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# Chirality-Organized Ferrocene Receptor Bearing Podand Dipeptide Chains (–L-Ala-L-Pro-NHPyMe) for the Selective Recognition of Dicarboxylic Acids

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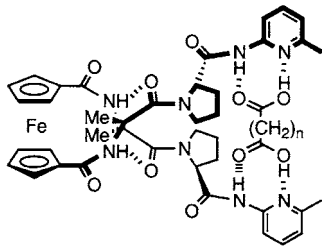
## ABSTRACT




**The ferrocene receptor bearing the podand dipeptide chains (–L-Ala-L-Pro-NHPyMe) was found to provide a chirality-organized binding site through two intramolecular interchain hydrogen bonds between CO (Ala) and NH (another Ala) of each podand dipeptide chain. The size-selective and chiral recognition of dicarboxylic acids was achieved by multipoint hydrogen bonds of the binding site.**

Organization of host molecules by self-assembly is a useful strategy for forming active receptors.[1] Metal-templated organization has been exploited to provide oriented binding sites, resulting in the construction of artificial receptors for selective recognition.[2] Architectural control of self-assembly utilizing hydrogen bonding of amino acids as observed in proteins, which are organized into well-defined three-dimensional structures, is considered to be a convenient approach to desired molecular receptors. On the other hand, ferrocenes are recognized as an organometallic scaffold for molecular receptors based on redox properties and two rotatory coplanar cyclopentadienyl (Cp) rings with ca. 3.3 Å separation.[3] Ferrocenylboronic acid[4] and α-ferrocenylalkylamine[5] derivatives have been reported as chiral redox-active receptors. In a previous paper, the introduction of podand dipeptide chains into a ferrocene was reported to induce chirality organization through intramolecular interchain hydrogen bonds.[6] This finding prompted us to investigate the potential use of the organized structure as a receptor. We herein report the selective recognition of dicarboxylic acids through multipoint hydrogen bonds of the

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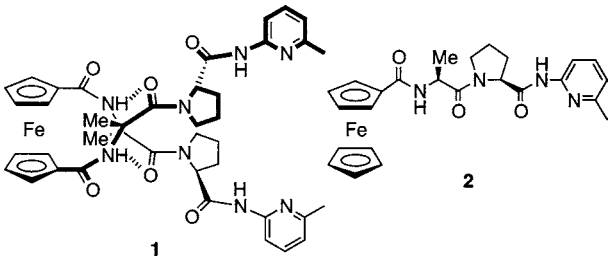


**Figure 1.** Ferrocenes **1** and **2** bearing the dipeptide chains.

chirality-organized ferrocene receptor **1** bearing the podand dipeptide chains (−L-Ala-L-Pro-NHPyMe).

The ferrocene receptor **1** was designed to incorporate L-alanyl-L-proline as a dipeptide capable of hydrogen bonding and imposing a conformational constraint on the peptide backbone. Ferrocene **1** was synthesized from H-L-Ala-L-Pro-NHPyMe and 1,1′-bis(chlorocarbonyl)ferrocene as shown in Figure 1.[7] The single-crystal X-ray structure determination of **1** confirmed the two intramolecular hydrogen bonds between CO (Ala) and NH (another Ala) of each podand dipeptide chain (N(1)···O(2*), 2.918 Å; N(1*)···O(2), 3.010 Å) to induce the chirality organization through an intramolecular conformational regulation (Figure 2).[8] The additional

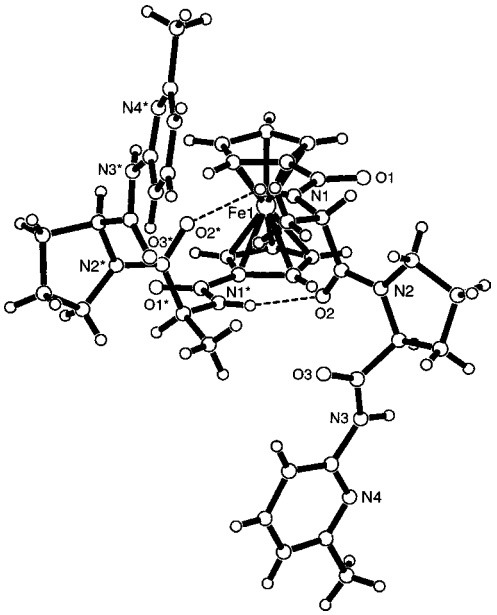


**Figure 2.** Molecular structure of **1**.

NH adjacent to the pyridyl moiety of **1** participates in the intermolecular hydrogen bonding with CO adjacent to the ferrocene unit of the neighboring molecule instead of intramolecular hydrogen bonding (Figure S1, Supporting Information).

A chirality-organized structure in solution was investigated by circular dichroism (CD) spectrometry. Ferrocene **1** exhibited an induced CD around the absorbance of the ferrocene function, although such induced CD was not observed in the case of ferrocene **2** bearing only one dipeptide chain (−L-Ala-L-Pro-NHPyMe) (Figure 3). These results suggest that the chirality organization through intramolecular hydrogen bonds is maintained even in $CH_2Cl_2$. In the $^1$H NMR spectrum of **1** in $CDCl_3$ ($5.0 \times 10^{-3}$ M), only one kind of Ala N−H resonance was detected at a lower field (8.84 ppm) than that of **2** ($1.0 \times 10^{-2}$ M, 6.69 ppm). The FT-IR spectrum of **1** in $CH_2Cl_2$ ($1.0 \times 10^{-3}$ M) showed the 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 formed in the solution. Variable-temperature $^1$H NMR studies of **1** ($5.0 \times 10^{-3}$ M in $CDCl_3$ between 223 and 323 K) showed $\Delta\delta/\Delta T$ values of Ala N−H of −3.4 ppb/K. This result supports a strong hydrogen bonding for **1**. A large downfield shift of the additional N−H resonance adjacent to the pyridyl moiety of **1** was observed by the addition of aliquots of DMSO-$d_6$ to $CDCl_3$ ($5.0 \times 10^{-3}$ M; $CDCl_3$, 8.78 ppm; $CDCl_3$/DMSO-$d_6$ (9:1), 9.62 ppm), although the Ala N−H resonance of **1** was not perturbed ($CDCl_3$, 8.84 ppm; $CDCl_3$/DMSO-$d_6$ (9:1), 8.96 ppm). These findings indicate that the additional NH adjacent to the pyridyl moiety is not hydrogen bonded in solution. The N−H stretching band at 3399 cm$^{-1}$ in the FT-IR spectrum of **1** in $CH_2Cl_2$ ($1.0 \times 10^{-3}$ M) also supports the non-hydrogen bonded N−H. The NH adjacent to the

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(7) Selected data are as follows**. Compound 1:** mp 148−150 °C (uncorrected); IR ($CH_2Cl_2$, $1.0 \times 10^{-3}$ M) 3399, 3307, 1697, 1634 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$, $5.0 \times 10^{-3}$ M) $\delta$ 8.84 (d, 2H, $J$ = 7.2 Hz), 8.78 (s, 2H), 7.91 (d, 2H, $J$ = 8.4 Hz), 7.55 (dd, 2H, $J$ = 8.4, 7.5 Hz), 6.87 (d, 2H, $J$ = 7.5 Hz), 4.90−4.88 (m, 4H), 4.86−4.74 (m, 4H), 4.54−4.52 (m, 2H), 4.31−4.29 (m, 2H), 3.99−3.91 (m, 2H), 3.71−3.66 (m, 2H), 2.45−2.11 (m, 14H), 1.33 (d, 6H, $J$ = 7.2 Hz); FAB-MS $m/z$ 791 ($M^+ + 1$). Anal. Calcd for $C_{40}H_{46}N_8O_6Fe\cdot H_2O$: C, 59.41; H, 5.98; N, 13.86. Found: C, 59.07; H, 5.64; N, 13.47. **Compound 2:** mp 95−97 °C (uncorrected); IR ($CH_2Cl_2$, $2.0 \times 10^{-3}$ M) 3411, 1701, 1636 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$, $1.0 \times 10^{-2}$ M) $\delta$ 8.86 (s, 1H), 7.96 (d, 1H, $J$ = 8.1 Hz), 7.57 (dd, 1H, $J$ = 8.1, 7.2 Hz), 6.89 (d, 1H, $J$ = 7.2 Hz), 6.69 (d, 1H, $J$ = 7.5 Hz), 4.99−4.90 (m, 1H), 4.74−4.69 (m, 3H), 4.35−4.34 (m, 2H), 4.22 (s, 5H), 3.87−3.79 (m, 1H), 3.74−3.67 (m, 1H), 2.45 (s, 3H), 2.38−2.32 (m, 1H), 2.24−2.06 (m, 3H), 1.50 (d, 3H, $J$ = 6.6 Hz); FAB-MS $m/z$ 489 ($M^+ + 1$). Anal. Calcd for $C_{25}H_{28}N_4O_3Fe\cdot H_2O$: C, 59.30; H, 5.97; N, 11.06. Found: C, 58.93; H, 6.08; N, 10.67.

(8) Crystal data for **1**: $C_{40}H_{46}N_8O_6Fe\cdot CHCl_3$, fw = 910.08, orthorhombic, space group $P2_12_12_1$ (No. 19), $a$ = 12.0206(3) Å, $b$ = 37.225(1) Å, $c$ = 10.9413(3) Å, $V$ = 4895.8(2) Å$^3$, $Z$ = 4, $D_{calcd}$ = 1.235 g/cm$^3$, $R$ = 0.088, $R_w$ = 0.243.

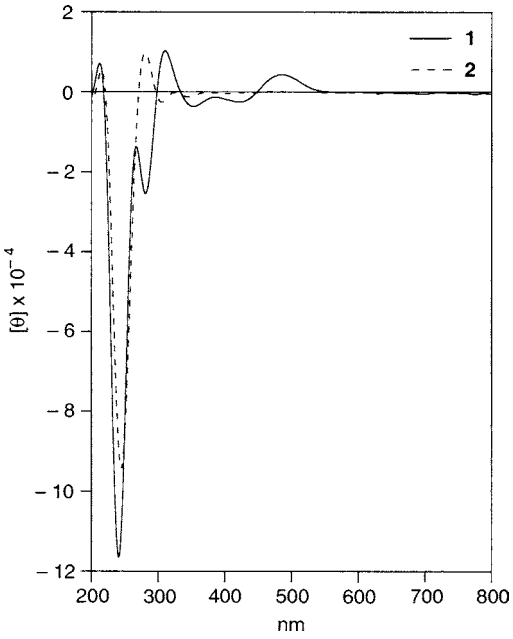


**Figure 3.** CD spectra of **1** and **2** in $CH_2Cl_2$ ($1.0 \times 10^{-4}$ M).

pyridyl moiety is expected for hydrogen bonding with dicarboxylic acids.

In the ferrocene receptor **1**, the two amido pyridyl moieties as hydrogen bonding sites are well arranged for dicarboxylic acids by chirality organization through two intramolecular hydrogen bonds. Initially, the dicarboxylic acid binding properties of **1** were investigated using $^1$H NMR spectroscopy and association constants were measured for dicarboxylic acids **3** possessing various chain lengths (Scheme 1 and Table 1). $^1$H NMR studies in $CDCl_3$/acetone-$d_6$ (5:1) revealed a considerable downfield shift of the pyridine amide protons

**Scheme 1**

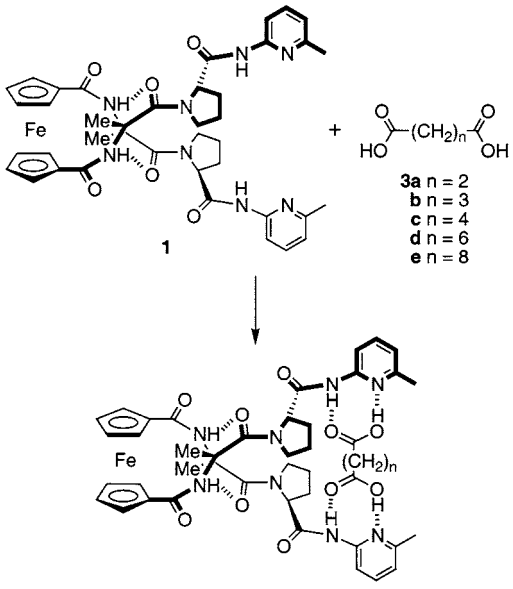


**Table 1.** $K_a$ Values of **1**

| guest | $K_a$ [M$^{-1}$][a] |
|---|---|
| succinic acid ($n = 2$) **3a** | $2.8 \times 10^2$ |
| glutaric acid ($n = 3$) **3b** | $3.7 \times 10^3$ |
| adipic acid ($n = 4$) **3c** | $2.1 \times 10^4$ |
| suberic acid ($n = 6$) **3d** | $7.7 \times 10^3$ |
| sebacic acid ($n = 8$) **3e** | $5.9 \times 10^3$ |
| benzoyl-L-glutamic acid **3f** | $5.5 \times 10^3$ |
| benzoyl-D-glutamic acid **3g** | $3.7 \times 10^2$ |

[a] $K_a$ = association constants. Values were determined by $^1$H NMR titration ($CDCl_3$/acetone-$d_6$ (5:1)).

of **1** ($\Delta\delta$ 1.04 ppm) upon addition of 1 molar equiv of **3c**, suggesting that amido pyridyl moieties serve as binding sites for the dicarboxylic acid. The dicarboxylic acid−receptor stoichiometry was confirmed to be 1:1 by Job plots. Titration of **1** in $CDCl_3$/acetone-$d_6$ (5:1) with a series of dicarboxylic acids **3** showed appreciable association constants. It should be noted that a higher association constant for adipic acid (**3c**, $K_a = 2.1 \times 10^4$ M$^{-1}$) was observed as compared with succinic acid (**3a**, $K_a = 2.8 \times 10^2$ M$^{-1}$) and glutaric acid (**3b**, $K_a = 3.7 \times 10^3$ M$^{-1}$). This difference can probably be attributed to the complementary size of the binding space of **1** for adipic acid. Furthermore, suberic acd (**3d**, $K_a = 7.7 \times 10^3$ M$^{-1}$) and sebacic acid (**3e**, $K_a = 5.9 \times 10^3$ M$^{-1}$) with longer chain lengths exhibited a smaller constant. Since an induced CD around the absorbance of the ferrocene function of **1** hardly changed upon addition of 5 molar equiv of **3c**, the chirality organization through two intramolecular hydrogen bonds seems to be maintained in the recognition process to afford a rigid binding site for the selective recognition.

To evaluate the chiral recognition ability of **1**, the chiral discrimination properties of **1** were examined with biologically important glutamic acids. It is noteworthy that benzoyl-L-glutamic acid (**3f**, $K_a = 5.5 \times 10^3$ M$^{-1}$) is bound approximately 15 times more tightly to **1** than benzoyl-D-glutamic acid (**3g**, $K_a = 3.7 \times 10^2$ M$^{-1}$). The chirality-organized binding site of **1** is capable of discriminating the chirality of guest molecules.

In conclusion, ferrocene **1** bearing the podand dipeptide chains (−L-Ala-L-Pro-NHPyMe), which is conformationally regulated by two intramolecular hydrogen bonds between CO (Ala) and NH (another Ala) of each podand dipeptide chain, was demonstrated to provide the chirality-organized binding site for size-selective recognition of dicarboxylic acids. The chirality-organized binding site permitted **1** to behave as a receptor, differentiating guest molecules on the basis of chirality. Studies on the application of chirality organization of ferrocenes bearing podand dipeptide chains to chiral recognition and asymmetric reaction are now in progress.

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**Supporting Information Available:** Text giving experimental details for the synthesis and characterization of ferrocenes **1** and **2**, tables of X-ray crystallographic data for **1**, and a packing diagram of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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