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手性二茂铁色氨酸化合物[Fc-(CO-*L*-Trp-OMe)$_2$]的合成和结构表征

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摘要:由色氨酸甲酯和 1,1′-二茂铁二羧酸合成了化合物 **1**[Fc-(CO-*L*-Trp-OMe)$_2$],并对化合物 **1** 在固体和溶液中的结构进行了表征。单晶结构表明,该化合物通过 2 个分子内氢键,形成了规则的手性构象。通过分子间的氢键,形成了二维网状结构。对化合物 **1** 的乙腈溶液进行了 CD 谱的测定,结果表明,该化合物在溶液中呈现 P 螺旋构象。^{1}H NMR 谱和 FTIR 谱也证实了该化合物在固体和溶液状态中都形成了含分子内氢键的构象。

关键词:二茂铁氨基酸;分子内氢键;手性
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Synthesis and Structural Characterization of a Chirality Organization of Ferrocenoyl Peptide [Fc-(CO-*L*-Trp-OMe)$_2$]

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Abstract: The disubstituted ferrocenoyl peptide **1** [Fc-(CO-*L*-Trp-OMe)$_2$] was prepared from ferrocenedicarboxylic acid (Fc(OH)$_2$) and tryptophan methyl ester. The structure of **1** was studied in the solid state and in solution. The single-crystal structure shows that **1** displays a 1,2′-conformation and two intramolecular hydrogen bondings between CO (Trp) and NH (another Trp) of each peptide chain induce the chirality-organized structure. Additional intermolecular H-bonding in **1** allows the formation of a 2D net. CD spectra were recorded for **1** in MeCN. It clearly shows a *P*-helical arrangement of the ferrocene moiety. ^{1}H NMR spectroscopy in $CDCl_3$ and FTIR spectroscopy in KBr also conform the ordered, intramolecular hydrogen bonded conformation in both solid and solution states. CCDC: 675521.

Key words: ferrocenoyl peptide; intramolecular hydrogen bond; chirality

0 Introduction

In re cent years, bioorganometallic chemistry of ferrocene has developed rapidly[1,2]. The stability of the ferrocenyl group, the large variety of derivatives, and its favorable electrochemical properties have made ferrocene and its derivatives very popular molecules for biological applications and for conjugation with biomolecules. As ferrocene and its derivatives play an important role in bioorganometallic chemistry, bioconjugates of ferrocene with amino acids and peptides, proteins, carbohydrates and others have been investigated extensively[3]. In particular, disubstituted ferrocenoyl peptides which give chemical models of hydrogen-bonding of peptide strands attracts much attention[4~8]. The advantages of using a disubstituted

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ferrocene backbone are that the inter-ring spacing of ferrocene is ca. 0.33 nm which is appropriate for hydrogen bonding of the attached peptide strands, the co-planarity of the cyclopentadienyl (Cp) rings reduces conformational possibilities, and the rotational capabilities of the ring provide a spectroscopic handle for the transition from random to ordered conformation[7]. Therefore, the utilization of ferrocene as a scaffold is considered to be one strategy to examine the hydrogen-bonding ability of peptide strands[9,10]. From this point of view, we introduced the peptide chains (-*L*-Trp-OMe) into ferrocene to expect an ordered structure based on two rigid intramolecular hydrogen bonds and a *P*-helical arrangement arrangement in the crystal packing. Herein, we report the synthesis, crystal structure and chirality of a disubstituted ferrocenoyl peptide [Fc-(CO-*L*-Trp-OMe)$_2$].

1 Experimental

1.1 General

All reagents and solvents were purchased from commercial sources and were further purified by the standard methods, if necessary. The compound (*L*-Trp-OMe) and 1,1′-bis(chlorocarbonyl)-ferrocene were prepared according to the method described in the literature[4,11]. IR spectra were recorded on a VACTOR 22 Bruker spectrophotometer with KBr pellets in the 4 000~400 cm^{-1} regions. ^{1}H NMR spectroscopic measurements were recorded on a Bruker AM-500 NMR spectrometer, using TMS ($SiMe_4$) as an internal reference at room temperature. The elemental analyses of C, H and N were performed on a Perkin-Elmer 2400 Ⅱ elemental analyzer.

1.2 Synthesis of compound 1

To a stirred mixture of the (*L*-Trp-OMe) (1.31 g, 6.0 mmol) and triethylamine (3.5 mL, 25 mmol) in dichloromethane (20 mL) was added 1,1′-bis(chlorocarbonyl)-ferrocene (3.0 mmol) in dichloromethane (30 mL) dropwise under argon at 0 ℃. The mixture was stirred at 0 °C for 1 h and then at room temperature for 8 h. The resulting mixture was diluted with dichloromethane, washed with saturated $NaHCO_3$ aqueous solution and brine, and then dried over anhydrous Na_2SO_4. The resulting solution was evaporated in vacuo to remove most solvent and yellow powder of compound **1** was filtered out and dried under vacuum. Yield: 75%; IR (KBr, cm^{-1}): 3 396(N-H), 1 727 (C=O), 1 637(C=O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.51 (s, 2H), 7.69(d, *J*=7.8 Hz, 2H), 7.65(d, *J*=7.8 Hz, 2H), 7.42(d, *J*=8.0 Hz, 2H), 7.25(s, 2H), 7.22(t, *J*=7.4 Hz, 2H), 7.16(t, *J*=7.5 Hz, 2H), 5.07(m, 2H), 4.64(d, *J*=19 Hz, 4H), 4.14 (d, *J*=11 Hz, 4H), 3.46 (m, 2H), 3.16(m, 2H), 1.66 (s, 6H). Anal. calc. for $C_{36}H_{34}eN_4O_6\cdot H_2O$: H 5.24, C 62.44, N 8.09. Found: H 5.0, C 62.3, N 8.2.

1.3 CD measurements

CD spectra were recorded using a JASCO J-810 spectropolarimeter in the deaerated acetonitrile solution with the concentration (1.0×10^{-4} mol·L^{-1}) under N_2 at 25 ℃.

1.4 X-ray structure analysis

Single-crystal X-ray diffraction data for compound **1** were collected on a Siemens SMART-CCD diffractometer with graphite-monochromatized Mo $K\alpha$ (λ = 0.071 073 nm) using the SMART and SAINT programs. The structures were solved by direct methods and refined on F^2 by full-matrix least-squares methods with SHELXTL version 5.1. All non-hydrogen atoms of compound **1** were refined anisotropically. Hydrogen atoms were localized in their calculation positions and refined by using the riding model. Crystallographic data were summarized in Table 1.

CCDC: 675521.

Table 1 Crystallographic data for compound 1

Formula	$C_{36}H_{36}FeN_4O_7$	*c* / nm	3.110 1(5)
Formula weight	692.54	*V* / nm^3	7.450 7(19)
Crystal color	Orange	*Z*	8
Crystal system	Orthorhombic	D_{calc} / (g·cm^{-3})	1.235
Space group	$P2_12_12_1$	Goodness of fit (F^2)	1.073
Temperature / K	291(2)	R_1[a]	0.061 4

Continued Table 1

a / nm	1.138 1(2)	wR_2[b]	0.125 9
b / nm	2.104 9(3)		

[a] $R_1=\sum||F_o|-|F_c||/\sum|F_o|$;

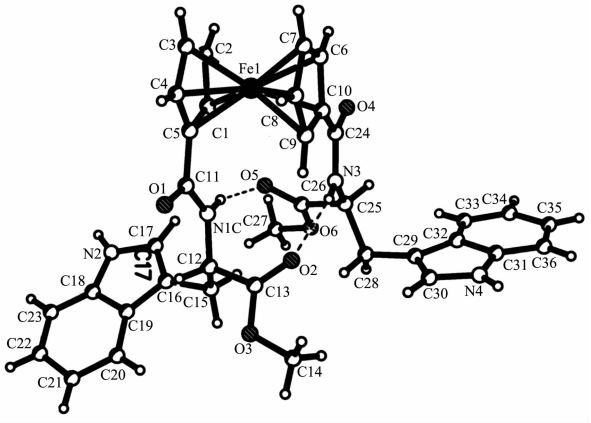
[b] $wR_2=[\sum w(F_o^2-F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$, $w=1/[\sigma^2(F_o^2)+(aP)^2+bP]$, where $P=[F_o^2+2F_c^2]/3$.

2　Results and discussion

Coupling of *L*-Trp-OEt to ferrocene dicarboxylic acid ($Fc(OH)_2$) resulted in the formation of the desired disubstituted ferrocenoyl peptide **1** as an yellow solid. It was fully characterized by ^{1}H NMR, FTIR, CD, and X-ray crystallographic analyses.

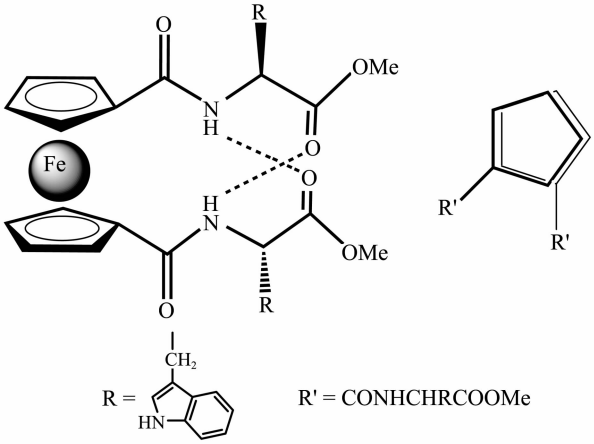
2.1　Structures in solid state

Orange crystals of **1** suitable for single crystal X-ray diffraction were obtained from methanol by slow evaporation at room temperature. The compound crystallized in the Orthorhombic system with space group $P2_12_12_1$. The crystal structure of **1** consists of a ferrocenoyl peptide unit and one disordered solvent water molecule. The structure of ferrocenoyl peptide shown in Fig.1 revealed the formation of two intramolecular hydrogen bondings between CO (Trp) and NH (another Trp) of each amino acid chain. The N-H-O bond angle deviates only slightly from linearity, and N-O distances around 0.31 nm indicate fairly strong hydrogen bonds (Table 2). As shown in Scheme 1, the incorporation of the amino acid chains (-*L*-Trp-OMe) into ferrocene has been demonstrated to achieve a 1,2′ -conformation which is stabilized by the two intramolecular hydrogen bonds. The molecule interacts with its adjacent neighbors through H-bonding, resulting in the formation of a 2-dimensional H-bonding net, in which the NH of the indole and the CH_3 of the OMe are available for participating in intermolecular hydrogen bonding with CO adjacent to the ferrocene unit (N(6A)⋯O(10B), 0.307 0 nm; C(14A)⋯O(10B), 0.337 3 nm, Fig.2). It is forced into a *P*-helical arrangement in all molecules in the crystal packing. The result is similar to the report by Hirao and his coworkers,



Solvent molecules were omitted for clarity

Fig.1　Molecular structure of compound **1**



Scheme 1　Left: Compound **1**, stabilized by two symmetrical intramolecular interstrand hydrogen bonds; Right: Schematic drawing of the *P*-helical arrangement of the metallocene in the 1,2′-conformation

Table 2　Hydrogen bonds for compound 1

Type[a]	Donor	Acceptor	D⋯A / nm	D–H⋯A / (°)
Intra	N1	O5	0.314 0(4)	162
Inter	N2	O7 (*x*−1, *y*+1, *z*)	0.282 3(5)	165
Intra	N3	O2	0.301 4(4)	157
Inter	N4	O1 (−*x*, *y*−1/2, −*z*+1/2)	0.290 4(4)	150

[a] Inter, intermolecular; intra, intramolecular.

which also present a *P*-helical conformation in their *L*-amino acid derivatives of ferrocene-1,1′-dicarboxylic acid[4,12,13].

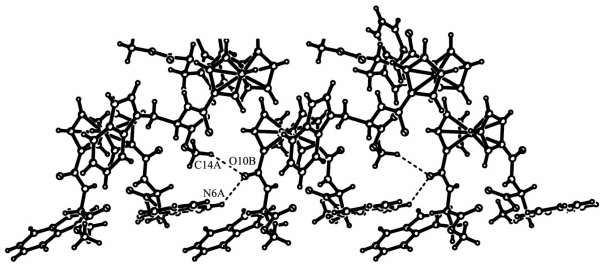


Fig.2 H-bonding interactions between adjacent molecules involving the interactions of the FcC=O group with the ester OCH_3 and with the NH of the indole

The IR of **1** shows only one N-H stretch at 3 396 cm^{-1}. Amide N-H stretches below 3 400 cm^{-1} are diagnostic of hydrogen bonded NH protons[14,15]. In support of this idea, the IR data suggesting the presence of two identical intramolecular hydrogen bonds in compound **1**.

2.2 Structures in solution

Although solid state structures provide reliable and accurate data about the molecular constitution, they may not be representative for the structure in solution. Herein, ^1H NMR spectroscopy and CD spectroscopy were used to obtain information of the structure in solution.

In the ^1H NMR spectra of **1** in $CDCl_3$, both Cp-Trp-OMe portions are magnetically equivalent due to a C_2 symmetry axis, and therefore only one set of signals corresponding to both tryptophan portions of the molecule is observed. It is important to point out that for compound **1**, the N-H of the tryptophan which is attached to the Fc group show resonance above 7 ppm, indicating its involvement in hydrogen bonds in nonpolar solvents[16]. These results indicate that the intramolecular hydrogen bonds between the peptide chains of 1 appear to be present even in solution.

In order to determine structure in solution, CD spectrometry of compound **1** in MeCN was recorded. As shown in Fig.3, bands between 300~600 nm are characteristic for metal-centred transitions. Much stronger bands are observed for bands originating from the amino acids between 240~300 nm. A strong Cotton effect at about 480 nm indicates a chiral conformation at the ferrocene moiety[17,18] producted by hydrogen bonding interaction between the two chiral peptide strands. The positive signal correlates with a *P*-helical arrangement of the substituents as the energetically favourable conformation.

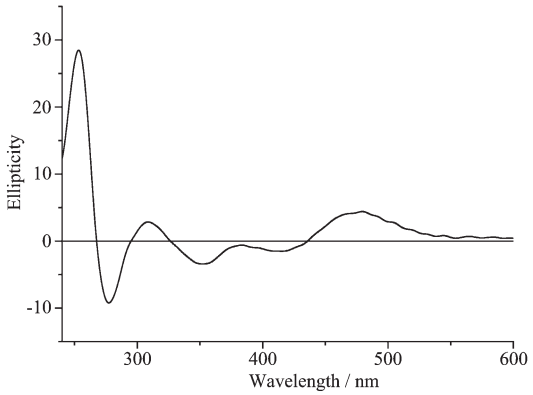


Fig.3 CD spectra of **1** in MeCN (1.0×10^{-4} mol·L^{-1})

3 Conclusion

Through the combination of ferrocene and animo acid, compound **1** was synthesized and structurally characterized in both solid and solution states by ^1H NMR, FTIR, CD, and X-ray crystallographic structural analysis. It offers the possibility of including an electrochemically active group into the peptide backbone. The solid structure of compound **1** conforms that it adopts a 1,2′-conformation allowing intramolecular H-bonding involving the two amides on opposite Cp rings. In addition, it allows extensive intermolecular H-bonding to adjacent molecules forming 2D nets. Another noteworthy feature of the compound is that it forms two intramolecular hydrogen bonds even in solution as shown by its ^1H NMR spectra in $CDCl_3$. CD spectra suggests a *P*-helical chirality of the ferrocene for the peptide strands from a strong positive band around 480 nm. Further studies will include investigation into the oligotryptophan chain growing in length and this work is in progress.

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