Complexation Stabilized Conformational Regulation of Ferrocene Bearing Podand Dipeptide Chains (-L-Ala-L-Pro-NHPy)

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The structural characterization of the palladium complex of the ferrocene **1** bearing podand dipeptide chains (-L-Ala-L-Pro-NHPy) was demonstrated. The ferrocene **1** forms the 1:1 *trans* complex **2** with $PdCl_2(MeCN)_2$ to stabilize the intramolecular conformational regulation in both solution and solid states. The crystal structure of **2** revealed a pseudohelical conformation through palladium binding and chirality organization via sterically constrained moieties (Pro) and intramolecular hydrogen bondings between CO (Ala) and NH (another Ala) of each podand dipeptide chain (N(1)···O(2*), 2.88 Å; N(1*)···O(2), 2.97 Å), giving a 10-membered hydrogen-bonded ring. Such an ordered conformation was supported by the induced circular dichroism. Another noteworthy feature of the ferrocene **1** is its strong tendency to self-assemble through participation of all available hydrogen-bonding donors in the solid state.

Introduction

Metal ions have been known to exhibit a variety of properties in proteins, the most important of which is the stabilization of the structures required for biological functions.[1] Metal ions also play a crucial role in the redox processes of proteins.[1] The incorporation of metal coordination sites into peptides has been focused on the stabilization of secondary structures[2] and catalytic activities.[3] In these peptide complexes, chirality organization is considered to be achieved. Gilbertson has used phosphine-containing β-turn ligands as asymmetric catalysts.[3b] We have already demonstrated that the introduction of podand dipeptide chains into ferrocene permits chirality organization through intramolecular interchain hydrogen bondings.[4] The introduction of metal coordination sites into peptide chains is envisaged to stabilize the conformational regulation and provide asymmetric catalysts by metal complexation. From this point of view, we herein report the structural characterization of the palladium complex of the ferrocene **1** bearing podand dipeptide chains (-L-Ala-L-Pro-NHPy) to elucidate the conformational regulation. An advantage of the use of L-alanyl-L-proline as a dipeptide depends on a hydrogen-bonding site and a sterically constrained proline as a well-known turn inducer in proteins.

Results and Discussion

The ferrocene **1** was synthesized from H-L-Ala-L-Pro-NHPy and 1,1′-bis(chlorocarbonyl)ferrocene (Figure 1). X-ray crystallographic analysis was performed in order to clarify an intramolecular conformational control in the ferrocene **1** (Tables 1−3). Numbering of selected atoms of the ferrocene **1** is shown in Figure 2. The single-crystal X-ray structure determination of **1** confirmed the chirality organization through an intramolecular conformational regulation by the formation of two intramolecular hydrogen bondings between CO (Ala) and NH (another Ala) of each podand dipeptide chain (N(1)···O(2*), 3.01 Å; N(1*)···O(2), 2.98 Å), affording a 10-membered hydrogen-bonded ring (Figure 3). In the ^{1}H NMR spectrum of the ferrocene **1** in $CDCl_3$ (1.0×10^{-2} M), only one kind of Ala N−H resonance was detected at a lower field (8.80 ppm) (Table 4). The FT-IR spectrum of **1** in CH_2Cl_2 (1.0×10^{-3} M) showed a hydrogen-bonded N−H stretching band at 3309 cm^{-1}. Two identical intramolecular hydrogen bonds between the podand dipeptide chains of **1** are indicated to be

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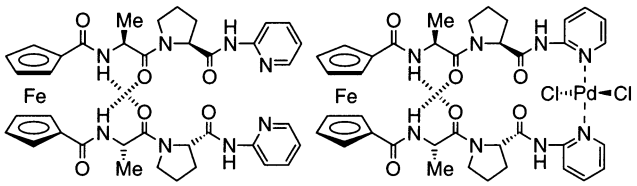


1 **2**

Figure 1. Ferrocenes bearing podand dipeptide chains.

Table 1. Crystallographic Data for 1 and 2

	1	**2**
formula	$C_{38}H_{42}N_8O_6Fe\cdot 2CHCl_3$	$C_{38}H_{42}N_8O_6FePdCl_2$
fw	1001.40	939.95
cryst syst	monoclinic	orthorhombic
space group	$P2_1$ (No. 4)	$P2_12_12_1$ (No. 19)
a, Å	12.0007(3)	14.004(9)
b, Å	14.9429(4)	26.97(2)
c, Å	14.8288(2)	11.686(8)
β, deg	109.212(5)	
V, Å^3	2511.1(1)	4414(4)
Z	2	4
D_{calcd}, g cm^{-3}	1.324	1.414
μ(Mo Kα), cm^{-1}	6.68	9.08
T, °C	23	23
λ(Mo Kα), Å	0.71069	0.71069
R^a	0.113	0.066
$R_w{}^b$	0.323	0.215

[a] $R = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $R_w = [\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$.

Table 2. Hydrogen Bonds for 1 and 2

crystal	type[a]	donor	acceptor	D···A (Å)
1	intra	N(1)	O(2*)	3.01(1)
	intra	N(1*)	O(2)	2.98(1)
	inter	N(3)	O(1a*)	3.05(1)
	inter	N(3*)	O(1b)	2.92(1)
	inter	N(3c*)	O(1)	2.92(1)
	inter	N(3d)	O(1*)	3.05(1)
2	intra	N(1)	O(2*)	2.88(1)
	intra	N(1*)	O(2)	2.97(1)

[a] Abbreviations: inter, intermolecular; intra, intramolecular.

Table 3. Torsion Angles (deg) for 1 and 2

	angle[a]	**1**	**2**
ϕ_1	C(6)−N(1)−C(7A)−C(8)	−91(1)	−86(1)
ψ_1	N(1)−C(7A)−C(8)−N(2)	163(1)	164.2(9)
ω_1	C(7A)−C(8)−N(2)−C(9A)	170(1)	−174.7(9)
ϕ_2	C(8)−N(2)−C(9A)−C(10)	−59(1)	−60(1)
ψ_2	N(2)−C(9A)−C(10)−N(3)	143(1)	−41(1)
ϕ_1*	C(6)−N(1*)−C(7A*)−C(8*)	−85(1)	−83(1)
ψ_1*	N(1*)−C(7A*)−C(8*)−N(2*)	151(1)	164(1)
ω_1*	C(7A*)−C(8*)−N(2*)−C(9A*)	171(1)	−177(1)
ϕ_2*	C(8*)−N(2*)−C(9A*)−C(10*)	−81(1)	−71(1)
ψ_2*	N(2*)−C(9A*)−C(10*)−N(3*)	167(1)	−32(1)

[a] Symbol used for torsion angles in peptides (IUPAC-IUB Commission on Biochemical Nomenclature).

formed in solution. The ferrocene **1** exhibited an induced circular dichroism (CD) around the absorbance of the ferrocene function (Figure 4). These findings suggest chirality organization through intramolecular hydrogen bondings even in solution.

On the basis of observations, the effect of metal binding in the intramolecular conformational regulation was studied. Complexation of the ferrocene **1** with $PdCl_2(MeCN)_2$ afforded the 1:1 *trans* complex **2**. The *trans* conformation was confirmed by a far infrared Pd−Cl stretching band at 347 cm^{-1} (Nujol). The downfield shift of an equivalent set of pyridyl protons in the ^{1}H NMR spectrum of **2** implies the equal coordination of

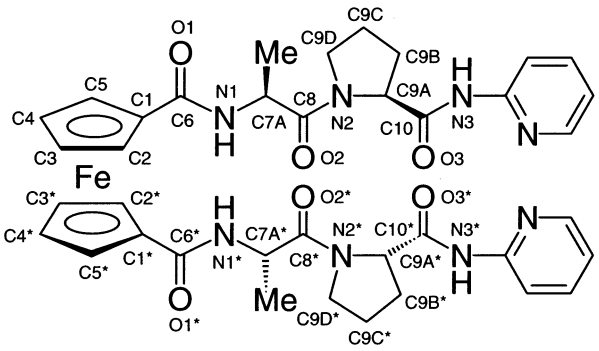


Figure 2. Numbering of selected atoms of **1**.

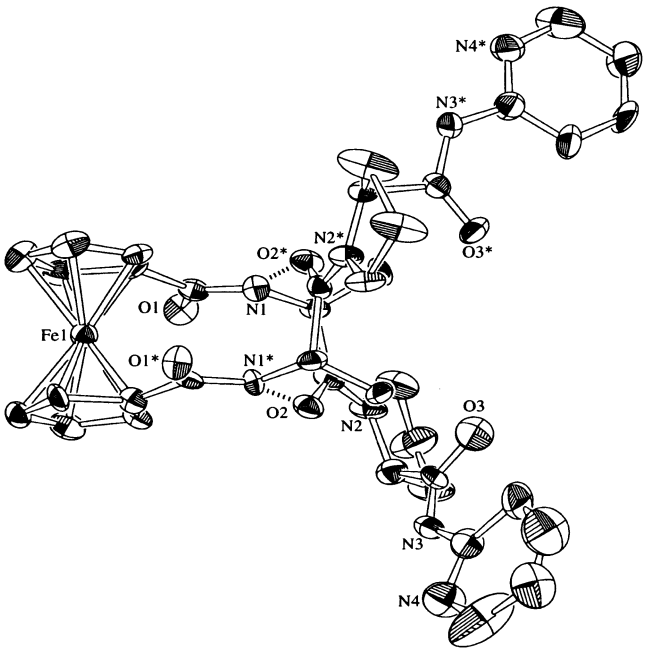


Figure 3. Molecular structure of **1** (30% probability ellipsoids; hydrogen atoms omitted for clarity).

Table 4. Selected Spectroscopic Data for 1 and 2

	^{1}H NMR, N−H (ppm)[a]		FT-IR, ν_{N-H} (cm^{-1})[b]
	$CDCl_3$	$CDCl_3$/DMSO-d_6 (9:1)	CH_2Cl_2
1	8.80	8.97	3405
	9.04	9.87	3309
2	8.99	8.99	3320
	10.17	10.19	3244

[a] Concentration 1.0×10^{-2} M. [b] Concentration 1.0×10^{-3} M.

two pyridyl nitrogen atoms to palladium (Figure 5). Interestingly, the more downfield shift of the Ala N−H resonance was observed in the palladium complex **2** as compared with that of **1**. The Ala N−H resonance of **2** was not perturbed by the addition of aliquots of DMSO-d_6 to $CDCl_3$ (1.0×10^{-2} M, $CDCl_3$: 8.99 ppm; $CDCl_3$/DMSO-d_6 (9:1): 8.99 ppm), although a slightly downfield shift of the Ala N−H resonance was observed in the case of **1** (1.0×10^{-2} M, $CDCl_3$: 8.80 ppm; $CDCl_3$/DMSO-d_6 (9:1): 8.97 ppm), indicating the stabilization of the intramolecular hydrogen bondings by complexation. The N−H stretching band at 3244 cm^{-1} in the FT-IR spectrum of **2** in CH_2Cl_2 (1.0×10^{-3} M) also supports the formation of the strong hydrogen bonds. These results reveal that complexation strengthens intramolecular hydrogen bondings to stabilize an intramolecular

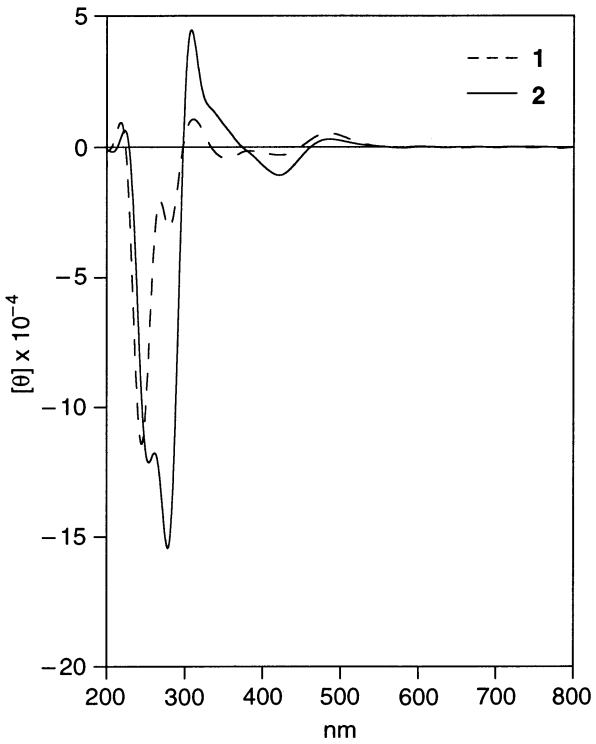


Figure 4. CD spectra of **1** and **2** in CH_2Cl_2 (1.0×10^{-4} M).

conformational regulation. Furthermore, the stabilization of an intramolecular conformational regulation through complexation was convincingly evidenced by observing an intrinsic induced CD (Figure 4).

Further structural information was obtained by a single-crystal X-ray structure determination to support the results of the solution state. The crystal structure of **2** revealed a pseudohelical conformation through palladium binding and the preservation of two C_2-symmetrical intramolecular hydrogen bondings between CO (Ala) and NH (another Ala) of each podand dipeptide chain (N(1)···O(2*), 2.88 Å; N(1*)···O(2), 2.97 Å) to give

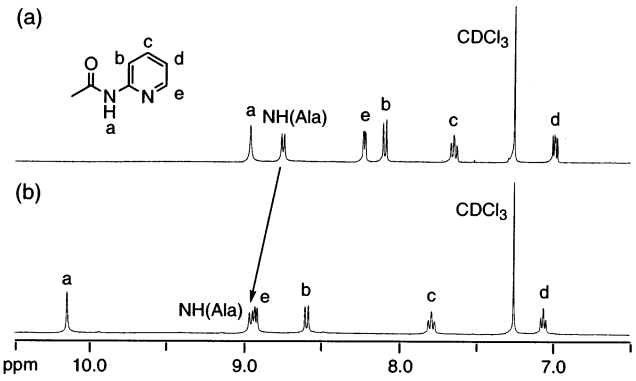
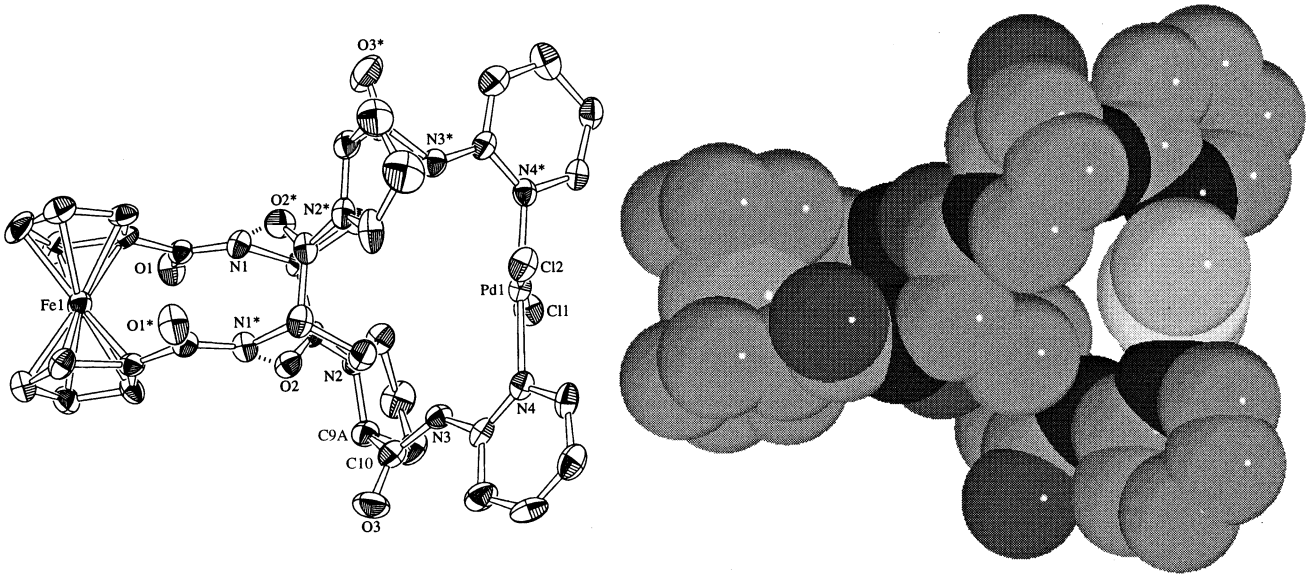


Figure 5. Downfield region of the ^{1}H NMR spectra of (a) **1** and (b) **2**.

a 10-membered hydrogen-bonded ring as depicted in Figure 6. The palladium complex **2** was found to be almost C_2-symmetrical, being consistent with the spectroscopically equivalent pyridyl protons of **2** in ^{1}H NMR. Two pyridyl nitrogen atoms of each podand dipeptide chain coordinate *trans* to palladium.[5] Another interesting feature in the structure is the dihedral angle between the least-squares planes of the coordinated pyridyl rings. The chirality organization through intramolecular hydrogen bondings (Ala) and sterically constrained moieties (Pro) requires rotation of the pyridyl rings, resulting in the conformation to set the dihedral angle, 75.6°, between the least-squares planes of the two pyridyl rings. The most noteworthy structural difference between **1** and **2** was observed in the torsion angle ψ_2 defined as N(2)−C(9A)−C(10)−N(3) (**1**, 143° and 167°; **2**, −41° and −32°) (Table 4). The coordination of the pyridyl nitrogen to the palladium atom requires further rotation of the peptide chain, resulting in the observed torsion angles. In this conformation, the NH adjacent to the pyridyl moiety could not participate in intermolecular hydrogen bonding, although the NH adjacent to the pyridyl moiety of **1** is available for participating in the intermolecular hydrogen bonding



(a) (b)

Figure 6. (a) Molecular structure of **2** (30% probability ellipsoids; hydrogen atoms omitted for clarity). (b) Space-filling representation of the molecular structure of **2** (hydrogen atoms omitted for clarity).

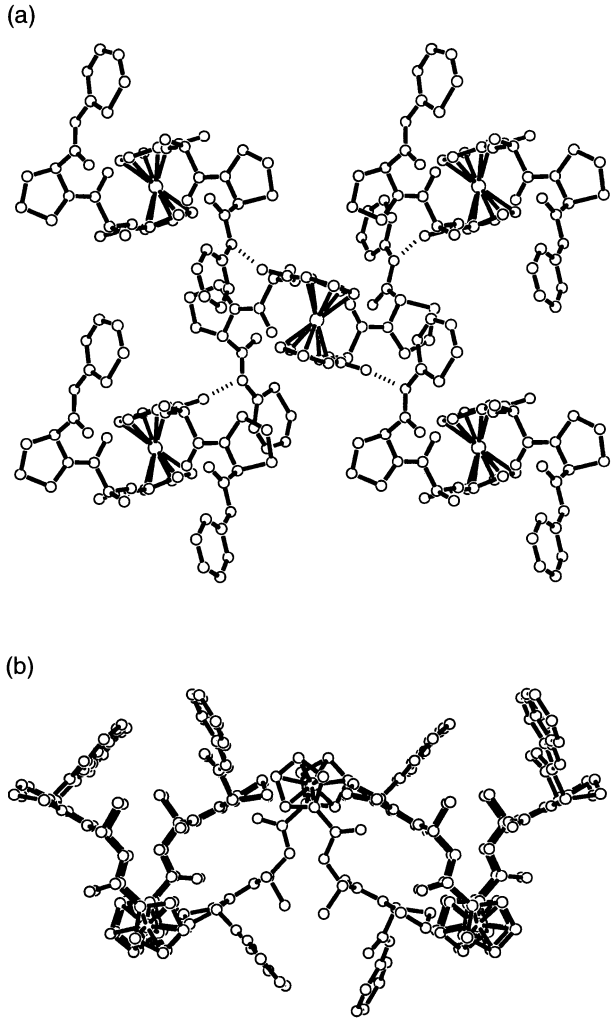


Figure 7. (a) Top view and (b) side view of the crystal packing of **1**. Each molecule is connected to four neighboring molecules by continuous intermolecular hydrogen bonds.

with CO adjacent to the ferrocene unit. The highly organized self-assembly was achieved in the crystal packing of **1**, wherein each molecule is connected to four neighboring molecules through NH···O═C bonds (Figure 7).

In conclusion, the complexation of the ferrocene **1** bearing podand dipeptide chains (-L-Ala-L-Pro-NHPy) with $PdCl_2(MeCN)_2$ was demonstrated to stabilize the intramolecular conformational regulation in both solution and solid states. The single-crystal X-ray structure determination of the palladium complex **2** confirmed the pseudohelical conformation through palladium binding and chirality organization via the intramolecular hydrogen bondings (Ala) and sterically constrained moieties (Pro). Another noteworthy feature of the ferrocene **1** is its strong tendency to self-assemble through participation of all available hydrogen-bonding donors in the solid state. Studies on the application of chirality organization of ferrocenes bearing podand dipeptide chains to molecular recognition and asymmetric reaction are now in progress.

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Experimental Section

General Methods. All reagents and solvents were purchased from commercial sources and were further purified by the standard methods, if necessary. Melting points were determined on a Yanagimoto Micromelting Point Apparatus and were uncorrected. Infrared spectra were obtained with a Perkin-Elmer Model 1605 FT-IR. ^{1}H NMR spectra were recorded on a JEOL JNM-GSX-400 (400 MHz) spectrometer with tetramethylsilane as an internal standard. Mass spectra were run on a JEOL JMS-DX303HF mass spectrometer.

Preparation of the Ferrocene 1 Bearing Podand Dipeptide Chains (-L-Ala-L-Pro-NHPy). To a stirred mixture of H-L-Ala-L-Pro-NHPy (131.2 mg, 0.50 mmol) and triethylamine (348 μL, 2.5 mmol) in dichloromethane (5 mL) was dropwise added 1,1′-bis(chlorocarbonyl)ferrocene (77.7 mg, 0.25 mmol) in dichloromethane (5 mL) under argon at 0 °C. The mixture was stirred at 0 °C for 1 h and then at room temperature for 4 h. The resulting mixture was diluted with dichloromethane, washed with saturated $NaHCO_3$ aqueous solution and brine, and then dried over Na_2SO_4. The solvent was evaporated in vacuo. Purification was performed by a recycling preparative HPLC (Japan Analytical Industry Co. Ltd., Model LC-908), equipped with JAIGEL-1H and -2H columns (GPC, $CHCl_3$ as an eluent). The ferrocene **1** was isolated in 88% yield by recrystallization from chloroform. Mp: 268−270 °C (uncorrected). IR (CH_2Cl_2, 1.0×10^{-3} M): 3405, 3309, 1701, 1635 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 5.0×10^{-3} M): δ 8.93 (s, 2H), 8.76 (d, 2H, J = 7.3 Hz), 8.23 (ddd, 2H, J = 4.9, 1.8, 0.7 Hz), 8.10 (ddd, 2H, J = 8.4, 0.9, 0.7 Hz), 7.66 (ddd, 2H, J = 8.4, 7.3, 1.8 Hz), 7.00 (ddd, 2H, J = 7.3, 4.9, 0.9 Hz), 4.91−4.90 (m, 2H), 4.89−4.88 (m, 2H), 4.84−4.78 (m, 4H), 4.54−4.52 (m, 2H), 4.31−4.30 (m, 2H), 3.97−3.91 (m, 2H), 3.69−3.65 (m, 2H), 2.39−2.31 (m, 2H), 2.25−2.14 (m, 6H), 1.33 (d, 6H, J = 7.3 Hz). FAB-MS m/z 763 ($M^+ + 1$). Anal. Calcd for $C_{38}H_{42}N_8O_6Fe \cdot 1.5H_2O$: C, 57.80; H, 5.74; N, 14.19. Found: C, 57.81; H, 5.57; N, 14.46.

Preparation of the Palladium Complex 2. A mixture of **1** (38.1 mg, 0.050 mmol) and $PdCl_2(MeCN)_2$ (13.0 mg, 0.050 mmol) was stirred in acetonitrile (3.0 mL) under argon at room temperature for 2 h. After evaporation of the solution, the complex **2** was isolated in 98% yield by recrystallization from ethyl acetate/hexane. Mp: 244−246 °C (dec). IR (CH_2Cl_2, 1.0×10^{-3} M): 3320, 3244, 1712, 1639 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 5.0×10^{-3} M): δ 10.16 (s, 2H), 8.99 (d, 2H, J = 7.3 Hz), 8.94 (dd, 2H, J = 6.3, 1.8 Hz), 8.61 (d, 2H, J = 8.8 Hz), 7.80 (ddd, 2H, J = 8.8, 7.5, 1.8 Hz), 7.07 (dd, 2H, J = 7.5, 6.3 Hz), 5.00−4.99 (m, 2H), 4.97−4.88 (m, 2H), 4.87−4.86 (m, 2H), 4.61−4.57 (m, 2H), 4.55−4.53 (m, 2H), 4.33−4.31 (m, 2H), 3.93−3.87 (m, 2H), 3.79−3.74 (m, 2H), 2.43−2.35 (m, 2H), 2.20−2.11 (m, 2H), 2.10−1.93 (m, 4H), 1.53 (d, 6H, J = 7.3 Hz). FAB-MS m/z 940 ($M^+ + 1$). Anal. Calcd for $C_{38}H_{42}N_8O_6FePdCl_2$: C, 48.56; H, 4.50; N, 11.92. Found: C, 48.38; H, 4.31; N, 11.52.

CD Measurements. CD spectra were recorded using a JASCO J-720 spectropolarimeter in a deaerated dichloromethane solution with the concentration 1.0×10^{-4} M under argon at 25 °C.

X-ray Structure Analysis. All measurements for **1** were made on a Rigaku RAXIS-RAPID imaging plate diffractometer with graphite-monochromated Mo Kα radiation. All measurements for **2** were made on a Rigaku AFC5R diffractometer with graphite-monochromated Mo Kα radiation and a rotating anode generator. The structures of **1** and **2** were solved by direct methods and expanded using Fourier techniques. The absolute structure of **2** was determined by the dipeptide of a starting material. 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. Crystallographic details are given in Table 1. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-153674 for **1** and CCDC-153675 for **2**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (int) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].

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Supporting Information Available: Tables of X-ray crystallographic data for **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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