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Communication

Structural characterization and complexation behavior of ferrocene bearing dipeptide chain (-L-Ala-L-Pro-NHPy)

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Abstract

Ferrocene **1** bearing dipeptide chain (-L-Ala-L-Pro-NHPy) was synthesized and characterized by spectroscopy and X-ray crystallography. The single-crystal X-ray structure determination of the ferrocene **1** revealed that a hydrogen-bonded network is formed in an antiparallel manner to give a highly organized assembly, wherein each molecule is connected to two neighboring molecules through N–H···N and N–H···O intermolecular hydrogen bonds, forming a seven-membered intermolecularly hydrogen-bonded ring. The ferrocene **1** served as a monodentate ligand to form the 2:1 *trans*-complex **2** with $PdCl_2(MeCN)_2$. The rotational barrier of the two pyridyl rings in the palladium(II) complex **2** was 10.1 kcal mol^{-1}. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Ferrocene; Dipeptide; Hydrogen bond; Crystal packing; Palladium complex; Bioorganometallic chemistry

1. Introduction

Architectural control of molecular self-organization is of great importance for the development of functional materials [1]. Functionalities of proteins considerably depend on their highly-ordered molecular assemblies, in which secondary structures such as α-helices, β-sheets, and β-turns play an important role in protein folding [2]. Secondary structures are mostly driven by hydrogen bonding and hydrophobic interaction of side chains. The utilization of such self-assembling properties of peptides is considered to be one of the most useful strategies to highly-ordered systems. Furthermore, controlled arrangement of redox-active moieties is envisaged to be a convenient approach to modulate the redox properties. Ferrocenes have attracted much attention in their application to materials due to a reversible redox couple and rotatory cyclopentadienyl rings [3]. Redox-active ferrocenes bearing a long alkylene chain have been revealed to be aggregated along the backbone of double helical DNA to afford redox-active (outer) and hydrophobic (inner) spheres around the double helical core [4]. On the other hand, ferrocenes have been focused as a molecular scaffold to study the hydrogen bonding properties of peptide strands [5]. We have also demonstrated in a previous paper that the incorporation of the podand dipeptide chains into ferrocene leads to the chirality organization through intramolecular interchain hydrogen bondings [6]. Another route to an efficient redox system is invoked in the introduction of coordination sites to peptides for complexation. In this paper, we design the ferrocene **1** bearing dipeptide chain (-L-Ala-L-Pro-NHPy) with an additional pyridyl moiety, which is capable of participating in hydrogen bonding and binding to metal salt, and structural characterization and complexation behavior of **1** are described.

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Table 1
Crystallographic data for **1**

Formula	$C_{24}H_{26}N_4O_3Fe{\cdot}H_2O$
Molecular weight	492.36
Crystal system	Monoclinic
Space group	C_2 (no. 5)
Unit cell dimensions	
a (Å)	25.855(4)
b (Å)	7.647(3)
c (Å)	22.146(4)
β (°)	149.327(3)
V (A^3)	2233(1)
Z	4
D_{calc} (g cm^{-3})	1.464
μ (Mo–K$_\alpha$) (cm^{-1})	7.14
T (°C)	23
λ (Mo–K$_\alpha$) (Å)	0.71069
R [a]	0.038
R [b]	0.108

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

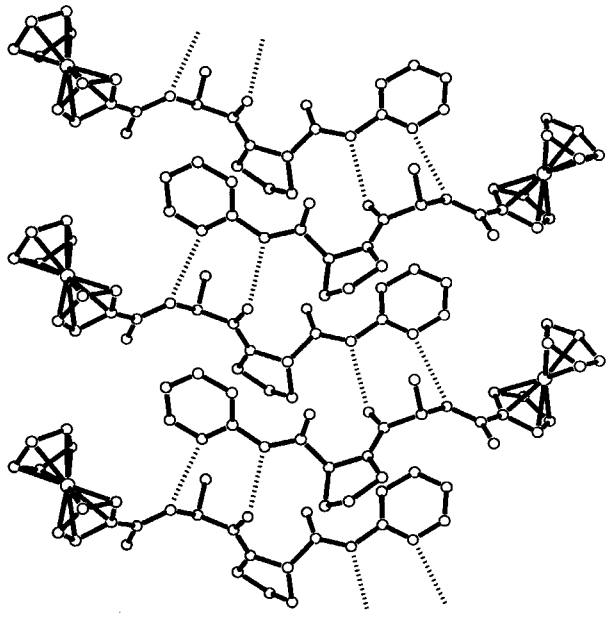


Fig. 2. A layer containing an antiparallel arrangement of the crystal packing of **1**. Each molecule is connected to two neighboring molecules by continuous intermolecular hydrogen bonds.

2. Results and discussion

The ferrocene **1** bearing dipeptide chain (-L-Ala-L-Pro-NHPy) was synthesized from H-L-Ala-L-Pro-NHPy and (chlorocarbonyl)ferrocene. The dipeptide chain is designed to contain an additional pyridyl moiety for hydrogen bonding and coordination. The thus-obtained ferrocene **1** was characterized fully by spectral data and elemental analysis. The pyridylamide N–H and Ala N–H resonances were detected at 9.25 and 6.63 ppm, respectively, in the ^{1}H-NMR spectrum of **1** ($CDCl_3$, 1.0×10^{-2} M). These N–H resonances were perturbed by the addition of aliquots of DMSO-d_6 to $CDCl_3$ (9.85 and 6.93 ppm, respectively). The FT-IR spectrum of **1** in CH_2Cl_2 (2.0×10^{-2} M) showed non-hydrogen bonded N–H stretching bands at 3410 cm^{-1}. These results indicate that the ferrocene **1** is present in a non-hydrogen bonded state in the solution.

Further structural information of **1** was obtained by a single-crystal X-ray structure determination (Table 1). The torsion angle, 14.0°, defined as C(1)–C(centroid)–C(centroid)–C(16) indicates almost the *eclipsed* orientation of two cyclopentadienyl rings of **1** as depicted in Fig. 1. The appended pyridyl amide moiety is capable of participating in intermolecular hydrogen bonding. Instead of the intramolecular hydrogen bond, a hydrogen-bonded network is formed in an antiparallel manner to give a highly organized assembly, wherein each molecule is connected to two

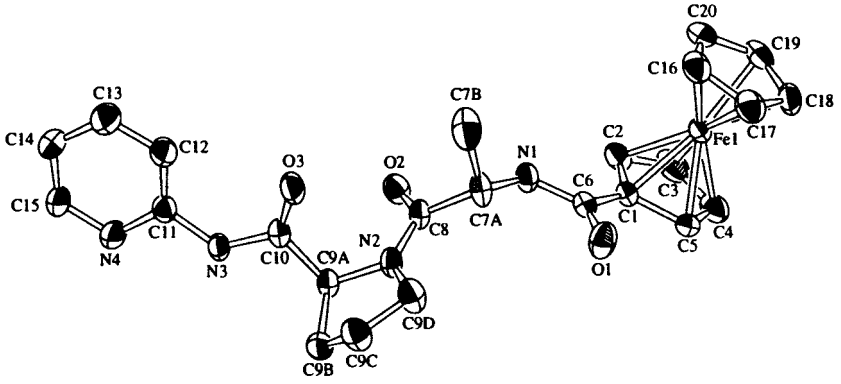
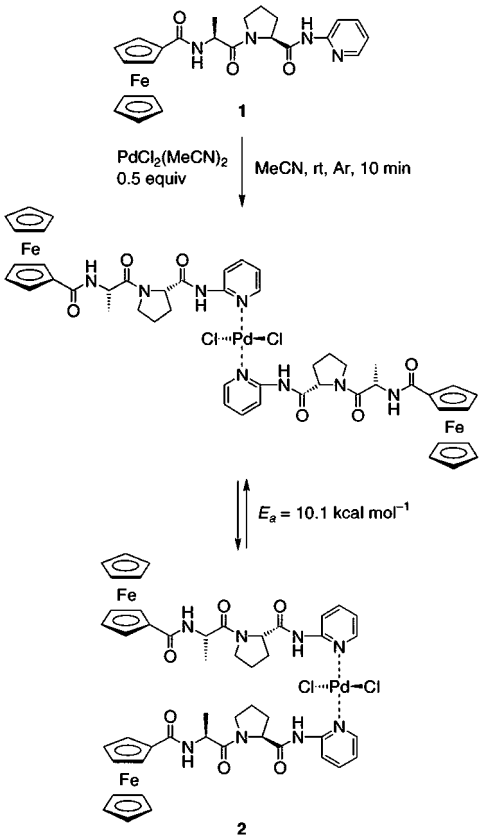


Fig. 1. Molecular structure of **1** (40% probability ellipsoids). Hydrogen atoms are omitted for clarity. Selected bond distances (Å) and torsion angles (°): O(1)–C(6), 1.230(7); N(1)–C(6), 1.35(1); O(2)–C(8), 1.231(7); N(2)–C(8), 1.335(6); O(3)–C(10), 1.203(6); N(3)–C(10), 1.37(1); C(6)–N(1)–C(7A)–C(8), −124.0(6); N(1)–C(7A)–C(8)–N(2), 138.7(4); C(7A)–C(8)–N(2)–C(9A), 171.5(3); C(8)–N(2)–C(9A)–C(10), −73.3(3); N(2)–C(9A)–C(10)–N(3), 176.1(2).

neighboring molecules through N–H···N and N–H···O intermolecular hydrogen bonds (N(1)···N(4a), 3.153(7) Å; N(3a)···O(2), 2.902(5) Å), forming a seven-membered intermolecularly hydrogen-bonded ring (Fig. 2). Furthermore, the ferrocene moieties arrange in a herringbone motif, and the dipeptide moieties are assembled to form the columns. The formation of the intermolecular hydrogen bonds requires rotation of the peptide chain, resulting in the observed torsion angles (ψ_1: N(1)–C(7A)–C(8)–N(2) = 138.7(4), ψ_2: N(2)–C(9A)–C(10)–N(3) = 176.1(2)). Such a hydrogen-bonded network in an antiparallel manner was not observed in the case of the ferrocene bearing dipeptide chain (-L-Ala-L-Pro-OEt) [6b]. Thus, the appended pyridyl amide moiety plays an important role in self-organization through participation in hydrogen bondings.

Since the ferrocene **1** is envisaged to serve as a monodentate ligand, complexation behavior of **1** was investigated. Treatment of **1** with $PdCl_2(MeCN)_2$ afforded the 2:1 *trans*-complex **2** (Scheme 1). The structure of the isolated complex was elucidated by spectral data. The *trans* conformation was confirmed by far infra-red Pd–Cl stretching band at 353 cm^{-1} (Nujol). The down-field shift of pyridyl ring protons in ^{1}H-NMR supports the coordination of pyridyl nitrogen atom to palladium. Molecular dynamics in solution was studied by variable temperature ^{1}H-NMR spectroscopy



Scheme 1.

of the palladium complex **2**. Lowering the temperature led to the separated resonances of the pyridyl protons. This result indicates a rotational barrier of the pyridyl groups about palladium. *Ortho* substitution on the pyridyl ring is supposed to be referred to the rotation isomerism. The rotational barrier E_a for the isomerism was calculated as 10.1 kcal mol^{-1} from the Arrhenius equation. Two dipeptide strands of the palladium complex **2** could rotate with respect to each other about the palladium center by the ball bearing motion of two pyridyl rings.

The electrochemical properties of **2** were studied by cyclic voltammetry. A reversible oxidation wave of the ferrocenyl moiety was observed at $E_{1/2}$ value of 0.16 V versus Fc/Fc^+ as an internal standard. The palladium complex **2** showed a slightly cathodic shift of 20 mV in comparison with the uncomplexed ferrocene **1** ($E_{1/2}$ = 0.18 V), indicating a cathodic perturbation of the ferrocene redox couple by the complexation.

In conclusion, the ferrocene **1** bearing dipeptide chain (-L-Ala-L-Pro-NHPy) was demonstrated to create a highly organized assembly through the intermolecular hydrogen-bonded network in an antiparallel manner. The appended pyridyl moiety was found to be capable of participating in hydrogen bonding and binding to metal salt. Ferrocenyl two dipeptide strands of the palladium complex **2** could rotate with respect to each other about the palladium center by the ball bearing motion of two pyridyl rings. Transition metal complexes with amino acids and peptides are of importance from the view point of bioorganometallic chemistry [7]. Further investigation including redox and receptor chemistry is now in progress.

3. Experimental

All reagents and solvents were purchased from commercial sources and purified by the standard methods, if necessary. (Chlorocarbonyl)ferrocene was prepared by the standard procedure from ferrocenecarboxylic acid and oxalyl chloride. H-L-Ala-L-Pro-NHPy was prepared with normal method by coupling of Boc-L-Ala-L-Pro-OH with 2-aminopyridine using EDCI, followed by removal of the *t*-butyloxycarbonyl protective group.

*3.1. Synthesis of the ferrocene **1** bearing dipeptide chain (-L-Ala-L-Pro-NHPy)*

To a stirred solution of H-L-Ala-L-Pro-NHPy (65.6 mg, 0.25 mmol) and triethylamine (139 μl, 1.0 mmol) in dichloromethane (5 ml), (chlorocarbonyl)ferrocene (62.1 mg, 0.25 mmol) in dichloromethane (5 ml) was dropwise added under argon at 0 °C. The mixture was stirred at 0 °C for 1 h and then at room temperature

(r.t.) 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, using $CHCl_3$ as an eluent). The ferrocene **1** was isolated in 73% yield by recrystallization from toluene. M.p. 205–206 °C (uncorrected); IR (CH_2Cl_2 (2.0×10^{-2} M), cm^{-1}): 3410, 1701, 1635; ^{1}H-NMR (400 MHz, $CDCl_3$ (1.0×10^{-2} M)): δ 9.25 (s, 1H), 8.31 (dd, 1H, $J = 4.8$, 1.8 Hz), 8.16 (d, 1H, $J = 8.3$ Hz), 7.68 (ddd, 1H, $J = 8.3$, 7.4, 1.8 Hz), 7.03 (dd, 1H, $J = 7.4$, 4.9 Hz), 6.63 (d, 1H, $J = 7.8$ Hz), 5.00–4.93 (m, 1H), 4.80–4.78 (m, 1H), 4.71–4.69 (m, 2H), 4.36–4.35 (m, 2H), 4.22 (s, 5H), 3.84–3.78 (m, 1H), 3.71–3.65 (m, 1H), 2.49–2.43 (m, 1H), 2.24–2.00 (m, 3H), 1.49 (d, 3H, $J = 6.8$ Hz); MS (FAB) m/z 474 [M^+]; Anal. Calc. for $C_{24}H_{26}N_4O_3Fe \cdot H_2O$: C, 58.55; H, 5.73; N, 11.38. Found: C, 58.74; H, 5.46; N, 11.38%.

3.2. Preparation of the palladium complex **2**

A solution of **1** (23.7 mg, 0.050 mmol) and $PdCl_2(MeCN)_2$ (6.5 mg, 0.025 mmol) was stirred in acetonitrile (3.0 ml) under argon at r.t. for 10 min. Most of the solvent was evaporated under vacuum. Addition of hexane to the solution afforded the complex **2** in 96% yield. M.p. 172–174 °C (decomp.); IR (CH_2Cl_2 (1.0×10^{-2} M), cm^{-1}): 3421, 3313, 1716, 1651 cm^{-1}; ^{1}H-NMR (400 MHz, CD_2Cl_2 (1.0×10^{-2} M)): δ 11.11 (s, 2H), 9.13 (dd, 2H, $J = 4.9$, 1.8 Hz), 8.23 (d, 2H, $J = 8.4$ Hz), 7.73 (ddd, 2H, $J = 8.4$, 7.2, 1.8 Hz), 6.94 (dd, 2H, $J = 7.2$, 4.9 Hz), 6.80 (d, 2H, $J = 7.3$ Hz), 5.05–5.02 (m, 2H), 5.01–4.93 (m, 2H), 4.76 (br s, 2H), 4.53 (br s, 2H), 4.35 (br s, 2H), 4.26 (br s, 2H), 4.19 (s, 10H), 3.87–3.81 (m, 2H), 3.76–3.71 (m, 2H), 2.47–2.42 (m, 2H), 2.27–2.06 (m, 6H), 1.46 (d, 6H, $J = 7.0$ Hz); MS (FAB) m/z 1126 [M^+]; Anal. Calc. For $C_{48}H_{52}N_8O_6Fe_2PdCl_2 \cdot H_2O$: C, 50.39; H, 4.76; N, 9.79. Found: C, 50.36; H, 4.75; N, 9.70%.

3.3. X-ray structure analysis

The measurement was made on a Rigaku AFC5R diffractometer with graphite-monochromated Mo–K_α radiation and a rotating anode generator. The data were collected at a temperature of 23 ± 1 °C using the ω–2θ scan technique to a maximum 2θ value of 55.0°. The structure of **1** was solved by heavy-atom Patterson methods and expanded using Fourier techniques. 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.

4. Supplementary material

Crystallographic data (excluding structure factors) for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 154487 for compound **1**. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1233-336-033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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