Calix[4]arenes Containing Ferrocene Amide as Carboxylate Anion Receptors and Sensors

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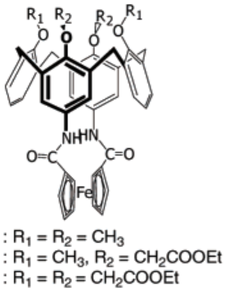
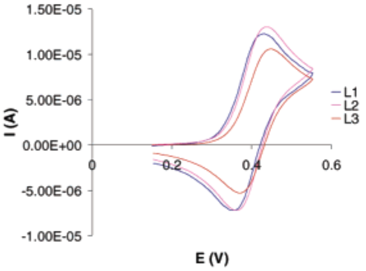


L1 : $R_1 = R_2 = CH_3$
L2 : $R_1 = CH_3$, $R_2 = CH_2COOEt$
L3 : $R_1 = R_2 = CH_2COOEt$



Calix[4]arene derivatives containing amide ferrocene units at the wide rim and ethyl ester groups at the narrow rim, L1–L3, were synthesized and their anion binding and sensing properties were investigated. It was found from ^{1}H NMR titrations that L1–L3 were able to bind selectively with carboxylate anions. Moreover, cyclic voltammetry and square wave voltammetry showed that L1–L3 were able to act as electrochemical sensors for carboxylate anions.

Anion recognition is an area of interest for biological systems and environmental pollutants. It is thus important to fabricate new anion sensors or develop new techniques for sensing anions. Artificial molecules are constructed to have anion binding sites linked to a sensory unit. Generally, chemists have employed either hydrogen bonding receptors or cationic receptors such as amide, guanidinium, pyridinium, and urea or thiourea groups for binding anions.[1] Ferrocene and cobaltocene have been used as electrochemical responding units, as they give a reversible redox couple in cyclic voltammograms. Additionally, cyclopentadienes can be easily modified. Beer and co-workers are pioneers in making metallocene amide receptors for binding and sensing anions.[2]

Recently, ion-pair recognition has been recognized by supramolecular chemists due to its potential applications in metal ion and anion attraction or metal-controlled anion sensing devices.[3] Beer and co-workers have synthesized a number of ditopic receptors that can undergo selective ion-pair recognition. Rhenium(I) bipyridyl amide crown ether receptors were found to complex KCl ion pairs.[4a] A tripodal tris(amido benzo-15-crown-5) ligand was found to cooperatively bind chloride, iodide, and perrhenate anions via co-bound crown ether-complexed sodium cations.[4b] Reinhoudt and co-workers have synthesized an elegant calix[4]arene derivative with cation binding ester groups on the narrow rim and anion binding urea groups on the wide rim. The compound was able to bind Cl^- efficiently in the presence of Na^+.[5]

Our group is interested in synthesizing ion-pair receptors and sensors. Calix[4]arene is an excellent supramolecular

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(1) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609.

(2) (a) Beer, P. D.; Graydon, A. R.; Johnson, A. O. M.; Smith, D. K. *Inorg. Chem.* **1997**, *36*, 2112. (b) Beer, P. D.; Drew, M. G. B.; Hesek, D.; Nam, K. C. *Organometallics* **1999**, *18*, 3933.

(3) Gale, P. A. *Coord. Chem. Rev.* In press.

(4) (a) Redman, J. E.; Beer, P. D.; Dent, S. W.; Drew, M. G. B. *Chem. Commun.* **1998**, 231−232. (b) Beer, P. D.; Hopkins, P. K.; McKinney, J. D. *Chem. Commun.* **1999**, 1253−1254.

(5) Scheerder, J.; van Duynhoven, J. P. M.; Engbersen, J. F. J.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1090.

building block for this purpose. We synthesized a tripodal amine-capped calix[4]arene. In its ammonium form, the receptor increased its affinity for Br^- in the presence of K^+.[6] In this paper, we report new receptors and sensors for both cations and anions. Our strategy is to attach the cation binding groups, ethyl esters, to the narrow rim of calix[4]-arene and the sensory units, ferrocenes, to the amide units acting as anion receptors at the wider rim. The ethyl ester groups also serve as inhibitors for phenyl ring rotation. We have thus synthesized three calix[4]arene derivatives, **L1**−**L3** (Figure 1).

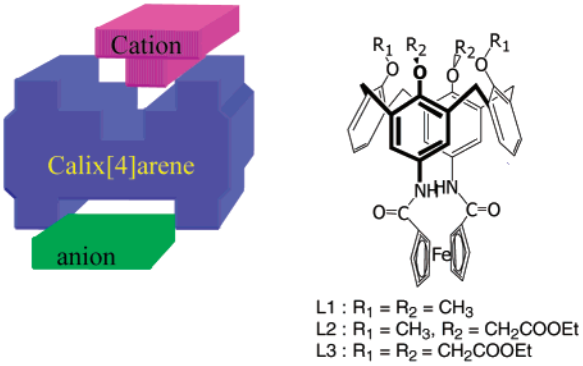

Figure 1. Schematic diagram for designed receptors.

The preparation of ethylester ferrocene amide and methoxy ferrocene amide calix[4]arenes **L1**−**L3** was reported previously.[7] NMR techniques such as COSY, NOESY, HMQC, and HMBC indicated that **L1** and **L2** exist as mixtures of cone and partial cone conformations (Supporting Information), while **L3** is in a cone conformation.

We studied the binding ability of the three ligands toward anions such as $PhCO_2^-$, $CH_3CO_2^-$, $H_2PO_4^-$, HSO_4^-, NO_3^-, Cl^-, Br^-, and I^- as their tetrabutylammonium salts by ^1H NMR titrations in CD_3CN. The NH protons of the amide groups in the three compounds were monitored. For all ligands, the NH signal did not shift upon addition of Br^-, I^-, NO_3^-, or HSO_4^-, signifying that **L1**−**L3** did not form complexes with these anions. Upon addition of $PhCO_2^-$ or $CH_3CO_2^-$, significant downfield shifts of the NH protons of **L1**−**L3** were observed due to hydrogen bonding interactions. Smaller shifts of the NH signals were found in the cases of $H_2PO_4^-$ and Cl^-. The titration curves for **L3** with $PhCO_2^-$, $CH_3CO_2^-$, $H_2PO_4^-$, and Cl^- are shown in Figure 2. Two different N*H* signals were observed at 8.09 and 7.86 ppm for **L1** and at 8.10 and 7.88 ppm for **L2** belonging to the amide NH protons of their partial cone and cone conformations, respectively. In CD_3CN, both cone and partial cone conformation ratios of **L1** and **L2** are constant. Therefore, ^1H NMR titrations can be carried out and *K* values can be calculated for each conformation. Stability constants of compounds **L1**−**L3** toward various anions calculated by the program EQNMR[8] are summarized in Table 1.

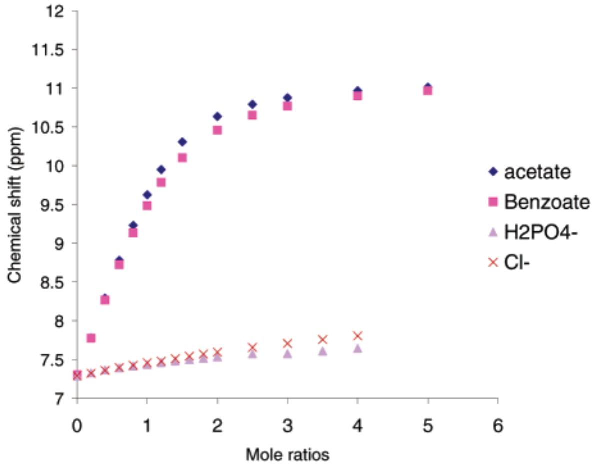

Figure 2. Titration curves of **L3** with various anions in CD_3CN.

Table 1. Stability Constants of Compounds **L1**−**L3** toward Various Anions at Room Temperature in CD_3CN-d^3 (M^{-1})

	L1		**L2**		**L3**
anions	PC	C	PC	C	C
$PhCOO^-$	540	472	139	100	915
CH_3COO^-	826	741	227	174	1200
$H_2PO_4^-$	34	a	91	94	a
Cl^-	32	a	49	86	29

[a] PC = partial cone conformation; C = cone conformation a. *K* values could not be refined. All association constants have errors of less than 10%.

Compounds **L1**−**L3** possess amide NH groups that can form bidentate-like hydrogen bonding interactions with carboxylate anions and $H_2PO_4^-$. Moreover, all ligands bind preferentially with acetate over benzoate because acetate is more basic than benzoate.[9] Interestingly, **L3** has a higher affinity for anions compared to **L1** and **L2** since **L3** is rigidified by four bulky ethyl ester groups to give a high degree of preorganization. Ethyl ester groups on aromatic rings are also electron-withdrawing groups. This enhances the acidity of the amide NH protons. Cl^- and $H_2PO_4^-$ anions give smaller *K* values than acetate and benzoate, probably due to the mismatched structure for spherical and tetrahedral anions.

The effects of alkali metal ions on the anion affinity of compound **L3** have also been studied. Unfortunately, upon

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(6) Tuntulani, T.; Poompradub, S.; Thavornyutikarn, P.; Jaiboon, N.; Ruangpornvisuti, V.; Chaichit, N.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* **2001**, *42*, 5541.

(7) Tomapatanaget, B.; Tuntulani, T. *Tetrahedron Lett.* **2001**, *42*, 8105. Details of syntheses and characterization can be found in Supporting Information.

(8) Hynes, M. J. *J. Chem. Soc., Dalton Trans.* **1993**, 311.

(9) Izutsu, K. *Acid−Base Dissocation Constants in Dipolar Aprotic Solvents*; Blackwell Scientific Publications: Oxford, 1990.

addition of metal cations, white precipitates of metal salts always formed and the chemical shift of the NH protons did not change. This suggests that the added metal ions formed complexes with the bound anions and precipitated as salts. This also implies that the metal cations bind loosely in the ethyl ester cavity. However, the complexation of the ligands with alkali metals such as Na^+, K^+, Rb^+, and Cs^+ can be studied by ESI mass spectrometry. The molecular mass peaks of complexes between **L3** and Na^+, K^+, Rb^+, and Cs^+ were found at 1059.90, 1076.00, 1122.39, and 1169.81 *m*/*z*, respectively.

The electrochemical properties of ligands **L1**−**L3** can be studied by cyclic voltammetry and square wave voltammetry. Cyclic voltammetry (CV) and square wave voltammetry (SWV) were performed using solutions of **L1**−**L3** (1×10^{-3} M) prepared in anhydrous acetonitrile with 0.1 M Bu_4NPF_6 as a supporting electrolyte and using a glassy carbon working electrode, a Ag/Ag^+ reference electrode, and a Pt wire counter electrode. The potential was scanned in the range of 0.15−0.55 V at 50 mV/s. Cyclic voltammograms of **L1**−**L3** showed reversible redox couples of ferrocene/ferricinium at $E_{1/2}$ of 0.383, 0.399, and 0.417 mV, respectively, as shown in Figure 3.

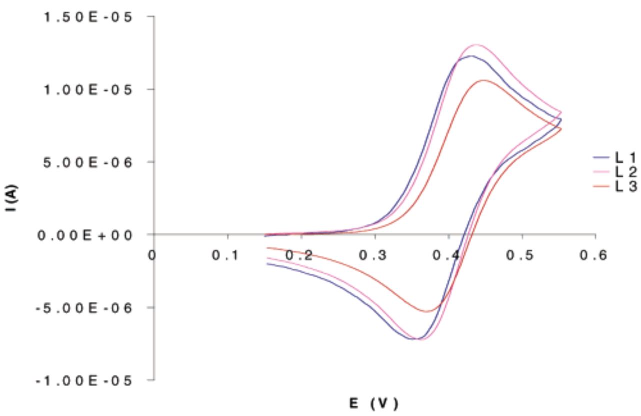


Figure 3. Cyclic voltammograms of **L1**−**L3**.

In light of results from ^{1}H NMR titrations, acetate, benzoate, $H_2PO_4^-$, and Cl^- were subjected to electrochemical investigation in order to study the effect of anions on the electron-transfer process of the ferrocene units in **L1**−**L3**. Titrations were carried out by addition of aliquots of tetrabutylammonium salts of benzoate, acetate, $H_2PO_4^-$, and Cl^-, followed by CV and SWV measurements at a scan rate of 50 mV/s. Addition of anions was generally varied from 0.2 to 4.0 equiv. Titrations of **L1**−**L3** with benzoate anion display a progressive appearance of a new oxidation wave at a less positive potential and a progressive disappearance of the initial oxidation and reduction wave. In a square wave voltammogram, it has been found that a new wave gradually appears at a less positive potential, while the initial wave decreases and disappears completely. The replacement of the initial wave by the new one is complete after addition of excess anionic species (2.5 equiv). In the case of cyclic voltammograms, the complexes of all ligands and anions (benzoate and acetate) result in quasireversible voltammograms when 0.2−3.0 equiv of anions were added and voltammograms became completely irreversible after adding 4 equiv of anions. Presumably, the ferricinium (Fc^+) unit enhances binding with anionic species through electrostatic interactions (ion-pairing interactions). Anions, then, inhibit the electron-transfer back to ferrocene (Fc). Cyclic voltammograms and square wave voltammograms of **L3** with benzoate are shown in Figure 4.

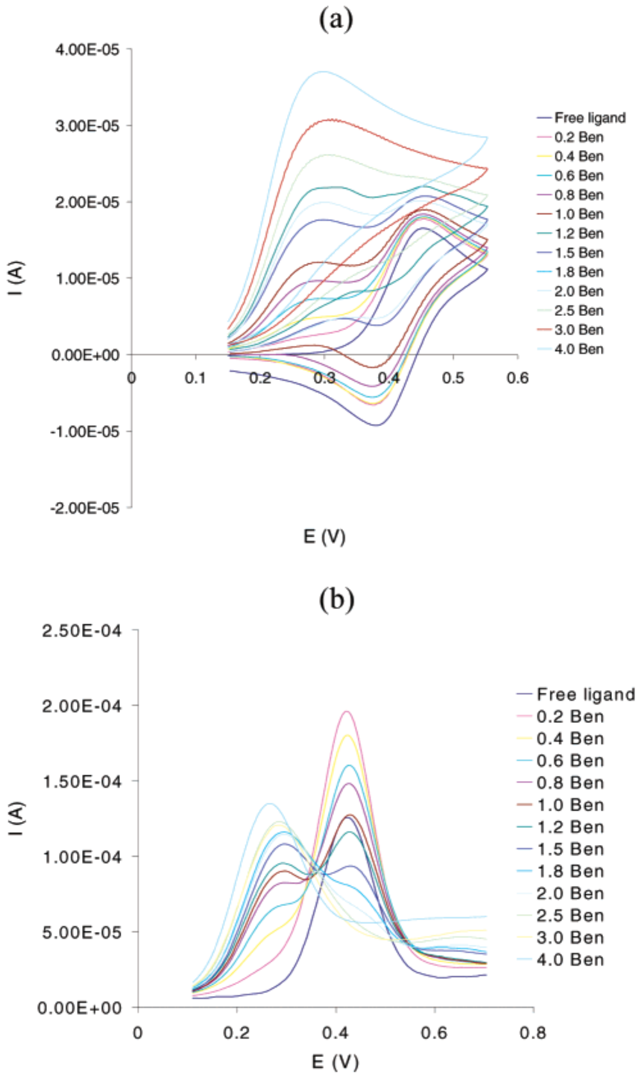
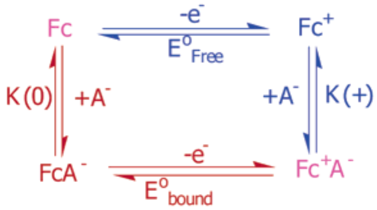


Figure 4. Titrations of **L3** and benzoate in CH_3CN with 0.1 M TBAPF and a scan rate of 50 mV/s: (a) CV titrations and (b) SWV titrations. Ben = benzoate.

The mechanism of electrochemical and anion binding processes can be deduced as shown in Scheme 1 and is similar to the Echegoyen−Kaifer model.[10] The complexes of Fc^+A^- can occur by two pathways. In one pathway, Fc may bind anionic species via amide NH groups by hydrogen bonding interactions to produce the complex of FcA^-, which

Scheme 1. Mechanism of Electrochemical Properties for Complexes



is then oxidized to give Fc^+A^-. Alternatively, a Fc unit is first oxidized to a Fc^+ unit and subsequently binds anions, exploiting the synergy of hydrogen bonding interactions via the NH groups and electrostatic interactions. This causes the enhancement of binding ability of the ferricinium form toward anions.

The enhancement of binding constants ($K_{(+)}/K_{(0)}$) upon complexing anions to the ferricinium forms can be calculated from the relationship shown in eq 1.[10]

$$nF(E^\circ_{\text{bound}} - E^\circ_{\text{free}}) = RT \ln(K_{(+)}/K_{(0)}) \qquad (1)$$

$K_{(+)}$ = association constant of anion with ferricinium

$K_{(L)}$ = association constant of anion with ferrocene

Astruc and co-workers reported the enhancement of the binding constants of ferricinium units toward anions in their ferrocene amide dendrimer upon electrochemical oxidation of the ferrocene units.[11] They found that cyclic voltammogram of their dendrimers showed reversible peak shifts to less positive potentials upon addition of $H_2PO_4^-$ and they could calculate $K_{(+)}$ values. In our case, due to the quasi-reversible behavior of the cyclic voltammograms upon addition of anions, we can calculate only the binding enhancements as shown in Table 2.

Table 2. Binding Enhancements ($K_{(+)}/K_{(0)}$) of **L1**−**L3** with Various Anions Measured by Cyclic Voltammetry Techniques in CH_3CN with 0.1 M TBAPF and a Scan Rate at 50 mV/s

	L1	**L2**	**L3**
$C_6H_5COO^-$	85	200	200
CH_3COO^-	23	99	158
$H_2PO_4^-$	a	a	a
Cl^-	a	a	a

[a] Values could not be calculated.

From the results in Table 2, the ferricinium forms of **L1**−**L3** prefer to bind benzoate. The electrons on benzoate are stabilized by the aromatic ring, resulting in a stable negative charge, and the electron cloud of the aromatic ring also enhances the electrostatic interaction with the ferricinium form. Interestingly, the cyclic voltammograms of titrations of the three ligands with $H_2PO_4^-$ and Cl^- show only a slight shift in potential. The binding enhancement for these anions cannot be calculated. The electrochemical results thus agree with the ^1H NMR titration in that all three ligands recognize carboxylate anions better than $H_2PO_4^-$ and Cl^-.

In summary, we synthesized three calix[4]arene derivatives and found that all ligands can be anion receptors and sensors. All three ligands have selectivity for carboxylate anions. Enhancement of binding constants by electrostatic interactions takes place for the ferricinium forms of **L1**−**L3**.

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Supporting Information Available: Detailed experimental procedures, two-dimensional NMR spectra of **L1** and **L2**, ^1H NMR titration plots, and CV and SWV plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Miller, S. R.; Gustowski, D. A.; Chen, Z.-H.; Gokel, G. W.; Echegoyen, L.; Kaifer, A. E. *Anal. Chem.* **1988**, *60*, 2021.

(11) (a) Valerio, C.; Fillllaut, J.-L.; Ruiz, J.; Guittard, J.; Astruc, D. *J. Am. Chem. Soc*. **1997**, *119*, 2588. (b) Ruiz, J.; Medel, M. J. R.; Daniel, M.-C.; Blais, J.-C.; Astruc, D. *Chem. Commun.* **2003**, 464. (c) Daniel, M.-C.; Ruiz, J.; Astruc, D. *J. Am. Chem. Soc.* **2003**, *125*, 1150.