Research Article

Synthesis and Characterization of Ferrocene Derivatives and Preliminarily Electrocatalytic Oxidation of L-Cysteine at Nafion-Ferrocene Derivatives Modified Glassy Carbon Electrode

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Five new structural ferrocene derivatives (**2a~2e**) were firstly synthesized and characterized by ¹H NMR, ¹³C NMR, ESI-MS, and XRD. Subsequently, the preliminarily electrocatalytic oxidation of L-cysteine (L-Cys) at nafion-ferrocene derivatives modified glassy carbon electrode (GCE) has also been investigated by cyclic voltammetry. The results showed that **2e** can dramatically electrocatalyze the oxidation of L-cysteine at its modified GCE in 0.1 mol L⁻¹ NaNO₃ aqueous solution with a quasireversible process with $\Delta E_p \approx 55$ mV.

1. Introduction

Ferrocene derivatives have attracted considerable attention for their potential applications as nonlinear optical devices, functional materials in electrochemical sensor [1–4], and chiral catalysts [5–7]. In addition, ferrocene derivatives have also attracted wide interest for their considerably biological activities [8–15]. For example, the ferroquine (FQ, SSR97193, Figure 1) is about to complete phase II clinical trials as a treatment for uncomplicated malaria [16].

L-Cysteine (L-Cys) plays a crucial role in both bio- and environmental chemistry and can be applied in many biochemical processes and diagnosis of disease states. Especially, L-Cys provides a modality for the intramolecular crosslinking of proteins through disulfide bonds to support their secondary structures and functions. Therefore, it is very important to develop simple and effective methods to trace L-Cys detection. Many methods, such as spectrometric method [17], chromatography [18], and electrochemical method [19–23], have been used to detect the trace content of L-Cys.

However, electrochemical method has attracted considerable attention for simple operation, fast response, and sensitive in situ detection.

The oxidation of L-Cys at Hg, Au, Ag, Pt, and diamond electrodes has been reported [24–27]. However, the direct oxidation of L-Cys at GCE is very sluggish. Ferrocene derivatives have been used as the selective probes for detecting the trace ions, biomacromolecules [28–32]. Nafion is a special material, which possesses widespread applications in the field of electrochemistry analysis, chemical sensor, and nanomaterials [33, 34]. According to our survey, no electrocatalytic oxidation of L-Cys at the nafion-ferrocene derivatives modified GCE has been reported. In this work, five new structural ferrocene derivatives (**2a~2e**) (Scheme 1) were firstly synthesized and then confirmed by IR, ¹H NMR, ¹³C NMR, MS, and XRD. Subsequently, their preliminarily electrocatalytic oxidation of L-Cys at the nafion-ferrocene derivatives modified GCE has also been investigated.

FIGURE 1

SCHEME 1: Synthetic routes of ferrocene derivatives.

2. Experimental Details

2.1. Materials and Apparatus. 2-Chloro-4,6-dimethoxy-[1,3,5]triazine (CDMT), *N,N'*-dicyclohexylcarbodiimide (DCC), 1-hydroxybenzotriazole (HOBt), 6-Chloro-1-hydroxybenzotriazole (6-Cl-HOBt), 1-hydroxyl-7-azabenzotriazole

(HOAt), 4-dimethylaminopyridine (DMAP), and *N*-methylmorpholine (NMM) were purchased from Aladdin Reagent company. 5 wt% Nafion solution (DuPont, USA) and other chemicals were commercially available and used without further purification. All melting points were determined on X-4 micro-melting points apparatus and

values are uncorrected. ^1H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a 400 MHz Bruker AVANCE III spectrometer in CDCl_3 . The chemical shifts are expressed in ppm relative to tetramethylsilane (TMS) as the internal standard; ESI-MS was performed on a DECAX-30000 LCQ Deca XP (70 Ev). FTIR spectra were recorded on Spectrum One with KBr disks in the 600–3600 cm^{-1} region. All electrochemical experiments were carried out using an electrochemistry workstation CHI760 (CH Instrument Inc., USA). The working electrode used in cyclic voltammetry experiments was a CHI104 glassy carbon electrode with a geometric area of ca. 0.15 cm^2 ; a twisted platinum wire auxiliary electrode and Ag/AgCl served as the reference electrode. Tetrahydrofuran (THF) was distilled over sodium and benzophenone before being used; all electrolyte solutions were prepared with doubly distilled water.

2.2. Synthesis Parts

2.2.1. Synthesis of 2-Ferrocene Carboxylic Acid-1,3-dicyclohexyl-isourea (2a) [35]. Ferrocene carboxylic acid **1** (0.46 g, 2 mmol) and DCC (0.453 g, 2.2 mmol) were added into a 100 mL one necked round bottom flask with 20 mL dry THF. This mixture was stirred under cold bath and a THF solution (10 mL) containing DMAP (0.268 g, 2.2 mmol) was added dropwise by syringe, the mixture was stirred under cold bath for 30 min, and then temperature rose naturally to room temperature. The completion of reaction was judged from the simple TLC analysis. The mixture was evaporated under reduced pressure and the residual directly purified by column chromatography (EtOAc/petroleum ether: 5:1 to 2:1) to give the desired compound **2a**.

Light yellow solid (0.75 g, 86% yield). M.p. 173°C, IR (cm^{-1}): 3235 (NH), 3039 (=C–H), 2931 (C–H), 1701 (O=C–O–), 1598 (C=C), 1542 (C=N), 1182 (C–O); ^1H NMR (CDCl_3) δ = 0.92–1.33 (m, 8H), 1.35–1.66 (m, 5H), 1.79–1.85 (m, 6H), 1.99–2.09 (m, 2H), 3.48–3.53 (m, 1H), 4.19 (s, 5H, C_5H_5), 4.28 (t, J = 2.0 Hz, 2H of C_5H_4), 4.67 (t, J = 1.6 Hz, 2H of C_5H_4), 6.04 (d, J = 6.4 Hz, 1H, O=C–NH); ^{13}C NMR (CDCl_3) δ = 24.6, 25.4, 25.5, 26.3, 30.9, 31.1, 31.2, 31.3, 32.6, 47.7, 49.8, 56.8, 70.4, 77.9 (C_5H_4), 70.3 (C_5H_5), 154.9 (C=N), 171.9 (–C=O); MS (ESI): m/z 436 $[\text{M}]^+$.

2.2.2. Synthesis of Ferrocene Carboxylic Acid Benzotriazol-1-yl Ester (2b). Ferrocene carboxylic acid **1** (0.46 g, 2 mmol), DCC (0.453 g, 2.2 mmol), and HOBt (0.337 g, 2.5 mmol) were added into a 100 mL one necked round bottom flask with 20 mL dry THF. This mixture was stirred under cold bath and a THF solution (10 mL) containing DMAP (0.268 g, 2.2 mmol) was added dropwise by syringe, the mixture was stirred under cold bath for 30 min, and then temperature rose naturally to room temperature. The completion of reaction was judged from the simple TLC analysis. The mixture was evaporated under reduced pressure and the residual purified directly by column chromatography (EtOAc/petroleum ether: 5:1 to 2:1) to give the desired compound **2b**.

Light yellow solid (0.638 g, 92% yield). M.p. 141–142°C, IR (cm^{-1}): 3035 (=C–H), 1776 (O=C–O–), 1441 (C=C), 1261

(C=N), 1054 (C–O), 768 (Ph); ^1H NMR (CDCl_3) δ = 4.42 (s, 5H, C_5H_5), 4.67 (t, J = 2.0 Hz, 2H of C_5H_4), 5.07 (t, J = 1.0 Hz, 2H of C_5H_4), 7.39–7.45 (m, 2H), 7.52 (d, J = 7.2 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H); ^{13}C NMR (CDCl_3) δ = 63.7, 70.8, 73.5 (C_5H_4), 71.0 (C_5H_5), 108.4, 120.5, 124.7, 128.6, 128.9, 143.6 (benzotriazol-ring), 168.3 (–O–C=O); MS (ESI): m/z 347 $[\text{M}]^+$.

2.2.3. Synthesis of Ferrocene Carboxylic Acid 6-Chloro-benzotriazol-1-yl Ester (2c). The detailed process for synthesis of **2c** is the same as of **2b**. Red crystal (0.723 g, 75% yield). M.p. 112–113°C, IR (cm^{-1}): 3100 (=C–H), 1792 (O=C–O–), 1445 (C=C), 1286 (C=N), 1029 (C–O), 881 (C–Cl), 827 (Ph); ^1H NMR (CDCl_3) δ = 4.47 (s, 5H, C_5H_5), 4.72 (t, J = 2.1 Hz, 2H of C_5H_4), 5.10 (t, J = 1.3 Hz, 2H of C_5H_4), 7.41 (dd, J = 1.6, 1.6 Hz, 1H), 7.49 (d, J = 1.6 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H); ^{13}C NMR (CDCl_3) δ = 63.7, 71.3, 73.9 (C_5H_4), 71.4 (C_5H_5), 108.6, 121.8, 126.4, 129.9, 135.5, 142.4 (benzotriazol-ring), 168.5; MS (ESI): m/z 482 $[\text{M}]^+$.

2.2.4. Synthesis Ferrocene Carboxylic Acid [1,2,3]triazolo[4,5-b]pyridin-3-yl Ester (2d). The detailed process for synthesis of **2d** is the same as synthesis of **2b**. Light yellow solid (0.557 g, 80% yield). M.p. 136–137°C, IR (cm^{-1}): 3108 (=C–H), 1775 (O=C–O), 1448 (C=C), 1265 (C=N), 1058 (C–O), 887; ^1H NMR (400 MHz, CDCl_3) δ = 4.44 (s, 5H, C_5H_5), 4.61 (s, 2H of C_5H_4), 5.03 (s, 2H of C_5H_4), 7.38 (dd, J = 4.8, 4.8 Hz, 1H), 8.38 (d, J = 8.4 Hz, 1H), 8.68 (d, J = 4.4 Hz, 1H); ^{13}C NMR (CDCl_3) δ = 63.5, 71.1, 73.5 (C_5H_4), 71.3 (C_5H_5), 129.5, 135.1, 140.9, 151.7 ([1,2,3]triazolo[4,5-b]pyridin-ring), 168.1 (–O–C=O); MS (ESI): m/z 348 $[\text{M}]^+$.

2.2.5. Synthesis of Ferrocene Carboxylic Acid 4,6-Dimethoxy-[1,3,5]triazin-2-yl Ester (2e). Ferrocene carboxylic acid **1** (0.46 g, 2 mmol) and CDMT (0.438 g, 2.5 mmol) were added into a 100 mL one necked round bottom flask with 20 mL dry THF. This mixture was stirred under cold bath and a THF solution (10 mL) containing NMM (0.253 g, 2.5 mmol) was added dropwise by syringe, the mixture was stirred under cold bath for 30 min, and then temperature rose naturally to room temperature. The completion of reaction was judged from the simple TLC analysis. The mixture was evaporated under reduced pressure and the residual purified directly by column chromatography (EtOAc/petroleum ether: 5:1 to 2:1) to give the desired compound **2e**.

Light yellow solid (0.863 g, 92% yield). M.p. 90–92°C, FTIR (cm^{-1}): 3104 (=C–H), 2951 (C–H), 1747 (O=C–O), 1577 (C=C), 1469 (C=N), 1366 (C–O); ^1H NMR (400 MHz, CDCl_3) δ (ppm): 4.08 (s, 6H, 2OCH₃), 4.39 (s, 5H, C_5H_4), 4.56 (s, 2H of C_5H_4), 4.95 (s, 2H of C_5H_4); ^{13}C NMR (CDCl_3) δ = 56.4 (OCH₃), 70.6, 71.3, 73.1 (C_5H_4), 71.4 (C_5H_5), 167.9 (–C=O), 171.2, 174.5 ([1,3,5]triazin-ring); MS (ESI): m/z 369 $[\text{M}]^+$.

2.3. Electrochemistry

2.3.1. The Process for Preparation of the Solutions of Nafion-Ferrocene Derivatives. Compound **2a** (6.6 mg, 0.015 mmol)

FIGURE 2: Characteristic fragments of ^1H spectra of ferrocene ring in ferrocene derivatives **2a**~**2d**.

and 50 μL 5% nafion solution were added in a 2 mL centrifugal tube, then 1 mL of absolute alcohol was added, and the mixture was sonicated for 10 min to obtain the solution of $1.5 \times 10^{-2} \text{ mol L}^{-1}$ **2a**.

The detailed process for preparing the solutions of $1.5 \times 10^{-2} \text{ mol L}^{-1}$ **2b**, **2c**, **2d**, and **2e** is the same as **2a**.

2.3.2. General Process for Preparing the Modified Glassy Carbon Electrode and Preliminarily Electrocatalytic Oxidation of L-Cysteine. A GCE was polished with 0.1 μm $\alpha\text{-Al}_2\text{O}_3$, rinsed with doubly distilled water, sonicated in 1 mol L^{-1} H_2SO_4 for 5 min, and rinsed with doubly distilled water again prior to each experiment. Then, it was dried naturally.

A modified GCE was prepared by placing 5 μL of solution prepared in Section 2.3.1 onto the dried GCE surface by microsyringe. The electrode was dried naturally to obtain the modified GCE.

The modified GCE, a twisted platinum wire electrode, and Ag/AgCl electrode were dipped into 20 mL (V/V, 1:1) water solution of $6.0 \times 10^{-3} \text{ mol L}^{-1}$ L-Cys and 0.1 mol L^{-1} NaNO_3 . The Ag/AgCl electrode was connected to the main body of the cell through a luggin capillary whose end was connected on the modified GCE and positioned close to the electrode surface. The solution was thoroughly flushed with high purity nitrogen for 5 min before each run to remove the oxygen from the solution in the electrochemical cell. All experiments were carried out at room temperature.

3. Results and Discussion

3.1. Chemistry. Ferrocene derivatives (**2a**~**2e**) were firstly synthesized in higher yield and their structures were confirmed by IR, ^1H and ^{13}C NMR, and mass spectrometry.

There showed three kinds of proton signals for ferrocene core of the ferrocene derivatives (**2a**~**2e**) in ^1H NMR spectra (Figure 2), the protons of C_5H_5 showed a singlet, the C_5H_4 showed two triplets of **2a**~**2c**, but the C_5H_4 showed two

TABLE 1: Crystallographic data and structure refinement for **2c**.

Crystal Data	2c
Experical formula	$\text{C}_{17}\text{H}_{12}\text{ClFeN}_3\text{O}_2$
MW	381.60
Crystal system	monoclinic
Space group	P2(1)/c
a ($\text{\AA}$)	9.6361(8)
b ($\text{\AA}$)	13.7876(7)
c ($\text{\AA}$)	13.1082(8)
α ($^\circ$)	90.00
β ($^\circ$)	108.881(8)
γ ($^\circ$)	90.00
V ($\text{\AA}^3$)	1647.83(19)
Z	4
D_c (g cm^{-3})	1.538
μ (mm^{-1})	8.958
$F(000)$	776
θ range ($^\circ$)	4.80 to 74.56
Reflections collected/unique	6006/3248
R_{int}	0.0230
R_1, wR_2 ($I > 2\sigma(I)$)	$R_1 = 0.0361, wR_2 = 0.0911$
R_1, wR_2 (all data)	$R_1 = 0.0566, wR_2 = 0.1027$
GOF on F^2	0.999

singlets of **2d**. Three signals of the carbon atoms of C_5H_4 and one signal of carbon atom of C_5H_5 appear in ^{13}C NMR spectra, while two carbon signals of C_5H_4 appear upfield and one carbon signal of C_5H_5 appears downfield compared to the carbon signals of C_5H_5 .

3.2. X-Ray Crystallographic Study. X-ray diffraction data for **2c** was collected on a Siemens Smart CCD diffractometer equipped with a graphite-monochromated $\text{CuK}\alpha$ radiation ($\lambda = 1.54180 \text{ \AA}$). The structure was solved by direct method using the program SHELXL-97 and refined by full-matrix least-squares techniques on F^2 with SHELXL-97 program package [36, 37]. The molecular structure (Figure 3) and crystal data of **2c** are listed in Tables 1 and 2.

TABLE 2: Selected bond lengths (Å) and angles (°) for **2c**.

Bond lengths (Å)		Bond angle (°)	
Fe(1)–C(9)	2.007(3)	C(9)–Fe(1)–C(8)	41.50(12)
Fe(1)–C(1)	2.025(3)	C(9)–Fe(1)–C(2)	153.96(14)
C(9)–C(11)	1.445(4)	C(9)–Fe(1)–C(5)	127.51(17)
C(11)–O(12)	1.185(4)	C(8)–Fe(1)–C(10)	69.73(14)
O(13)–N(14)	1.362(3)	O(12)–C(11)–C(9)	130.8(3)
N(14)–C(22)	1.361(3)	O(13)–N(14)–N(15)	118.6(3)
C(20)–Cl(23)	1.730(3)	N(16)–C(17)–C(22)	109.1(3)
N(15)–N(16)	1.295(4)	N(14)–C(22)–C(21)	133.8(2)
C(19)–C(20)	1.408(4)	C(19)–C(20)–Cl(23)	117.6(2)

FIGURE 3: Crystal structure of **2c**. FIGURE 4: Cyclic voltammograms of (a) nafion modified GCE in $0.1 \text{ mol L}^{-1} \text{ NaNO}_3$; (b) nafion modified GCE in solution of $0.1 \text{ mol L}^{-1} \text{ NaNO}_3$ and $6.0 \times 10^{-3} \text{ mol L}^{-1} \text{ L-Cys}$; (c) **2e**-nafion modified GCE in $0.1 \text{ mol L}^{-1} \text{ NaNO}_3$ solution; (d) **2e**-nafion modified GCE in solution of $0.1 \text{ mol L}^{-1} \text{ NaNO}_3$ and $6.0 \times 10^{-3} \text{ mol L}^{-1} \text{ L-Cys}$.

3.3. Cyclic Voltammetric Behavior of Compounds **2a~2e and Nafion Modified GCE Electrocatalyze the Oxidation of L-Cys.** The preliminarily electrochemical oxidation of L-Cys with the nafion-ferrocene derivatives modified GCE in 0.1 mol L^{-1} different supporting electrolyte solutions, such as NaCl,

NaNO_3 , NaAc, and Na_2SO_4 , has been investigated by cyclic voltammetry. The results (Figure 4) showed that **2e** can promote the electrochemical oxidation of L-Cys dramatically in $0.1 \text{ mol L}^{-1} \text{ NaNO}_3$ solution with a quasireversible process with $\Delta E_p \approx 55 \text{ mV}$ (curve (d) in Figure 4), while direct oxidation of L-Cys at a GCE is very sluggish (curve (b) in Figure 4).

4. Conclusion

In this study, five ferrocene derivatives (**2a~2e**) were firstly synthesized and structurally characterized using spectroscopic methods. The preliminarily electrochemical oxidation of L-Cys with the nafion-ferrocene derivatives modified GCE in $0.1 \text{ mol L}^{-1} \text{ NaNO}_3$ solution has also been investigated by cyclic voltammetry. The results showed that **2e** can promote the electrochemical oxidation of L-Cys dramatically at its modified GCE with a quasireversible process with $\Delta E_p \approx 55 \text{ mV}$, while L-Cys itself showed a sluggish electrochemical response at GCE. Thus, **2e** modified GCE can be used to detect the trace L-Cys content. (The quantitative analysis of trace L-Cys and electrochemical kinetics of **2e** modified GCE are undergoing.) Based on this research, more ferrocene derivatives will be synthesized and the oxidation of L-Cys and other biological molecules at the modified GCE will be studied soon.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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