As a result, the self-assembled tetramer through the formation of hydrogen bonds and π-π interactions was formed in the crystal packing of **3** as shown in Figure 3d.

A chirality-organized structure in solution was examined by using ^{1}H NMR, FT-IR, and CD analyses. The signal of the Ala N-H of the ^{1}H NMR spectrum of the ferrocene-dipeptide conjugate **2**

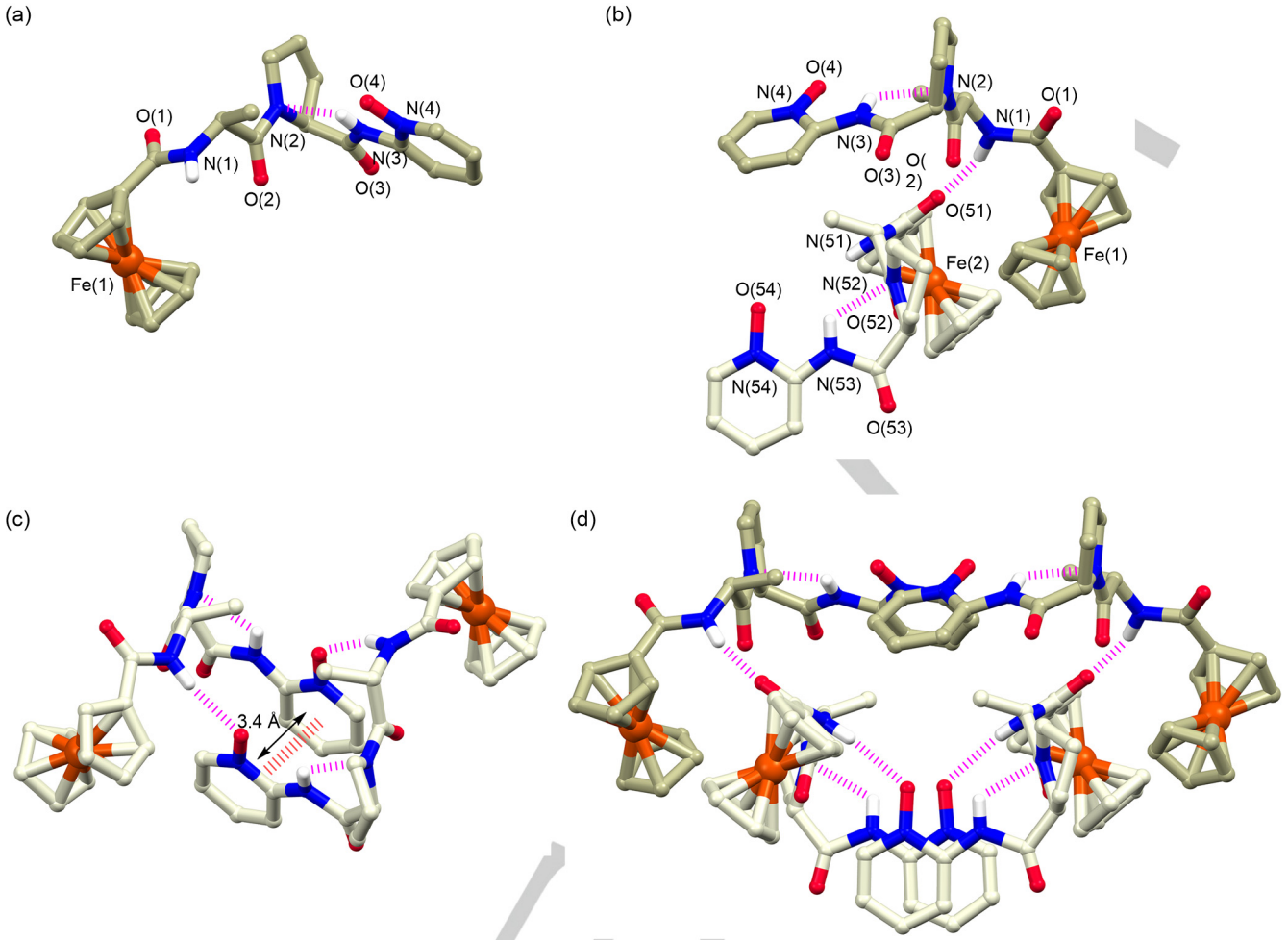


Figure 3. (a) Molecular structure of **3**, (b) the intermolecular hydrogen bond between two independent molecules, (c) π-π interaction between the pyridine *N*-oxide moieties, (d) the self-assembled structure through the formation of the 22-membered intermolecularly hydrogen-bonded ring and π-π interactions in the crystal packing of **3**. (hydrogen atoms, which are not involved in hydrogen bonding, are omitted for clarity).

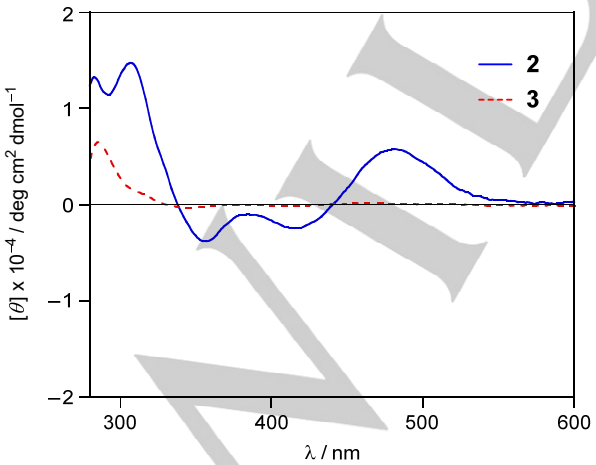


Figure 4. CD spectra of **2** and **3** in dichloromethane (**2**, 1.0 x 10^{-4} M; **3**, 2.0 x 10^{-4} M).

in CD_2Cl_2 was observed at a lower field (1.0 x 10^{-2} M, 8.56 ppm) than that of the ferrocene-dipeptide conjugate **3** (2.0 x 10^{-2} M in CD_2Cl_2, 6.55 ppm). The Ala N-H signal of **2** was not perturbed by the addition of aliquots of DMSO-d_6 to CD_2Cl_2 (CD_2Cl_2/DMSO-d_6 (9:1): 8.54 ppm) although a slightly down-field shift was observed with **3** (CD_2Cl_2/DMSO-d_6 (9:1): 6.92 ppm). Also, the FT-IR spectrum of **2** in CH_2Cl_2 (1.0 x 10^{-2} M) showed hydrogen-bonded N-H stretching bands at 3312 and 3274 cm^{-1} although N-H stretching bands were observed at 3420 and 3274 cm^{-1} in the FT-IR spectrum of **3** in CH_2Cl_2 (2.0 x 10^{-2} M). From these results, intramolecular hydrogen bonds were suggested to be formed even in solution in the ferrocene-dipeptide conjugate **2**. CD spectrometry is a useful technique to elucidate a chirality-organized structure. The ferrocene-dipeptide conjugate **2** showed an induced circular dichroism (ICD) at the absorbance region of the ferrocene moiety, wherein a positive Cotton effect at 480 nm indicates *P*-helical chirality of the ferrocenoyl moiety. The chirality-organized structure through intramolecular hydrogen bondings was found to be preserved even in solution. Such an ICD was not observed in the case of the ferrocene-dipeptide

conjugate **3** composed of only one dipeptide chain, suggesting that interchain intramolecular hydrogen bondings play a crucial role in the creation of the chirality-organized structure.

Conclusions

The L-Ala-L-Pro dipeptide having the C-terminal pyridine *N*-oxide moiety was introduced into the ferrocene organometallic scaffold as a central reverse-turn unit to design the ferrocene-dipeptide conjugates, Fc(-L-Ala-L-Pro-PyO)$_2$ (**2**) and Fc(-L-Ala-L-Pro-PyO)$_1$ (**3**), which were structurally elucidated by single-crystal X-ray structure determination. The chirality-organized structure through intramolecular antiparallel β-sheet-like hydrogen bonding was formed in the ferrocene-dipeptide conjugate **2** composed of two dipeptide chains, wherein a *P*-helical chirality of the ferrocenoyl moiety was induced. The right-handed molecular arrangement of peptide chains through hydrogen bonding was created in the crystal packing of **2**, wherein introduced pyridine *N*-oxide moieties were found to play an important role in the molecular assemblies through π-π interactions. The introduction of only one dipeptide chain into the ferrocene organometallic scaffold was found to eventuate in the self-assembled tetramer structure of the ferrocene-dipeptide conjugate **3** through the formation of intermolecular hydrogen bonds and π-π interactions between pyridine *N*-oxide moieties. The introduction of pyridine *N*-oxide moiety into the L-Ala-L-Pro dipeptide chain was domonstrated to afford additional assembly properties. Future work will concentrate on the application of the chirality-organized ferrocene-dipeptide conjugates for catalysis.

Experimental Section

General Considerations. All reagents and solvents were purchased from commercial sources and were further purified by the standard methods, if necessary. Bis(chlorocarbonyl)ferrocene and (chlorocarbonyl)ferrocene were prepared according to the literature method.[10] ^{1}H and ^{13}C NMR spectra were recorded on a JNM-ECS 400 (^{1}H NMR, 400 MHz; ^{13}C NMR, 100 MHz) spectrometer with tetramethylsilane as an internal standard. Mass spectra were run on a JEOL JMS-700 mass spectrometer.

Boc-L-Ala-L-Pro-PyO (**1**)**.** To a stirred mixture of Boc-L-Ala-L-Pro-OH (2.84 g, 9.9 mmol), 2-aminopyridine *N*-oxide (1.09 g, 9.9 mmol), 1-hydroxybenzotriazole (1.34 g, 9.9 mmol), and triethylamine (6.9 mL, 49.5 mmol) in dichloromethane (20 mL) was dropwise added a solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (4.88 g, 25.5 mmol) in dichloromethane (45 mL). Then, the mixture was stirred at ambient temperature for 62 h. The resulting mixture was washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl. After separating and discarding the water phase, the organic phase was dried on Na_2SO_4. After evaporation of the solvent, a mixture was purified by silica-gel column chromatography (from dichloromethane/methanol = 9:1 to dichloromethane/methanol = 1:1) to give Boc-L-Ala-L-Pro-PyO (**1**) (3.29 g, 8.7 mmol). Single crystals with diffraction-quality of **1** were grown by diffusion of hexane into dichloromethane solution of **1**. **1:** yield 88%; ^{1}H NMR (400 MHz, CD_2Cl_2, 1.0 x 10^{-2} M) δ 10.49 (br s, 1H), 8.35 (dd, *J* = 8.4, 2.0 Hz, 1H), 8.17 (dd, *J* = 6.8, 1.6 Hz, 1H), 7.31-7.27 (m, 1H), 7.00-6.94 (m, 1H), 5.35 (d, *J* = 6.4 Hz, 1H), 4.70 (dd, *J* = 8.0, 4.4 Hz, 1H), 4.54-4.47 (m, 1H), 3.78-3.66 (m, 2H), 2.29-2.04 (m, 4H), 1.42-1.40 (m, 12H); ^{13}C NMR (100 MHz, CD_2Cl_2, 1.0 x 10^{-2} M) 173.2, 170.4, 155.4, 144.1, 137.0, 127.2, 118.9, 114.5, 79.3, 61.3, 47.9, 47.4, 28.7, 28.1, 25.1, 18.5 ppm; HRMS (FAB) *m*/*z* calcd for $C_{18}H_{27}N_4O_5$ ([M+H]$^+$), 379.1981; found, 379.1976.

Ferrocene-dipeptide conjugate Fc(-L-Ala-L-Pro-PyO)$_2$ (**2**)**.** To a stirred solution of Boc-L-Ala-L-Pro-PyO (**1**) (0.53 g, 1.4 mmol) in methanol (10 mL) was added 15 mL of 1.0 M HCl/diethyl ether under argon at room temperature, and the mixture was stirred for 16 h. The solvent was removed in vacuo and the resulting residue was washed three times with anhydrous diethyl ether to give H-L-Ala-L-Pro-PyO hydrochloride. To a stirred mixture of the thus-obtained H-L-Ala-L-Pro-PyO hydrochloride, 4-dimethylaminopyridine (17.1 mg, 0.14 mmol), and triethylamine (0.98 mL, 7.0 mmol) in dichloromethane (15 mL) was dropwise added 1,1'-bis(chlorocarbonyl)ferrocene (0.218 g, 0.70 mmol) in dichloromethane (25 mL) under argon at 0 °C. The mixture was stirred at 0 °C for 1 h and then at room temperature for 16 h. The resulting mixture was washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl. After separating and discarding the water phase, the organic phase was dried on Na_2SO_4. After evaporation of the solvent, a mixture was purified by silica-gel column chromatography (from dichloromethane/methanol = 9:1 to dichloromethane/methanol = 1:1) to give Fc(-L-Ala-L-Pro-PyO)$_2$ (**2**) (0.349 g, 0.44 mmol). Single crystals with diffraction-quality of **2** were grown by diffusion of hexane into dichloromethane solution of **2**. **2:** yield 63%; ^{1}H NMR (400 MHz, CD_2Cl_2, 1.0 x 10^{-2} M) δ 10.35 (br s, 2H), 8.56 (d, *J* = 7.2 Hz, 2H), 8.36 (dd, *J* = 8.4, 2.0 Hz, 2H), 8.25 (dd, *J* = 6.8, 1.2 Hz, 2H), 7.33-7.29 (m, 2H), 7.02-6.98 (m, 2H), 4.87-4.85 (m, 2H), 4.77-4.76 (m, 2H), 4.75-4.68 (m, 4H), 4.45-4.43 (m, 2H), 4.27-4.26 (m, 2H), 3.95-3.89 (m, 2H), 3.75-3.69 (m, 2H), 2.39-2.30 (m, 2H), 2.20-2.11 (m, 6H), 1.14 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, CD_2Cl_2, 1.0 x 10^{-2} M) 175.3, 171.1, 170.2, 144.4, 137.5, 127.6, 119.2, 114.8, 76.5, 72.0, 71.2, 70.4, 70.3, 62.3, 47.7, 29.7, 25.8, 15.1 ppm; HRMS (FAB) *m*/*z* calcd for $C_{38}H_{42}N_8O_8Fe_1$ (M$^+$), 794.2475; found, 794.2490.

Ferrocene-dipeptide conjugate Fc(-L-Ala-L-Pro-PyO)$_1$ (**3**)**.** To a stirred solution of Boc-L-Ala-L-Pro-PyO (**1**) (0.303 g, 0.80 mmol) in methanol (10 mL) was added 12 mL of 1.0 M HCl/diethyl ether under argon at room temperature, and the mixture was stirred for 16 h. The solvent was removed in vacuo and the resulting residue was washed three times with anhydrous diethyl ether to give H-L-Ala-L-Pro-PyO hydrochloride. To a stirred mixture of the thus-obtained H-L-Ala-L-Pro-PyO hydrochloride, 4-dimethylaminopyridine (19.5 mg, 0.16 mmol), and triethylamine (1.12 mL, 8.0 mmol) in dichloromethane (15 mL) was dropwise added (chlorocarbonyl)ferrocene (0.218 g, 0.80 mmol) in dichloromethane (25 mL) under argon at 0 °C. The mixture was stirred at 0 °C for 1 h and then at room temperature for 43 h. The resulting mixture was washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl. After separating and discarding the water phase, the organic phase was dried on Na_2SO_4. After evaporation of the solvent, a mixture was purified by silica-gel column chromatography (from dichloromethane/methanol = 11:1 to dichloromethane/methanol = 1:1) to give Fc(-L-Ala-L-Pro-PyO)$_1$ (**3**) (0.232 g, 0.47 mmol). Single crystals with diffraction-quality of **3** were grown by diffusion of hexane into dichloromethane solution of **3**. **3:** yield 59%; ^{1}H NMR (400 MHz, CD_2Cl_2, 1.0 x 10^{-2} M) δ 10.52 (br s, 1H), 8.38 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.19 (dd, *J* = 6.4, 1.2 Hz, 1H), 7.33-7.28 (m, 1H), 7.01-6.97 (m, 1H), 6.54 (d, *J* = 7.6 Hz, 1H), 4.95-4.88 (m, 1H), 4.73 (dd, *J* = 8.0, 4.8 Hz, 1H), 4.68-4.65 (m, 2H), 4.35-4.34 (m, 2H), 4.21 (s, 5H), 3.89-3.82 (m, 1H), 3.79-3.73 (m, 1H), 2.28-2.07 (m, 4H), 1.53 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2, 1.0 x 10^{-2} M) 173.5, 170.8, 169.7, 144.5, 137.4, 127.6, 125.3, 119.3, 114.9, 76.1, 70.9, 70.2, 68.7, 68.5, 61.9, 47.1, 29.1, 25.6, 18.8 ppm; HRMS (FAB) *m*/*z* calcd for $C_{24}H_{26}N_4O_4Fe_1$ (M$^+$), 490.1303; found, 490.1298.

CD Measurements. CD spectra were recorded using a JASCO J-720 spectropolarimeter in an deaerated dichloromethane solution with the concentration 1.0 x 10^{-4} M for **2** and 2.0 x 10^{-4} M for **3** at 25 °C under argon.

Single-crystal X-ray Structure Determination. All measurements for **1** were made on a Rigaku R-AXIS RAPID diffractometer using graphite monochromated Cu Kα radiation. All measurements for **2** and **3** were made on a Rigaku R-AXIS RAPID diffractometer using graphite monochromated Mo Kα radiation. The structures of **1**, **2**, and **3** were solved by direct methods[11] and expanded using Fourier techniques. All calculations were performed using the CrystalStructure crystallographic software package[12] except for the refinement, which was performed using SHELXL.[13] The non-hydrogen atoms were refined anisotropically. The H atoms involved in hydrogen bonding were located in electron density maps. The remainder of the H atoms were placed in idealized positions and allowed to ride with the C atoms to which each was bonded. The data of **2** and **3** were also refined by using the SQUEEZE routine function in PLATON to solve the structures. Crystallographic details are given in Table 1. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1534928 for **1**, CCDC-1534929 for **2**, and CCDC-1534930 for **3**. 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].

Acknowledgements

This work was supported in part by "JSPS KAKENHI Grant Number JP16H01024 in Precisely Designed Catalysts with Customized Scaffolding". The authors thank Dr. Hideki Sugimoto and Prof. Shinobu Itoh for the single-crystal X-ray structure determination. Thanks are due to the Analytical Center, Graduate School of Engineering, Osaka University.

Keywords: ferrocene • dipeptide • hydrogen bond • chirality organization • bioorganometallic chemistry

[1] For reviews, see: a) V. Balzani, A. Credi, F.M. Raymo, J.F. Stoddart, *Angew. Chem. Int. Ed.* **2000**, *39*, 3348-3391; b) G.F. Swiegers, T.J. Malefetse, *Chem. Rev.* **2000**, *100*, 3483-3538; c) W.-Y. Sun, M. Yoshizawa, T. Kusukawa, M. Fujita, *Curr. Opin. Chem. Biol.* **2002**, *6*, 757-764; d) J.T. Davis, G.P. Spada, *Chem. Soc. Rev.* **2007**, *36*, 296-313; e) K. Tanaka, M. Shionoya, *Coord. Chem. Rev.* **2007**, *251*, 2732-2742; f) D. Pijper, B.L. Feringa, *Soft Matter* **2008**, *4*, 1349-1372; g) S. Horike, S. Shimomura, S. Kitagawa, *Nat. Chem.* **2009**, *1*, 695-704; h) R.S. Forgan, J.-P. Sauvage, J.F. Stoddart, *Chem. Rev.* **2011**, *111*, 5434-5464.

[2] G.A. Jeffrey, An Introduction to Hydrogen Bonding, 1st ed. Oxford University Press, New York, 1997.

[3] T. Moriuchi, T. Hirao, *Chem. Soc. Rev.* **2004**, *33*, 294-301.

[4] A. Togni, T. Hayashi, Ferrocenes, Wiley-VCH, Weinheim, 1995.

[5] a) G. Jaouen, A. Vessiéres, I.S. Butler, *Acc. Chem. Res.* **1993**, *26*, 361-369; b) R. Severin, R. Bergs, W. Beck, *Angew. Chem. Int. Ed.* **1998**, *37*, 1634-1654; c) R.H. Fish, G. Jaouen, *Organometallics* **2003**, *22*, 2166-2177; d) G. Jaouen, Bioorganometallics; Biomolecules, Labeling, Medicine. Wiley-VCH, Weinheim, 2006; e) C.G. Hartinger, P.J. Dyson, *Chem. Soc. Rev.* **2009**, *38*, 391-401; f) T. Hirao, T. Moriuchi, A. Groβ, Bioconjugates to Induce Chirality Organization. In: T. Hirao (Ed.), Functuionalized Redox Systems, Springer Japan, Japan, 2015, pp 111-150.

[6] a) R.S. Herrick, R.M. Jarret, T.P. Curran, D.R. Dragoli, M.B. Flaherty, S.E. Lindyberg, R.A. Slate, L.C. Thornton, *Tetrahedron Lett.* **1996**, *37*, 5289-5292; b) D. R. van Staveren, N. Metzler-Nolte, *Chem. Rev.* **2004**, *104*, 5931-5986; c) S.I. Kirin, H.-B. Kraatz, N. Metzler-Nolte, *Chem. Soc. Rev.* **2006**, *35*, 348-354; d) T. Moriuchi, T. Hirao, Ferrocene-Peptide Bioconjugates. In: G. Simonneaux (Ed.), Bioorganometallic Chemistry, Vol. 17. Springer-Verlag, Berlin Heidelberg, 2006, pp 143-175; e) M. Salmain, N. Metzler-Nolte, Bioorganometallic Chemistry of Ferrocene. In: P. Stepnicka (Ed.), Ferrocenes. John Wiley & Sons, Chichester, 2008, pp 499-639; f) A. Lataifeh, S. Beheshti, H.-B. Kraatz, *Eur. J. Inorg. Chem.* **2009**, 3205-3218; g) T. Moriuchi, T. Hirao, *Acc. Chem. Res.* **2010**, *43*, 1040-1051.

[7] a) A. Nomoto, T. Moriuchi, S. Yamazaki, A. Ogawa, T. Hirao, *Chem. Commun*. **1998**, 1963-1964; b) T. Moriuchi, A. Nomoto, K. Yoshida, T. Hirao, *J. Organomet. Chem.* **1999**, *589*, 50-58; c) T. Moriuchi, A. Nomoto, K. Yoshida, A. Ogawa, T. Hirao, *J. Am. Chem. Soc*. **2001**, *123*, 68-75; d) T. Moriuchi, A. Nomoto, K. Yoshida, T. Hirao, *Organometallics* **2001**, *20*, 1008-1013; e) T. Moriuchi, K. Yoshida, T. Hirao, *Organometallics* **2001**, *20*, 3101-3105; f) T. Moriuchi, K. Yoshida, T. Hirao, *J. Organomet. Chem.* **2003**, *668*, 31-34; g) T. Moriuchi, K. Yoshida, T. Hirao, *Org. Lett*. **2003**, *5*, 4285-4288: h) T. Moriuchi, T. Nagai, T. Hirao, *Org. Lett.* **2005**, *7*, 5265-5268; i) T. Moriuchi, T. Nagai, T. Hirao, *Org. Lett.* **2006**, *8*, 31-34; j) T. Moriuchi, T. Nagai, T. Fujiwara, N. Honda, T. Hirao, *Heterocycles* **2008**, *76*, 595-603.

[8] a) M. Nakajima, M. Saito, M. Shiro, S. Hashimoto *J. Am. Chem. Soc*. **1998**, *120*, 6419-6420; b) V. Derdau, S. Laschat, E. Hupe, W. A. König, I. Dix, P. G. Jones, *Eur. J. Inorg. Chem.* **1999**, 1001-1007; c) B. Tao, M. M.-C. Lo, G. C. Fu, *J. Am. Chem. Soc*. **2001**, *123*, 353-354; d) G. Chelucci, S. Baldino, G. A. Pinna, M. Benaglia, L. Buffa, S. Guizzetti *Tetrahedron* **2008**, *64*, 7574-7582; e) J. Chen, N. Takenaka, *Chem. Eur. J.* **2009**, *15*, 7268-7276.

[9] a) J. Jia, P. Hubberstey, N. R. Champness, M. Schröder, *Struct. Bond* **2009**, *132*, 135-161; b) M. Chen, S. Han, L. Jiang, S. Zhou, F. Jiang, Z. Xu, J. Liang, S. Zhang, *Chem. Commun.* **2010**, *46*, 3932-3934; c) N. R. Goud, N. J. Babu, A. Nangia, *Cryst. Growth Des.* **2011**, *11*, 1930-1939; d) R. Puttreddy, N. K. Beyeh, K. Rissanen, *CrystEngComm* **2016**, *18*, 4971-4976.

[10] F.W. Knobloch, W.H. Rauscher, *J. Polymer Sci.* **1961**, *54*, 651-656.

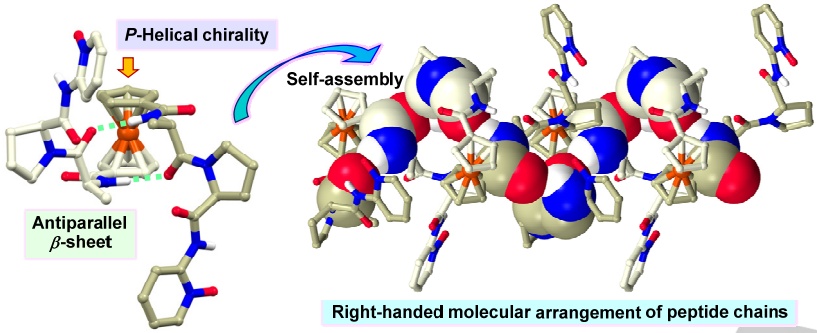
[11] M. C. Burla, R. Caliandro, M. Camalli, B. Carrozzini, G. L. Cascarano, L. De Caro, C. Giacovazzo, G. Polidori, R. Spagna, *J. Appl. Cryst.* **2005**, *38*, 381-388.

[12] CrystalStructure 4.2.2: Crystal Structure Analysis Package, Rigaku Corporation (2000-2016). Tokyo 196-8666, Japan.

[13] G. M. Sheldrick, *Acta Crystallogr. Sec. A.* **2008**, *64*, 112-122.

Entry for the Table of Contents (Please choose one layout)

FULL PAPER



Ferrocene-dipeptide conjugates having pyridine *N*-oxide moieties were designed to demonstrate the hydrogen bonding induced chirality organization, resulting in the highly-ordered molecular arrangements.

Toshiyuki Moriuchi, Hao Wu, Yoshiki Tayano, and Toshikazu Hirao**

Page No. – Page No.

Structural Characterization of Chirality-Organized Ferrocene-Dipeptide Conjugates Having Pyridine *N*-Oxide Moieties