

Novel redox receptors for ion-pair and α -amino acid: synthesis and complexation properties of calix[4]arene derivatives bearing large conjugated ferrocene groups

Fafu Yang · Zhiqiang Liu · Biqiong Hong ·
Hongyu Guo

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Abstract By reacting calix[4]arene 1,3-bi-hydrazide derivative (**2**) with formacylferrocene in “1 + 2” condensation mode, novel calix[4]arene derivative bearing two conjugated ferrocene groups (**3**) was obtained in yield of 88%. By reacting 1,3-bi-substituted [2-(*p*-formylphenoxy)ethyl-oxy]-*p*-*tert*-butylcalix[4]arene (**5**) with 1,1'-diacetylferrocene hydrazone (**4**) in “1 + 1” condensation mode, novel calix[4]arene derivative with 1,3-substituted large conjugated ferrocene bridge (**6**) was synthesized in yield of 83%. The structures and conformations of new compounds were confirmed by elemental analyses, IR spectra, ESI-MS, ^1H NMR, etc. The electrochemical cyclic voltammetry experiments revealed that compounds **3** and **6** possessed excellent reversible electrochemical properties. The ^1H NMR titration study showed that compound **6** possessed excellent complexation abilities for NaH_2PO_4 and glycine in 1:1 host–guest complex with the association constants of 3,850 and 2,460 M^{-1} , respectively.

Keywords Calix[4]arene · Ferrocene · Complexation · Redox · Ion pair · Amino acid

Introduction

Supramolecular electrochemical recognition plays important role in the research field of both supramolecular

chemistry and electrochemistry [1–3]. In recent years, some researches focused on using calixarenes as building block to construct the redox-active calixarene derivatives [4–8]. To reach this aim, some ferrocene-functioned calixarenes were synthesized and their electrochemical recognitions for guests were studied. For examples, Beer et al. reported series of ferrocene-functioned calixarenes [9, 10]. Tomapatanaget and Tuntulani [11, 12] synthesized a ferrocene-amide calixarenes with recognition for carboxylic anions. Guo et al. [13] found a ferrocene-based thiacalix[4]arene ditopic receptor for europium(III) and dihydrogenphosphate ion. Cheng and coworkers [14] discovered redox anion receptors based on calix[4]pyrrole bearing ferrocene amide. Moon and Kaifer [15] prepared a dimer of calix[4]arene bearing four ferrocene-urea groups. Lately, Shaabani and Shaghghi [16] observed a ferrocene amine-substituted calix[4]arene derivative with electrochemical response to lanthanides lately. In most cases, ferrocenes were introduced into calixarene platform by amide bond, ester bond, urea bond, carbonyl bond, and the redox-active response for guests was greatly influenced by the characteristic and structure of the linking groups.

Recently, the ion pairs and amino acids recognition were attracted much attention due to their potential application in ion probe, ion controlled sensor, biological systemic mimic, etc. The receptors containing two recognition sites, one for cation and one for anion, possess complexation abilities for ion pairs or zwitterionic amino acids. For examples, Vicens and coworkers [17] found a tripodal aza crown ether calix[4]arenes with binding abilities for ion pairs. Haino and coworkers [18] studied the energetics of ion pairs binding to calix[4]arene molecular containers. Sirit and coworkers [19] reported a chiral calix[4]azacrowns with recognition for amino acid derivatives. Jaffrezic-Renault and coworkers [20] investigated calix[4]arene based molecules for amino

F. Yang (✉) · Z. Liu · B. Hong · H. Guo
College of Chemistry and Materials, Fujian Normal University,
Fuzhou 350007, People's Republic of China
e-mail: yangfafu@fjnu.edu.cn

F. Yang
Fujian Key Laboratory of Polymer Materials, Fuzhou
350007, People's Republic of China

acid detection. Lately, Ohto and coworkers [21] reported the adsorption of amino acid derivatives on calixarene impregnated resins. However, to the best of our knowledge, no redox calixarene receptor for ion-pair or zwitterionic α -amino acid was studied up to now, although some calixarene derivatives with binding abilities for ion pairs or amino acids were reported.

In this present work, two novel calix[4]arene derivatives bearing large conjugated ferrocene groups has been designed and synthesized. The electrochemical investigation revealed that they are excellent redox receptors with reversible cyclic voltammetry curves, which were reported for the first time in calixarene-ferrocene chemistry. The calix[4]arene derivative bearing bridging-large conjugated ferrocene group (**6**) possessed excellent complexation abilities to NaH_2PO_4 and glycine, which were confirmed by the method of ^1H NMR titration study.

Experimental

^1H NMR spectra were recorded in CDCl_3 on a Bruker-ARX 400 instrument, using TMS as reference. ESI-MS spectra were obtained from DECA-30000 LCQ Deca XP mass spectrometer. The electrochemical experiments were carried out using a CHI 600A electrochemical apparatus. Elemental analyses were performed at Vario EL III Elemental Analyzer. IR spectra were recorded on a Thermo Nicolet AVATAR 5700 FTIR spectrometer using KBr pellets in spectral range $4,000\text{--}400\text{ cm}^{-1}$. 1,1'-Diacetylferrocene hydrazone (**4**) were prepared by condensation of 1,1'-diacetylferrocene with hydrazine hydrate according to the published procedures. Calix[4]arene bi-hydrazide derivative (**2**) and calix[4]arene bi-aldehyde derivative (**5**) were synthesized by our published procedure [22, 23]. All solvents were purified by standard procedures.

Synthesis of calix[4]arene derivative bearing two conjugated ferrocene groups (**3**)

The mixture of compound **2** (0.5 mmol) and formacylferrocene (1.0 mol) in 20 mL of CHCl_3 /methanol ($V:V = 1:1$) was stirred and refluxed. TLC detection indicated the disappearance of materials in 4 h. The solvent was evaporated. Then 10 mL methanol was added and stored in refrigerator overnight. The precipitation was formed and separated. After vacuum drying, compound **6** was obtained as amaranthine powder in 88% yield. m.p. $253\text{--}256\text{ }^\circ\text{C}$; IR (KBr, cm^{-1}): 1691 (C=O), 1606 (C=N); ^1H NMR (400 MHz, CDCl_3) δ ppm: 1.01 [s, 18H, C(CH₃)₃], 1.26 [s, 18H, C(CH₃)₃], 3.51 (bd, 4H, $J = 12.8\text{ Hz}$, ArCH₂Ar), 4.01–5.01 (m, 26H, OCH₂, ArCH₂Ar and FeH), 6.92

(s, 4H, ArH), 7.13 (s, 4H, ArH), 7.55 (s, 2H, CH), 8.20 (s, 2H, OH), 11.26 (s, 2H, NH); MS m/z (%): 1207.8 (MNa⁺, 100). Anal. calcd for C₇₀H₈₀O₆N₄Fe₂: C 70.92, H 6.80; N 4.72; found C 70.81, H 6.94; N 4.56.

Synthesis of calix[4]arene derivative with 1,3-substituted large conjugated ferrocene bridge (**6**)

The mixture of compound **4** (0.5 mmol) and **5** (0.5 mol) in 80 mL of CHCl_3 /methanol ($V:V = 1:1$) was stirred and refluxed. TLC detection indicated the disappearance of materials in 10 h. The solvent was evaporated. Then 10 mL methanol was added and stored in refrigerator overnight. The precipitation was formed and separated. After vacuum drying, compound **3** was obtained as red powder in 83% yield. m.p. $238\text{--}240\text{ }^\circ\text{C}$; IR (KBr, cm^{-1}): 1606 (C=N); ^1H NMR (400 MHz, CDCl_3) δ ppm: 1.08 [s, 18H, C(CH₃)₃], 1.30 [s, 18H, C(CH₃)₃], 2.52 (bs, 6H, CH₃), 3.39 (d, 4H, $J = 12.8\text{ Hz}$, ArCH₂Ar), 4.39 (d, 4H, $J = 12.8\text{ Hz}$, ArCH₂Ar), 4.36–5.01 (m, 16H, OCH₂ and FeH), 6.89 (d, 4H, $J = 8.0\text{ Hz}$, ArH), 6.96 (s, 4H, ArH), 7.03 (bs, 4H, ArH), 7.54 (d, 4H, $J = 8.0\text{ Hz}$, ArH), 7.87 (s, 2H, CH), 8.55 (s, 2H, OH); MS m/z (%): 1229.4 (MNa⁺, 100). Anal. calcd for C₇₆H₈₆O₆N₄Fe: C 75.64, H 7.18; N 4.64; found C 75.57, H 7.25; N 4.48.

Electrochemical studies

The electrochemical experiments were carried out using a CHI 600A electrochemical apparatus in in dry CH_2Cl_2 /MeCN ($V:V = 1:4$) with $n\text{-Bu}_4\text{NPF}_6$ (0.1 mol/L) as the supporting electrolyte at room temperature. A standard three-electrode cell consists of platinum electrode as working electrode, a platinum wire as counter electrode, and 0.01 mol/L Ag⁺/Ag as reference electrode. The scanning speed was 0.1 V/s. The ferrocenium/ferrocene redox couple was taken as the internal standard. All sample solutions were 1×10^{-3} mol/L.

^1H NMR titration experiments

Solutions of compound **6** (0.01 M) and guests (0.01 M) including $n\text{-Bu}_4\text{NH}_2\text{PO}_4$, NaPF₆, NaH₂PO₄ and glycine were prepared in DMSO-*d*₆ solutions. Typically, to 0.20 mL of solution of compound **6** in NMR tube was added corresponding equiv. of guest. In each NMR tube, the amount of DMSO-*d*₆ was then adjusted to the same quantity. The chemical shift of the OH and CH on the receptor was monitored at 30 °C. The program EQNMR was then used to analyze the resulting titration curves and to calculate stability constant values in M⁻¹ [24].

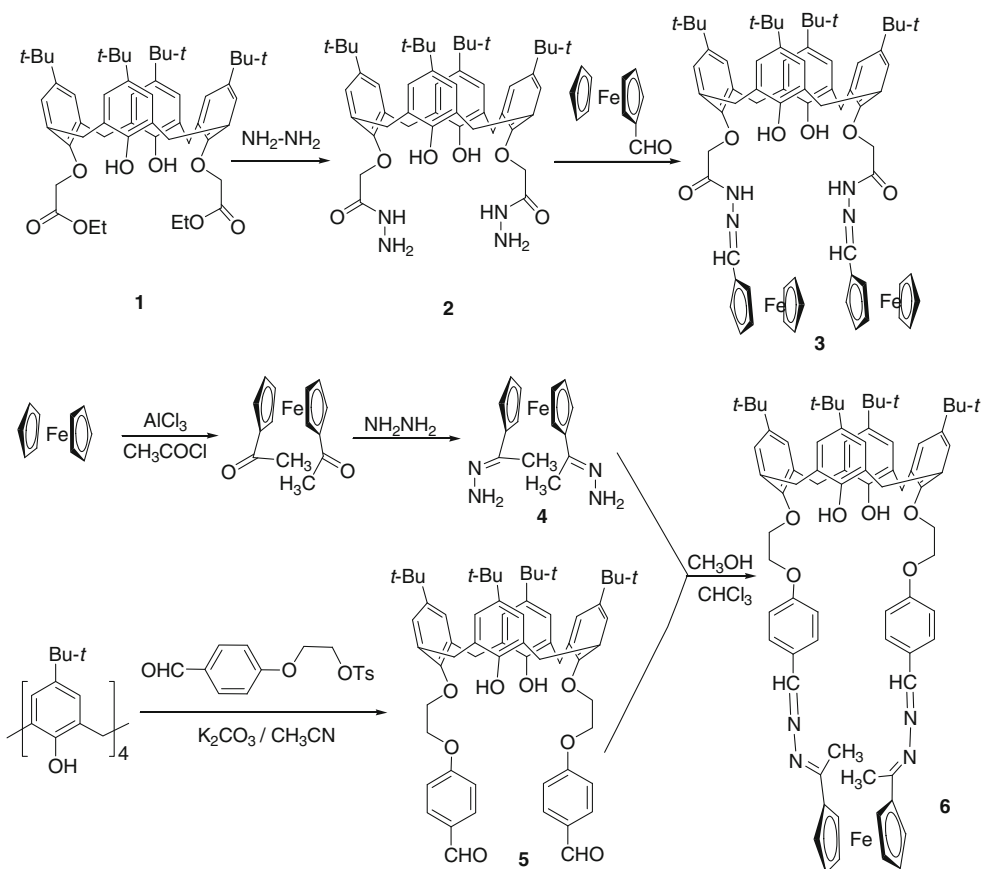
Results and discussion

Syntheses, structures and conformations

The synthetic routes were showed in Scheme 1. 1,1'-Diacetylferrocene hydrazone (**4**) were prepared by condensation of 1,1'-diacetylferrocene with hydrazine hydrate according to the published procedures. Calix[4]arene bi-hydrazide derivative (**2**) and calix[4]arene bi-aldehyde derivative (**5**) were synthesized by our published procedure [22, 23]. By condensation of calix[4]arene bi-hydrazide derivative (**2**) and formacylferrocene in $\text{CHCl}_3/\text{MeOH}$ (1:1, *V/V*) system, novel 1,3-substituted ferroceneacylhydrazone calix[4]arene derivative (**3**) was prepared in yield of 88%. On the other hand, by refluxing compound **4** with **5** in $\text{CHCl}_3/\text{MeOH}$ (1:1, *V/V*) for 10 h under diluted condition, the novel ferrocene-substituted calix[4]arene derivative **6** was obtained in “1 + 1” condensation mode after recrystallization with $\text{CHCl}_3/\text{MeOH}$ in yield of 83%. Both compounds **3** and **6** were obtained conveniently by precipitation in methanol in high yields. It was pity that we failed to accomplish the condensation of compound **2** with 1,1'-diacetylferrocene in all kinds of system or using acetic acid etc. as catalyst. Although some ferrocene-substituted

calixarene derivatives were synthesized by introducing ferrocene unit on calixarene platform with amide bond, ester bond, urea bond, carbonyl bond, however, compounds **3** and **6** were the first examples of ferrocene-substituted calix[4]-arene derivatives with Schiff-base bond and possessed a large π -electron conjugated system, which were favorable for conducting new electronic effect for redox-active. Moreover, the binding cavities of compounds **3** and **6** could be regarded as two binding sites. One site was composed of ethoxy groups and another site was composed of conjugated Schiff-base groups, which were similar to the structures of a calix[4]crown with ion-pair sites [14]. Thus, it was possible that compounds **3** and **6** could bind cations and anions concurrently, such as for ion-pairs and zwitterionic α -amino acids.

All new compounds were characterized by elemental analyses, IR spectra, ESI-MS spectra and ^1H NMR spectra. In the IR spectra, the disappearance of absorption peaks at $1,694\text{ cm}^{-1}$ (aldehyde groups) and the emergence of strong peaks at $1,606\text{ cm}^{-1}$ ($\text{C}=\text{N}$ groups) indicated the complete accomplish of condensation reaction. The ESI-MS spectra of compounds **3** and **6** showed clearly molecular ion peak at $1207.8\text{ (MNa}^+)$ and $1229.4\text{ (MNa}^+)$, respectively. In the ^1H NMR spectra, compounds **3** and **6** showed two singlets



Scheme 1

(1:1) for the *tert*-butyl groups, one pair of doublets (1:1) for the methylene bridges of the calix[4]arene skeleton. All the spectral data were in accordance with the assigned structures and certainly indicated that the calix[4]arene units adopt the cone conformation as showed in Scheme 1 [22, 23].

Electrochemical studies

The electrochemical properties of receptors **3** and **6** were investigated by method of cyclic voltammetry (CV) at room temperature. Cyclic voltammetry (CV) was performed using solutions of **3** and **6** (1×10^{-3} mol/L) prepared in dry $\text{CH}_2\text{Cl}_2/\text{MeCN}$ (V:V = 1:4) with $n\text{-Bu}_4\text{NPF}_6$ (0.1 mol/L) as the supporting electrolyte. A standard three-electrode cell consists of platinum electrode as working electrode, a platinum wire as counter electrode, and 0.01 mol/L Ag^+/Ag as reference electrode. Cyclic voltammograms of **3** and **6** showed reversible redox couples of ferrocene/ferrocenium at $E_{1/2} = 215$ and 286 mV, respectively, as shown in Figs. 1 and 2. The observation of only one redox wave for iron centers in compound **3** indicated no interaction between the ferrocene units.

^1H NMR titration study

The ^1H NMR titrations were employed to study the complexation properties in $\text{DMSO}-d_6$ at 30 °C. The ^1H NMR titration of host **6** for NaH_2PO_4 and glycine were carried out as representative complexation experiments. Figure 3 showed that, in the solution of host **6** with 1.0 equiv. $n\text{-BuN}_4\text{H}_2\text{PO}_4$, the shifts of OH and CH moved from 8.55 and 7.87 to 9.12 and 8.03, respectively. Moreover, the shifts of OH and CH moved further to 9.50 and 8.11 in the

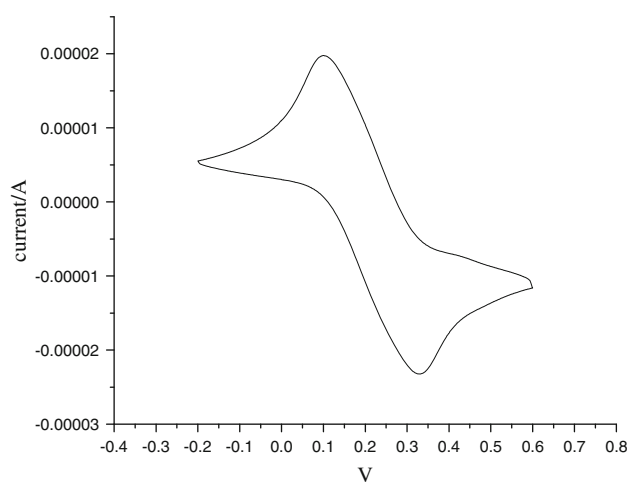


Fig. 1 Cyclic voltammogram of compound **3** (1 mM) in $\text{CH}_2\text{Cl}_2/\text{MeCN}$ (V:V = 1:4) containing $n\text{-Bu}_4\text{NPF}_6$ (0.1 M) as supporting electrolyte; scan rate = 100 mV/s

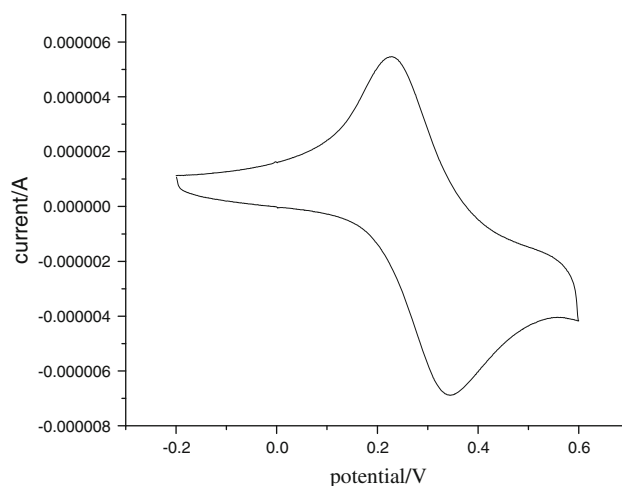


Fig. 2 Cyclic voltammogram of compound **6** (1 mM) in $\text{CH}_2\text{Cl}_2/\text{MeCN}$ (V:V = 1:4) containing $n\text{-Bu}_4\text{NPF}_6$ (0.1 M) as supporting electrolyte; scan rate = 100 mV/s

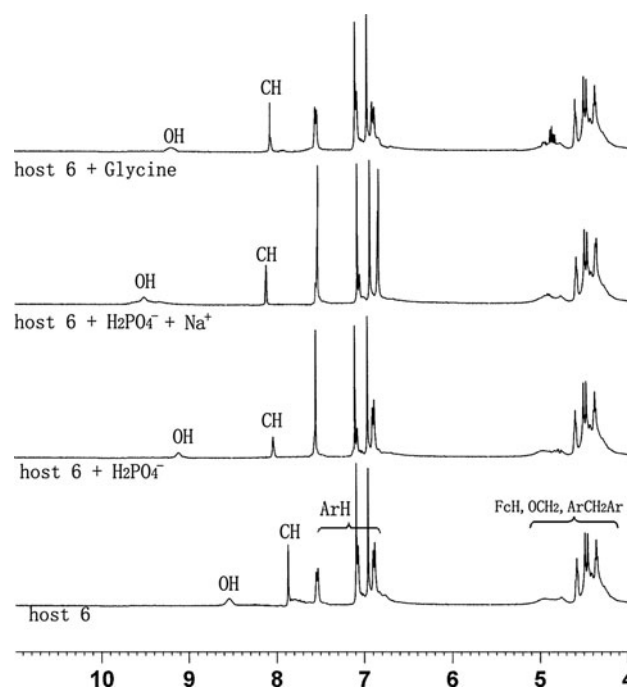


Fig. 3 ^1H NMR spectra of compound **6** in $\text{DMSO}-d_6$ solution on addition of 1.0 equiv. $n\text{-BuN}_4\text{H}_2\text{PO}_4$, 1.0 equiv. $n\text{-BuN}_4\text{H}_2\text{PO}_4 + 1.0$ equiv. NaPF_6 and 1.0 equiv. glycine, respectively

solution of host **6** with 1.0 equiv. $n\text{-BuN}_4\text{H}_2\text{PO}_4$ and 1.0 equiv. NaPF_6 . These results indicated that the presence of Na^+ increased the binding ability of receptor **6** towards H_2PO_4^- . On the other hand, the shifts of OH and CH moved to 9.21 and 8.10 in the solution of host **6** with 1.0 equiv. glycine, which indicated the host **6** also exhibited excellent complexation ability for zwitterionic α -amino acid. The plots between the mole ratios of NaH_2PO_4 or glycine: **6** and the OH chemical shift of host **6** were

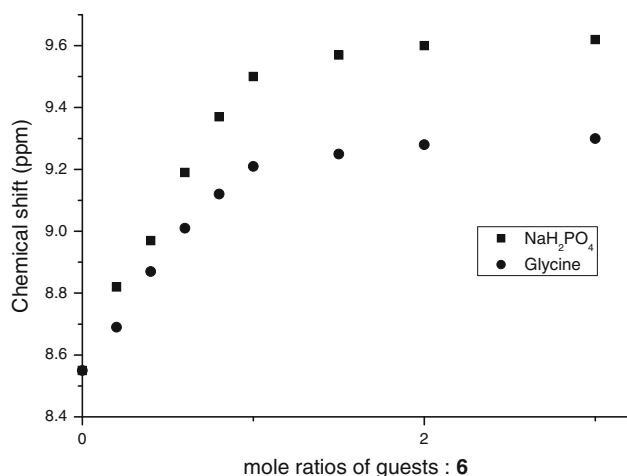


Fig. 4 Plots between mole ratios of guests: **6** and the OH chemical shifts

illustrated in Fig. 4. Job plot analysis indicated that host **6** binded NaH₂PO₄ and glycine in 1:1 host/guest ratio. The association constants of host **6** towards NaH₂PO₄ and glycine were calculated by the program EQNMR to be 3,850 and 2,460 M⁻¹, respectively [24]. These ¹H NMR titration study showed compound **6** possessed excellent complexation abilities for NaH₂PO₄ and glycine.

Conclusion

Two novel calix[4]arene derivatives bearing large conjugated ferrocene groups (**3** and **6**) were synthesized in high yields. The structures and conformations of all new compounds were confirmed by elemental analyses, IR spectra, ESI-MS, ¹H NMR, etc. The electrochemical investigation revealed that compounds **3** and **6** possessed excellent electrochemical reversible redox response properties. The ¹H NMR titration study showed that compound **6** possessed excellent complexation abilities for NaH₂PO₄ and glycine in 1:1 host–guest complex at 30 °C, and the association constants of compound **6** towards NaH₂PO₄ and glycine were 3,850 and 2,460 M⁻¹, respectively.

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