A highly ordered ferrocene system regulated by podand peptide chains

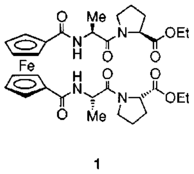
Akihiro Nomoto, Toshiyuki Moriuchi, Shuhei Yamazaki, Akiya Ogawa and Toshikazu Hirao*†

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Yamada-oka, Suita, Osaka 565-0871, Japan

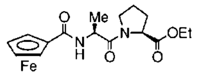
The ferrocene bearing the podand dipeptide chains, Ala-Pro-OEt, which are aligned parallel in solution by the two rigid intramolecular hydrogen bonds, manifests a novel helically ordered arrangement with one turn of 14.70 Å pitch height in the crystal packing possibly due to the intramolecular hydrogen bonds (the N–H···O=C distance is 2.06 Å) and the hydrophobic interaction of the podand dipeptide chains (the distance between the nearest ferrocene units is 4.54 Å).

Architectural control of molecular assemblies utilizing specific interactions as observed in biological systems is considered to be one of the most convenient approaches to highly ordered supramolecular systems, most of which are expected to exhibit novel functions.[1] In particular, hydrogen bonding has been exploited for the elaboration of regulated supramolecules such as dendrimers[2] and artificial peptides.[3] Crystal engineering has also contributed to a key technique for this purpose.[4] The incorporation of transition metal complexes into such highly structured biomolecules is envisioned to provide new biomaterials and efficient redox systems.[5] Ferrocenes, which possess a reversible redox couple and rotatory cyclopentadienyl moieties, have been regarded as useful organometallic scaffolds for molecular receptors[6] and peptide mimetic models.[7] We have already focused on such properties to demonstrate a unique coordination behavior of the ferrocenes bearing podand *N*-heterocyclic pendant groups.[8] Our system design described here is addressed by an efficient communication of podand peptide chains both intramolecularly and intermolecularly to order the redox-active ferrocene system.

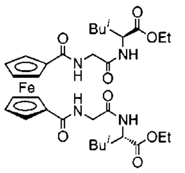
A chiral dipeptide, L-alanyl-L-proline, which is considered to consist of a hydrogen bonding site (Ala) and a hydrophobic moiety (Pro), is incorporated into a redox-active ferrocene scaffold.‡ Ferrocene derivatives **1** and **2** bearing two and one Ala-Pro-OEt chains, respectively, exhibited a reversible oxidation/reduction wave attributable to the Fe(III)/Fe(II) couple at 740 mV and 567 mV *vs.* SCE, respectively, which are indicative of the electron-withdrawing amide function.



1



2



3

X-Ray crystallography studies revealed several interesting structural features. The X-ray crystal structure of **1**§ is depicted in Fig. 1. Surprisingly, the two dipeptide chains of **1**, which have C_2 symmetry, are oriented in the same direction despite the free rotary cyclopentadienyl rings and sterically bulky proline moieites. This structure is considered to be stabilized by two C_2-symmetrical intramolecular hydrogen bonds between CO (Ala) and NH (another Ala) of each podand peptide chain. The N–H···O=C distance of the hydrogen bonds is 2.06 Å. Intermolecular hydrogen bonding was not observed even in the molecular packing. In contrast to the structure of **1**, each molecule of **2**¶ is connected by an intermolecular hydrogen-bonding network, in which the peptide chain is not arranged parallel to the chain of the next molecule. It is also noteworthy that the *β*-angle of **2** (defined as the angle between the plane of the cyclopentadienyl ring and C(ipso)–CO(bridging) bond) is 24.6° or 23.3°. This value is unexpectedly large compared with those of **1** (5.6°), probably due to the intermolecular hydrogen bonding. The conjugation between the cyclopentadienyl ring and carbonyl group of **2** is disturbed to some extent.

A striking feature is that **1** is found to be packed in a helical molecular arrangement with one turn of 14.70 Å pitch height [Fig. 1(b)], within which the distance between the closest ferrocene units is 4.54 Å. The proline rings and ethyl groups individually form the hydrophobic cores, which are considered to be one of the factors that control the crystal packing and permit the helical assembly. Such an assembly was not observed in the crystal structure of ferrocene **3**|| bearing podand glycyl-L-leucine chains although the isobutyl group is expected to form

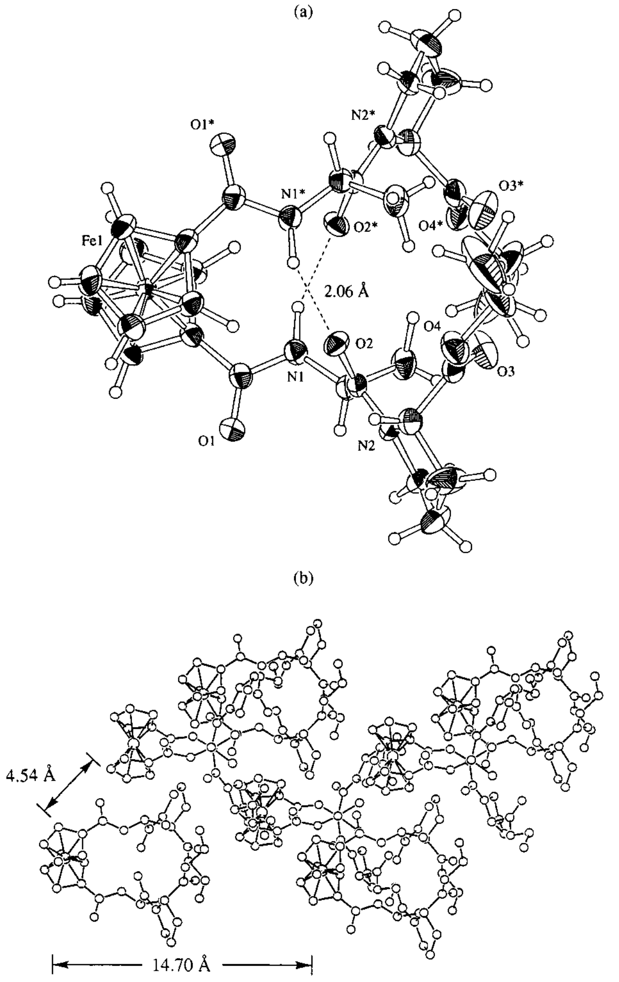


Fig. 1 (a) X-Ray crystal structure of ferrocene **1**. The hydrogen bonds are shown as dotted lines. (b) Crystal packing of ferrocene **1**.

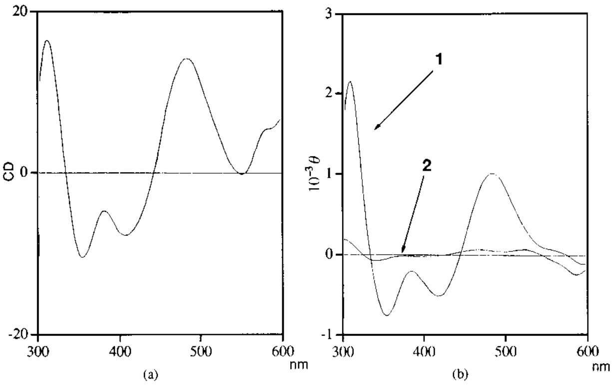


Fig. 2 (a) CD spectrum of ferrocene **1** in the solid state (KBr pellet) and (b) CD spectra of ferrocenes **1** and **2** in CH_3CN (5.0×10^{-4} M)

a hydrophobic core. A helical molecular arrangement is only characteristic of **1**.

The CD spectrum of **1** in the solid state (KBr pellet) showed Cotton effects corresponding to the absorbances of the ferrocene moiety in the UV–VIS spectrum [Fig. 2(a)]. The Cotton effects seem to be caused by the reflection of chirality of the regulated podand peptide chains possessing two rigid intramolecular hydrogen bonds. Furthermore, a similar CD spectrum for **1** was obtained in acetonitrile [Fig. 2(b)] in sharp contrast with the finding that such effects were not observed with **2** in both solid and solution states. This result suggests that the podand peptide chains of **1** are also regulated even in solution by the intramolecular hydrogen bonds.

The ^{1}H NMR spectrum of **1** exhibited only one kind of NH peak at lower field (δ = 8.95, 5.0 mM) as compared with **2** (δ = 6.58, 10.0 mM). These results indicate that the intramolecular hydrogen bonds of **1** are identical in CD_2Cl_2 solution.^{7b} Such bonding is also confirmed by the IR spectrum (CH_2Cl_2, $\nu_{\text{N–H}}$ **1**: 3301 cm^{-1}; **2** 3418 cm^{-1}).^{7b}

The oxidation of **1** to a ferrocenium species **1**$^+$ was achieved with CAN [cerium(IV) diammonium nitrate] to show the broad absorption around 657 nm in the UV–VIS spectrum. Interestingly, the Cotton effects were observed even in the CD spectrum of **1**$^+$. A similar oxidative transformation was performed electrochemically, and monitored by *in situ* CD measurement at 1.2 V *vs.* SCE. The Cotton effects of the above-mentioned ferrocenium species are independent of the presence of CAN. These results suggest that the rigid structure of **1** is maintained even in the oxidized form, presumably by the intramolecular hydrogen bonding.

In conclusion, we have designed and synthesized the novel peptide **1** containing a ferrocene unit, in which the podand dipeptide chains (Ala-Pro-OEt) are regulated in both solid and solution states by the two rigid intramolecular hydrogen bonds. Also, a novel helically ordered arrangement is achieved in the crystal packing, where the proline rings and ethyl groups individually form the hydrophobic cores. The present system is likely to be related to helical electron hopping. Studies on the effects of peptide chains and redox-switching properties are now in progress to disclose the scope of an ordered system based on peptide interactions.

This work was financially supported in part by a Grant-in-Aid for Exploratory Research from the Ministry of Education, Science and Culture, Japan and the Shorai Foundation for Science and Technology.

Notes and References

† E-mail: hirao@chem.eng.osaka-u.ac.jp

‡ Typical procedure for the synthesis of **1**. To a stirred mixture of 1,1′-ferrocenedicarboxylic acid chloride (0.10 mmol) and H-Ala-Pro-OEt·HCl (0.22 mmol) in dichloromethane (2 mL) was dropwise added triethylamine (0.50 mmol) under argon at 0 °C. After stirring at room temperature for 1 h, water (20 mL) was added to the mixture. Extraction with dichloromethane (3 × 10 mL) followed by evaporation gave the crude ferrocene **1**. Chromatography on an alumina column eluting with dichloromethane and recrystallization from dichloromethane afforded an orange solid in 58% yield. **1**: IR (KBr) 3315, 2991, 1740, 1632, 1544, 1434, 1372, 1336, 1292, 1186, 1026 cm^{-1}; IR (CH_2Cl_2, 1.0 mM) 3301 (N–H) cm^{-1}; ^{1}H NMR (600 MHz, CD_2Cl_2) δ 8.77 (d, 2H, J = 7.6 Hz), 4.85–4.78 (m, 6H), 4.59 (dd, 2H, J = 4.6, 4.3 Hz), 4.45–4.44 (m, 2H), 4.27–4.26 (m, 2H), 4.14–4.05 (m, 4H), 3.89–3.85 (m, 2H), 3.69–3.66 (m, 2H), 2.33–2.27 (m, 2H), 2.12–2.07 (m, 4H), 2.01–1.96 (m, 2H), 1.32 (d, 6H, J = 7.3 Hz), 1.26 (q, 6H, J = 7.0 Hz). **2**: IR (KBr) 3312, 2982, 1743, 1652, 1626, 1535, 1436, 1298, 1183 cm^{-1}; IR (CH_2Cl_2, 1.0 mM) 3418 (N–H) cm^{-1}; ^{1}H NMR (600 MHz, CD_2Cl_2) δ 6.60 (d, 1H, J = 6.9 Hz), 4.83 (quint. 1H, J = 6.9 Hz), 4.69–4.63 (m, 2H), 4.47 (dd, 1H, J = 8.6, 8.2 Hz), 4.35–4.33 (m, 2H), 4.21–4.10 (m, 7H), 3.77–3.73 (m, 1H), 3.66–3.62 (m, 1H), 2.27–2.22 (m, 1H), 2.12–1.94 (m, 3H), 1.42 (d, 3H, J = 6.9 Hz), 1.26 (t, 3H, J = 7.2 Hz). **3**: IR (KBr) 3283, 2959, 1745, 1634, 1552, 1454, 1371, 1304, 1197, 1028 cm^{-1}; IR (CH_2Cl_2, 1.0 mM) 3415, 3320 (N–H) cm^{-1}; ^{1}H NMR (600 MHz, CD_2Cl_2) δ 8.49 (t, 2H, J = 6.1 Hz), 6.48 (d, 2H, J = 10.8 Hz), 4.81–4.79 (m, 4H), 4.63–4.59 (m, 2H), 4.43–4.39 (m, 4H), 4.19 (q, 4H, J = 6.6 Hz), 3.95 (dd, 2H, J = 16.2, 6.1 Hz), 3.87 (dd, 2H, J = 16.2, 6.1 Hz), 1.74–1.57 (m, 6H), 1.28 (t, 6H, J = 6.6 Hz), 1.02–0.97 (m, 12H).

§ *Crystal data* for **1**: $C_{32}H_{42}N_4O_8Fe$, M = 666.55, tetragonal, space group $I4_1$, a = 14.978(4), c = 14.699(7) Å, V = 3297(1) Å^3, Z = 4, T = 23.0 °C, D_{calc} = 1.343 g cm^{-3}, μ(Mo-Kα) = 5.12 cm^{-1}, R = 0.048, R_w = 0.048 for 1975 independent observed reflections ($2\theta_{\text{max}}$ = 55.0°).

¶ *Crystal data* for **2**: $C_{21}H_{26}N_2O_4Fe$, M = 426.29, orthorhombic, space group $P2_12_12_1$, a = 17.834(3), b = 18.012(2), c = 12.623(2) Å, V = 4054.8(8) Å^3, Z = 8, T = 23.0 °C, D_{calc} = 1.397 g cm^{-3}, μ(Mo-Kα) = 7.72 cm^{-1}, R = 0.058, R_w = 0.056 for 5222 observed reflections ($2\theta_{\text{max}}$ = 55.1°).

‖ *Crystal data* for **3**: $C_{32}H_{46}N_4O_8Fe$, M = 670.58, triclinic, space group $P1$, a = 9.294(1), b = 11.783(1), c = 8.924(1) Å, α = 98.65(1), β = 116.481(9), γ = 81.41(1)°, V = 861.0(2) Å^3, Z = 1, T = 23.0 °C, D_{calc} = 1.293 g cm^{-3}, μ(Mo-Kα) = 4.90 cm^{-1}, R = 0.045, R_w = 0.040 for 3991 independent observed reflections ($2\theta_{\text{max}}$ = 55.1°). CCDC 182/965.

1 M. Engels, D. Bashford and M. R. Ghadiri, *J. Am. Chem. Soc.*, 1995, **117**, 9151; H. Mihara, Y. Haruta, S. Sakamoto, N. Nishino and H. Aoyagi, *Chem. Lett.*, 1996, 1; C. A. Mirkin, R. L. Letsinger, R. C. Mucic and J. J. Storhoff, *Nature*, 1996, **382**, 607; A. P. Alivisatos, K. P. Johnsson, X. Peng, T. E. Wilson, C. J. Loweth, M. P. Bruchez Jr. and P. G. Schultz, *Nature*, 1996, **382**, 609.

2 W. T. S. Huck, R. Hulst, P. Timmerman, F. C. J. M. van Veggel and D. N. Reinhoudt, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1006.

3 J. P. Schneider and J. W. Kelly, *Chem. Rev.*, 1995, **95**, 2169; J. S. Nowick, E. M. Smith and M. Pairish, *Chem. Soc. Rev.*, 1996, **25**, 401; D. A. Leigh, A. Murphy, J. P. Smart and A. M. Z. Slawin, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 728.

4 A. D. Burrows, C.-W. Chan, M. M. Chowdhry, J. E. McGrady and D. M. P. Mingos, *Chem. Soc. Rev.*, 1995, **24**, 329; F. D. Lewis, J.-S. Yang and C. L. Stern, *J. Am. Chem. Soc.*, 1996, **118**, 12029.

5 D. G. McCafferty, B. M. Bishop, C. G. Wall, S. G. Hughes, S. L. Mecklenberg, T. J. Meyer and B. W. Erickson, *Tetrahedron*, 1995, **51**, 1093; R. C. Mucic, M. K. Herrlein, C. A. Mirkin and R. L. Letsinger, *Chem. Commun.*, 1996, 555; A. B. Gretchikhine and M. Y. Ogawa, *J. Am. Chem. Soc.*, 1996, **118**, 1543; P. J. Dandliker, R. E. Holmlin and J. K. Barton, *Science*, 1997, **275**, 1465; P. A. Arnold, W. R. Shelton and D. R. Benson, *J. Am. Chem. Soc.*, 1997, **119**, 3181.

6 J. C. Medina, T. T. Goodnow, M. T. Rojas, J. L. Atwood, B. C. Lynn, A. E. Kaifer and G. W. Gokel, *J. Am. Chem. Soc.*, 1992, **114**, 10583; P. D. Beer, *Chem. Commun.*, 1996, 689.

7 (*a*) H. Eckert and C. Seidel, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 159; (*b*) R. S. Herrick, R. M. Jarret, T. P. Curran, D. R. Dragoli, M. B. Flaherty, S. E. Lindyberg, R. A. Slate and L. C. Thornton, *Tetrahedron Lett.*, 1996, **37**, 5289; (*c*) M. Kira, T. Matsubara, H. Shinohara and M. Sisido, *Chem. Lett.*, 1997, 89.

8 T. Moriuchi, I. Ikeda and T. Hirao, *Inorg. Chim. Acta*, 1996, **248**, 129; T. Moriuchi, I. Ikeda and T. Hirao, *J. Organomet. Chem.*, 1996, **514**, 153.

Received in Columbia, MO, USA, 13th November 1997; revised manuscript received 13th July 1998; 8/05780J