

A novel ferrocene-based thiacalix[4]arene ditopic receptor for electrochemical sensing of europium(III) and dihydrogen phosphate ions

Dian-Shun Guo,* Zhi-Peng Liu, Jian-Ping Ma and Ru-Qi Huang

Department of Chemistry, Shandong Normal University, Jinan 250014, PR China

Received 23 August 2006; revised 11 December 2006; accepted 12 December 2006

Abstract—We have synthesized a ferrocene-based 1,3-alternate thiacalix[4]arene ditopic receptor **3** that contains four identical polyether arms terminated with the ferrocene amide moieties. Our studies have revealed that this redox-active receptor can be used as an electrochemical sensor to recognize both europium (Eu^{3+}) and dihydrogen phosphate (H_2PO_4^-) ions with a high selectivity. © 2006 Elsevier Ltd. All rights reserved.

The design and synthesis of ditopic receptors that have the ability to selectively bind and sense cationic and anionic species is a new emerging topical field of supramolecular chemistry.¹ Such receptors are generally achieved through combining well-defined recognition centers with signalling moieties to enable detection of ion binding via optical and electrochemical methods.² In particular, the recognition and sensing of rare earth metal cations have attracted a growing attention largely because of the fast developing biomedical applications of the rare-earth-metal-containing systems in nuclear magnetic imaging, cancer therapy, fluoroimmuno-assays and luminescent labeling of biomolecules, as well as specific cleavage of DNA and RNA.³

Thiacalixarenes have recently emerged as new members of the calixarene family and become useful building blocks for the construction of ionophores due to their novel features such as excellent binding abilities toward transition metal cations and different conformational preferences, which result from the replacement of methylene linkages by sulfur atom bridges in the calixarene structure. However, much less known chemistry of thiacalixarenes and lack of general derivatizing methods markedly restrict their applications as molecular scaffolds in supramolecular chemistry.⁴

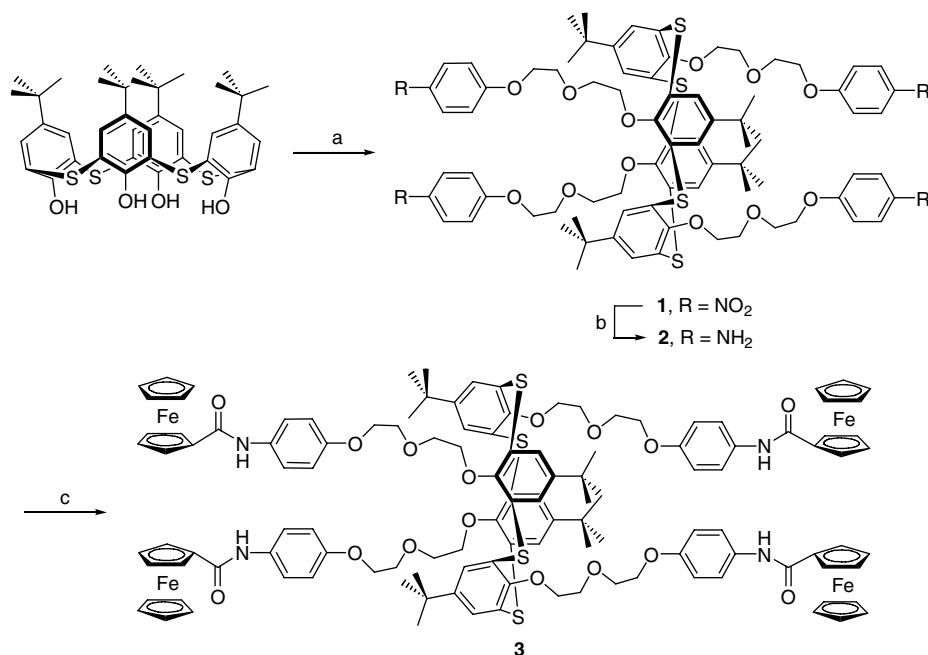
The calixarene structural frameworks have been modified for constructing a variety of elegant redox-active receptors. Notable examples include cobaltocenium- and ferrocene-appended calixarene ionophores.⁵ However, no ferrocene-based thiacalixarene receptors have been described so far.

As part of our efforts to develop new redox-active receptors capable of recognition and sensing of ionic or molecular guests, we report here the first synthesis of a novel ditopic ferrocene-based thiacalix[4]arene receptor **3** (Scheme 1), which contains four identical polyether linked ferrocene amide moieties and exhibits a remarkable selectivity for electrochemical sensing of europium(III) and dihydrogen phosphate ions, respectively.

The synthetic route of receptor **3** is depicted in Scheme 1. The reaction of *p*-tert-butylthiacalix[4]arene⁶ with 1-[2-(2-iodoethoxy)ethoxy]-4-nitrobenzene⁷ in CH_3CN solution using Cs_2CO_3 as base afforded nitro compound **1** (71% yield after chromatography), which was then converted to the corresponding amine **2** (95% yield) via reaction with $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ using Pd/C ⁸ as a catalyst. Receptor **3** was synthesized in a good yield (70%) through treatment of amine **2** with chlorocarbonylferrocene⁹ in the presence of triethylamine base. All new thiacalix[4]arene derivatives were characterized by ^1H , ^{13}C NMR, IR, Maldi MS, and elemental analyses, and the 1,3-alternate conformation of compound **1** was confirmed by X-ray structural analysis (see the [Supplementary data](#)).

Keywords: Thiacalix[4]arene; Ferrocene; Redox-active ditopic receptor; Electrochemical recognition; Sensor.

* Corresponding author. Tel.: +86 531 86180743; fax: +86 531 82615258; e-mail: chdsguo@sdnu.edu.cn



Scheme 1. Reagents and conditions: (a) 4-NO₂C₆H₄OCH₂CH₂OCH₂CH₂I, Cs₂CO₃, CH₃CN, reflux; (b) Pd/C (5%), NH₂NH₂·H₂O (85%), dioxane/ethanol, reflux and (c) chlorocarbonylferrocene, Et₃N, CH₂Cl₂, rt.

In order to evaluate the potential electrochemical sensing capabilities of the novel ditopic receptor **3**, its voltammetric behavior was investigated toward the cationic and anionic species. Cyclic voltammogram (CV) was recorded for **3** in CH₂Cl₂:CH₃CN (1:1) solution using *n*-Bu₄NClO₄ as the supporting electrolyte. The free receptor exhibited a single quasi-reversible wave at $E_{1/2} = 0.575$ V (vs. saturated calomel electrode reference) for the ferrocene–ferrocenium redox couple, which indicated that four ferrocene moieties in receptor **3** were all oxidized at the same potential or at similar ones without showing the detectable electronic communication among them.¹⁰

Upon progressive addition of stoichiometric equivalents of H₂PO₄[−] anion, a distinct two-wave behavior could be observed. The wave shifted negatively up to 275 mV upon addition of two equivalents of H₂PO₄[−] ion, concomitant with the electrochemical response turned to less reversible (Fig. 1a). This cathodic shift can be attributed to the hydrogen bindings of H₂PO₄[−] ion by NH protons of the amide groups in close proximity to the ferrocene redox centers of **3**, facilitating oxidation to ferrocenium. It should be noted that the two-wave behavior has been used as a diagnosis of a large value for the equilibrium constant of H₂PO₄[−] species by receptors of **3** type.¹¹ The stabilization of the ferrocenium state¹² and the binding enhancement factor (BEF)¹³ were 26.53 KJ mol^{−1} and 4.46 × 10⁵, respectively. Remarkably, the presence of AcO[−] and Br[−] anions, even in large excess, had no obvious effect on the CV properties of **3** (Table 1). These findings revealed that receptor **3** had a high selectivity for electrochemical sensing of H₂PO₄[−] anion.

As reported previously, the binding between the ferrocene-based receptor and cations generally results in an

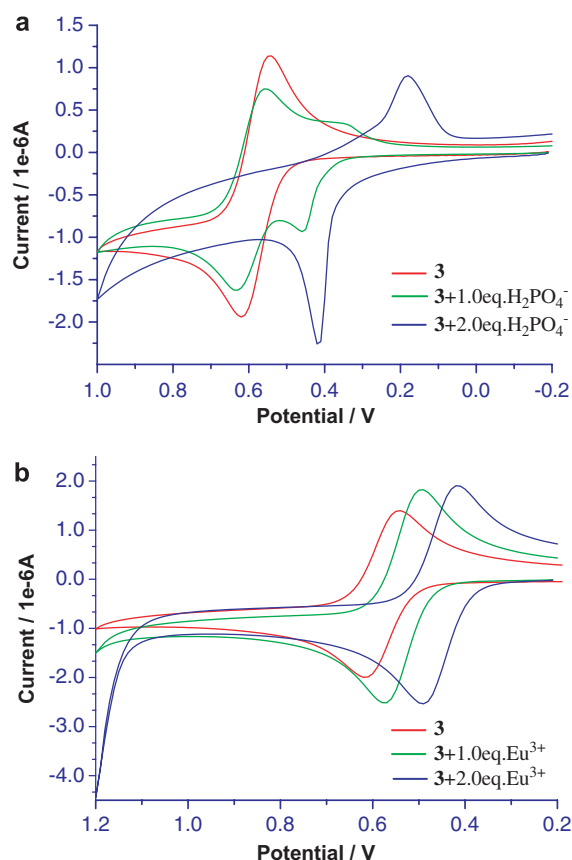


Figure 1. Cyclic voltammograms of **3** (a) **3** + H₂PO₄[−]; (b) **3** + Eu³⁺. Reagents and conditions: 5 × 10^{−4} M of **3** and 0.1 M *n*-Bu₄NClO₄ in CH₂Cl₂:CH₃CN (1:1) solution, Pt disk working electrode and scan rate = 100 mV s^{−1}.

anodic shift of the ferrocene–ferrocenium redox couple,¹⁴ because, once complexed, the ferrocene compound

Table 1. Electrochemical anion recognition data for receptor **3**^a

Anion	$\Delta E_{1/2}$ (mV)
H ₂ PO ₄ ⁻	275
AcO ⁻	0
Br ⁻	0

^a Conditions: 5×10^{-4} M of receptor **3** and 0.1 M *n*-Bu₄NClO₄ in CH₂Cl₂:CH₃CN (1:1), Pt disk working electrode, Pt auxiliary electrode, Hg/Hg₂Cl₂ reference electrode and scan rate = 100 mV s⁻¹. Errors \pm 10 mV.

may become more difficult to oxidize and therefore the ferrocenyl redox couple shifts to a higher potential. For example, Beer and co-workers¹⁵ reported a series of ferrocene-appended calixarene receptors and found the respective ferrocene–ferrocenium redox couple of these receptors showing anodic shifts with the addition of trivalent lanthanide ions. In our case, however, upon addition of increasing amounts of Eu³⁺ ion (as perchlorate salts) to receptor **3**, a surprising and significant cathodic shift of the wave was observed, in which the maximum perturbation of the CV was up to 130 mV obtained with 2 equiv of Eu³⁺ ion and the electrochemical response still remained reversible (Fig. 1b). This suggested that in some way the presence of the positively charged Eu³⁺ ion could unexpectedly increase the electron density at the ferrocenyl redox centers of receptor **3**.¹⁶ Similarly, with the negative shift, the stabilization of ferrocenium state of receptor **3** by Eu³⁺ ion was 12.54 KJ mol⁻¹ and, the BEF was 158. Moreover, there were no detectable electrochemical responses of the ferrocene centers toward Na⁺, K⁺, Mg²⁺, and Cu²⁺ ions (Table 2), although these cations may also be able to complex with receptor **3**.

To gain a better understanding of the binding of receptor **3** to Eu³⁺ ion, ¹H NMR titration experiments were carried out. Europium induced chemical shift changes were shown in Table 3. The –OCH₂, –C₆H₄–, and calix–ArH of receptor **3** revealed upfield-shift changes, indicating that Eu³⁺ ion was entrapped by the polyether linkages and sulfide bridges. In contrast, the NH exhibited 0.86 ppm downfield shifting upon the complexation, implying that the oxygen atoms of amide groups also coordinated with Eu³⁺ ion. These were in accordance with the results of the electrochemistry and suggested that **3** had two binding sites and could complex with two europium cations (see the Supplementary data).

In view of the existence of metal-centered spectroscopic properties of Eu³⁺ ion in complexes,¹⁷ the complexation

Table 2. Electrochemical cation recognition data for receptor **3**^a

Cation	$\Delta E_{1/2}$ (mV)
Na ⁺	0
K ⁺	0
Mg ²⁺	0
Cu ²⁺	0
Eu ³⁺	130

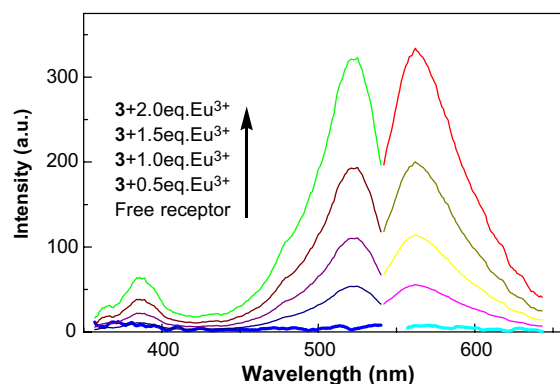
^a Conditions: 5×10^{-4} M of receptor **3** and 0.1 M *n*-Bu₄NClO₄ in CH₂Cl₂:CH₃CN (1:1), Pt disk working electrode, Pt auxiliary electrode, Hg/Hg₂Cl₂ reference electrode and scan rate = 100 mV s⁻¹. Errors \pm 10 mV.

Table 3. Eu³⁺-induced change in ¹H NMR chemical shifts of **3**: H₁ (NH), H_{2a,b} (ArH), H₃ (calix–ArH), H_{4a–d} (OCH₂)^a

Proton	$\Delta\delta$ (ppm)	Proton	$\Delta\delta$ (ppm)
H ₁	+ 0.86	H _{4a}	–0.05
H _{2a}	– ^b	H _{4b}	– ^b
H _{2b}	–0.14	H _{4c}	–0.10
H ₃	–0.16	H _{4d}	–0.12

^a Conditions: 5×10^{-2} M of Eu(ClO₄)₃ in DMSO-*d*₆ was added to 5×10^{-4} M of **3** in CDCl₃; the (+) and (–) imply downfield- and upfield-shift signs on Eu³⁺ complexation, respectively.

^b The change of chemical shifts was unable to calculate due to the overlap of the NMR peaks.

**Figure 2.** Changes in the fluorescence excitation and emission of **3** (5×10^{-4} M) upon the addition of Eu³⁺ ion.

behavior of receptor **3** with Eu³⁺ ion was further examined through the changes in the fluorescence spectrum of **3** in CH₂Cl₂:CH₃CN (1:1) solution, upon addition of Eu³⁺ ion (Fig. 2). The free receptor exhibited no fluorescence band, however, upon addition of Eu³⁺ ion, two excite bands were found at 389 and 526 nm, respectively. The excite band at 389 nm can be assigned to the characteristic excite band of Eu³⁺ ion.¹⁶ When excited at 389 nm, no Eu³⁺ characteristic emission band at about 612 nm could be observed, indicating that the Eu-centered luminescence was quenched by the four ferrocene moieties in receptor **3**, whereas excited at 526 nm, an emission band was found at 562 nm and a strong fluorescence enhancement of receptor **3** was obtained. These findings also suggested that there existed an electron transfer process between the excited state of Eu³⁺ and Fe²⁺ in ferrocene units.^{17,18} However, rational pathways for the extraordinary electrochemical recognition behavior of **3** toward Eu³⁺ ion are currently not fully understood.

In conclusion, we have synthesized and characterized a novel ditopic ferrocene-based thiacalix[4]arene receptor **3**, which possesses four polyether arms ended with ferrocene units and can electrochemically sense Eu³⁺ and H₂PO₄⁻ ions with a marked selectivity, respectively. The present work substantially extends the applications of thiacalixarenes as molecular scaffolds. The syntheses, ion pair sensing abilities and redox complexing mechanisms of receptor **3** type of compounds are currently under intensive investigations in our laboratory.

Acknowledgments

We gratefully acknowledge financial support from the National Natural Science Foundation of China (No. 20572064) and the State Key Laboratory of Elemento-Organic Chemistry.

Supplementary data

Detailed procedures and characterization of receptors, crystal, electrochemistry and ^1H NMR titration data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.12.047.

References and notes

- (a) Kirkovits, G. J.; Shriver, J. A.; Gale, P. A.; Sessler, J. L. *J. Inclusion Phenom. Macrocycl. Chem.* **2001**, *41*, 69–75; (b) Deetz, M. J.; Shang, M.; Smith, B. D. *J. Am. Chem. Soc.* **2000**, *122*, 6201–6207; (c) Shukla, R.; Kida, T.; Smith, B. D. *Org. Lett.* **2000**, *2*, 3099–3102; (d) Tozawa, T.; Misawa, Y.; Tokita, S.; Kubo, Y. *Tetrahedron Lett.* **2000**, *41*, 5219–5223; (e) Cooper, J. B.; Drew, M. G. B.; Beer, P. D. *J. Chem. Soc., Dalton Trans.* **2000**, 2721–2728; (f) Miyaji, H.; Collinson, S. R.; Prokés, I.; Tucker, J. H. R. *Chem. Commun.* **2003**, 64–65.
- (a) Martínez-Mañez, R.; Sancenón, F. *Chem. Rev.* **2003**, *103*, 4419–4476; (b) Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 191–221; (c) Beer, P. D.; Hayes, E. J. *Coord. Chem. Rev.* **2003**, *240*, 167–176.
- (a) Evans, C. H. *Biochemistry of the Lanthanides*; Plenum: New York, 1990; (b) Sessler, J. L.; Hoehner, V.; Kral, M. C.; Chin, K. O. A.; Davila, R. M. *Pure Appl. Chem.* **1996**, *68*, 1291–1294; (c) Parker, D.; Williams, J. A. *J. Chem. Soc., Dalton Trans.* **1996**, 3613–3628; (d) Hall, J.; Husken, D.; Schneider, H. J. *Angew. Chem., Int. Ed.* **1996**, *35*, 1219–1223; (e) Bünzli, J. C. G.; Piguet, C. *Chem. Rev.* **2002**, *102*, 1897–1928.
- (a) Iki, N.; Miyano, S. *J. Inclusion Phenom. Macrocycl. Chem.* **2001**, *41*, 99–105; (b) Hosseini, M. W. *Calixarenes*; Kluwer Academic Publishers: Dordrecht, 2001, pp 110–129; (c) Morohashi, N.; Iki, N.; Miyano, S. *J. Synth. Org. Chem. Jpn.* **2002**, *60*, 550–561; (d) Shokova, E. A.; Kovalev, V. V. *Russian J. Org. Chem.* **2003**, *39*, 1–28; (e) Lhoták, P. *Eur. J. Org. Chem.* **2004**, 1675–1692.
- (a) Beer, P. D.; Gale, P. A.; Chen, G. Z. *J. Chem. Soc., Dalton Trans.* **1999**, 1897–1909; (b) Cooper, J. B.; Drew, M. G. B.; Beer, P. D. *J. Chem. Soc., Dalton Trans.* **2000**, 2721–2728; (c) Tomapatanaget, B.; Tuntulani, T. *Tetrahedron Lett.* **2001**, *42*, 8105–8109; (d) Evans, A. J.; Beer, P. D. *Dalton Trans.* **2003**, 4451–4456; (e) Tomapatanaget, B.; Tuntulani, T.; Chailapakul, O. *Org. Lett.* **2003**, *5*, 1539–1542.
- Kumagai, H.; Hasegawa, M.; Miyanari, S.; Sugawa, Y.; Sato, Y.; Hori, T.; Ueda, S.; Kamiyama, H.; Miyano, S. *Tetrahedron Lett.* **1997**, *38*, 3971–3972.
- Sungho, Y.; Aaron, E. A.; Audrey, P. W.; Christopher, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16030–16031.
- Lhoták, P.; Svoboda, J.; Stibor, I. *Tetrahedron* **2006**, *62*, 1253–1257.
- Lau, H. H.; Hart, H. *J. Org. Chem.* **1959**, *24*, 280–281.
- Moon, K.; Kaifer, A. E. *J. Am. Chem. Soc.* **2004**, *126*, 15016–15017.
- Miller, S. E.; Gustowski, D. A.; Chen, Z. H.; Gokel, G. W.; Echegoyen, L.; Kaifer, A. E. *Anal. Chem.* **1988**, *60*, 2021–2024.
- Bourgel, C.; Boyd, A. S. F.; Cooks, G.; de Cremires, H. A.; Dulairon, F. M. A.; Rotello, V. M. *Chem. Commun.* **2001**, 1954–1955.
- Beer, P. D.; Gale, P. A.; Chen, G. Z. *J. Chem. Soc., Dalton Trans.* **1999**, 1897–1910.
- Plenio, H.; Aberle, C. *Chem. Eur. J.* **2001**, *7*, 4438–4446.
- Brindley, G. D.; Fox, O. D.; Beer, P. D. *J. Chem. Soc., Dalton Trans.* **2000**, 4354–4359.
- Beer, P. D.; Danks, J. P.; Heseck, D.; McAleer, J. F. *J. Chem. Soc., Chem. Commun.* **1993**, 1735–1737.
- Bünzli, J.-C. G.; Piguet, C. *Chem. Rev.* **2002**, *102*, 1897–1928.
- (a) Craig, D. P.; Ross, I. G. *J. Chem. Soc.* **1954**, 1589–1606; (b) Fry, A. J.; Liu, R. S. H.; Hammond, G. S. *J. Am. Chem. Soc.* **1966**, *88*, 4781–4782; (c) Wrighton, M. S.; Pdungsap, L.; Morse, D. L. *J. Phys. Chem.* **1975**, *79*, 66–71.