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Synthesis and Anion-Binding Properties of Novel Redox-Active Calixarene Receptors

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A novel synthetic approach towards redox-active calixarene-based receptors is described in which ferrocene fragments were introduced at the lower rim through anion-binding urea or amide connections. These derivatives were prepared in one pot by treating an amine-containing calixarene with ferrocenecarboxylic acid in the presence of diphenylphosphoryl azide and diisopropylethylamine. This method allows a convergent approach to these receptors and is readily adaptable to the introduction of other urea substituents. The anion-binding properties of these artificial receptors have been revealed by NMR spectroscopy and thoroughly investigated by electrochemical methods. We have assessed the importance of the urea–phosphate bonds in the observed electrochemical response by studying receptors in which the ferrocene reporters and binding fragments are closely associated or fully disconnected through a long alkyl chain. The experimental results clearly show the utmost importance of ion-pairing effects in the electrochemical recognition process, which account for most of the transduction signal in organic apolar media.

Introduction

Anion recognition and sensing are increasingly important research topics in supramolecular chemistry due to the involvement of various anions in biological and environmental subjects.[1,2] Chemists usually take advantage of a wide range of recognition fragments introduced into organic platforms to develop electrostatic, hydrophobic, π–π or hydrogen-bonding interactions, and NMR shifts or photochemical signals as transduction signals. Calixarenes are particularly interesting frameworks on which to build artificial anion-binding architectures.[3] Their dynamic properties, hydrophobic bowl-shaped structures and well-known chemical versatility are indeed fully suited to the straightforward synthesis of complex host molecules that allow multi-point recognition of anionic targets. In this study we have synthesized and investigated the anion-binding properties of novel artificial receptors with calixarene as the modular platform, urea units as anion-binding moieties and ferrocene as redox-active reporters. Urea fragments have already been introduced into the *para* positions of the calixarene skeleton mostly by direct linkage to elaborate supramolecular capsular materials[4–9] and anionic or ditopic receptors.[10–22]

The incorporation of metallocene fragments, usually cobaltocene or ferrocene, into such systems has been pursued essentially to act as sensors or to activate molecular level processes. Moon and Kaifer reported a redox-controlled dissociation of a self-assembled dimer,[23] whereas Beer et al. took advantage of the receptor's electrochemical activity as a signal of a recognition event.[24,25] They also pioneered the synthesis of metallocene-appended calixarenes for analytic purposes and for investigating electrochemical interactions between multi-redox architectures.[26,27] The most relevant examples include hetero-ditopic ferrocene receptors that contain two ethyl ester calix[4]arene units bridged by a ferrocene–amide moiety[28] and a tetraferrocenylcalixarene in which metallocenes have been directly introduced onto aniline-like fragments.[29]

In this paper, we report the synthesis and characterization of novel redox-active calixarene-based receptors in which ferrocene fragments have been introduced at the lower rim through anion-binding urea or amide connections. Their anion-binding properties have been investigated by electrochemical methods and by NMR spectroscopy.

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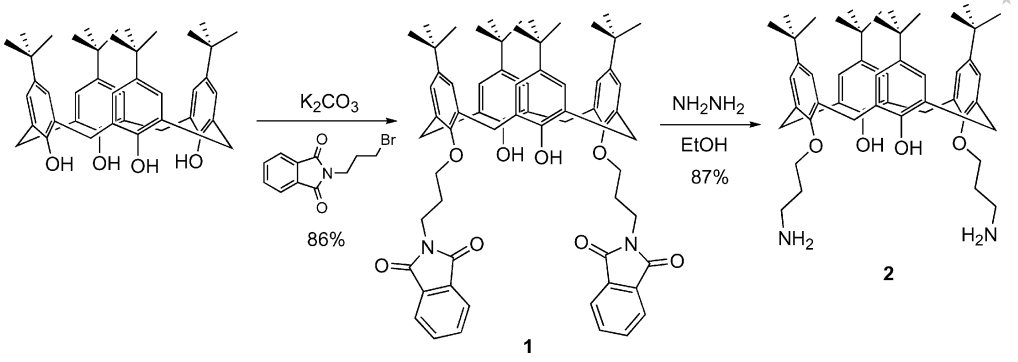


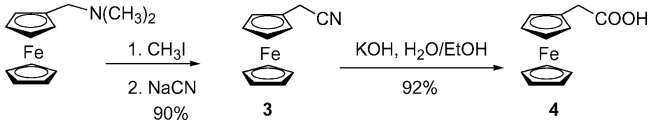
Scheme 1. Synthesis of the calixarene precursor **2** from *p-tert*-butylcalix[4]arene.[30]

Results and Discussion

Synthesis

The 25,27-bis(3-aminopropoxy)-5,11,17,23-tetra-*tert*-butyl-26,28-dihydroxycalix[4]arene (**2**; Scheme 1) was prepared in two steps from *p-tert*-butylcalix[4]arene as described in the literature.[30]

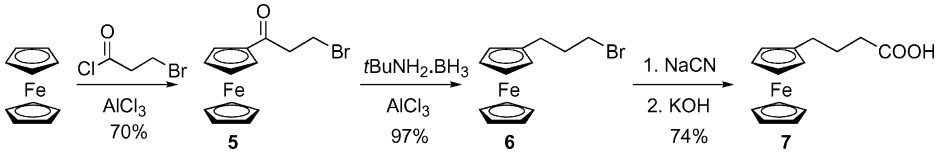
Ferrocenylacetic acid (**4**) as starting material (Scheme 2) was prepared as described in the literature from [(dimethylamino)methyl]ferrocene in good yield (83%).[31] The methyl iodide intermediate was treated with sodium cyanide to afford ferrocenylacetonitrile (**3**), which was then converted into the corresponding carboxylic acid.



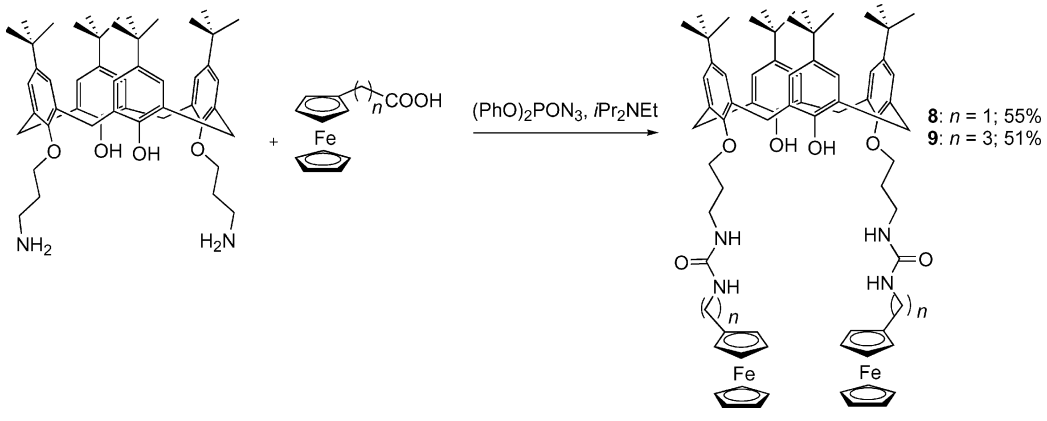
Scheme 2. Synthesis of ferrocenylacetic acid (**4**) from [(dimethylamino)methyl]ferrocene.[31]

4-Ferrocenylbutyric acid (**7**) has previously been prepared by the reaction of ferrocene with succinic anhydride followed by a Clemmensen reduction.[32] We report here an alternative approach from ferrocene in four steps with a 50% overall yield. After Friedel–Crafts acylation, the ketone was reduced to afford (3-bromopropyl)ferrocene (**6**). The last steps are identical to those detailed for the synthesis of ferrocenylacetic acid (**4**): formation of a cyanide, then hydrolysis (Scheme 3).

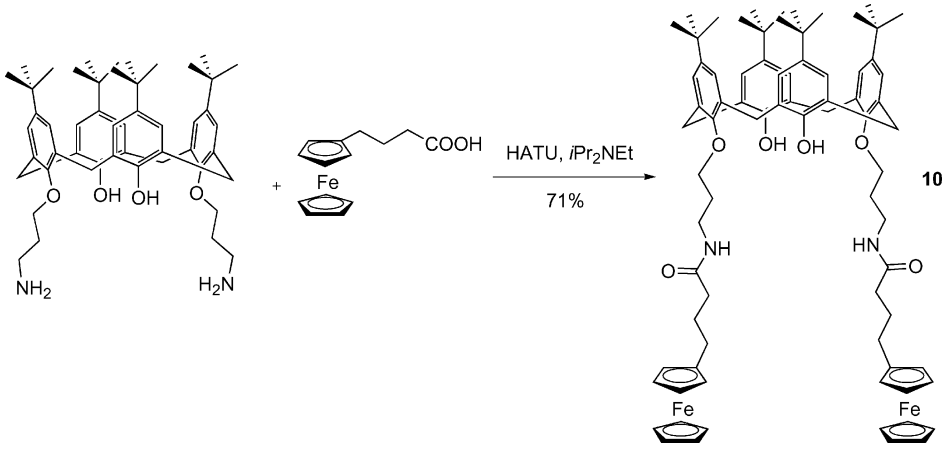
The ferrocenyl acid **7** and aminocalixarene **2** were linked through a urea connection by a Curtius rearrangement.[33] A number of approaches towards calixarene–ureas have already been investigated. Most of them were based on the use of commercially available isocyanates[34–36] or isocyanate derivatives of calixarenes.[37,38] Beer and co-workers



Scheme 3. Synthesis of 4-ferrocenylbutyric acid (**7**) from ferrocene.



Scheme 4. Linkage of ferrocene acid derivatives to the aminocalixarene **2** through a urea connection by a Curtius rearrangement.



Scheme 5. Synthesis of **10** from the coupling of aminocalixarene **2** with 4-ferrocenylbutyric acid (**7**).

have also reported the introduction of ferrocene–urea units into a calixarene skeleton by reaction with a ferrocene–carbamate.[29] In this study, the targeted redox-active receptors **8** and **9** were prepared in significant yields in one pot without isolating the isocyanate intermediate (Scheme 4). These derivatives were prepared by treating the calixarene–amine with ferrocene–carboxylic acid in the presence of diphenoxyphosphoryl azide and diisopropylethylamine. This method is a convergent approach based on the use of amino-functionalized calixarenes in the synthesis of urea derivatives and is readily adaptable to the introduction of other more complex urea substituents.

Metallocene redox-active fragments were also introduced into a calixarene framework by using the same starting materials and HATU [2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] as the coupling reagent. This straightforward peptide-based strategy allowed us to isolate **10** in 71% yield (Scheme 5).

The structures of **8**, **9** and **10** were clearly established by NMR spectroscopy and electrospray mass spectrometry. The cone conformations adopted in solution by the calixarene frameworks were deduced from the presence of resonance signals observed between δ = 31 and 32 ppm, which correspond to the $ArCH_2Ar$ fragments.[39]

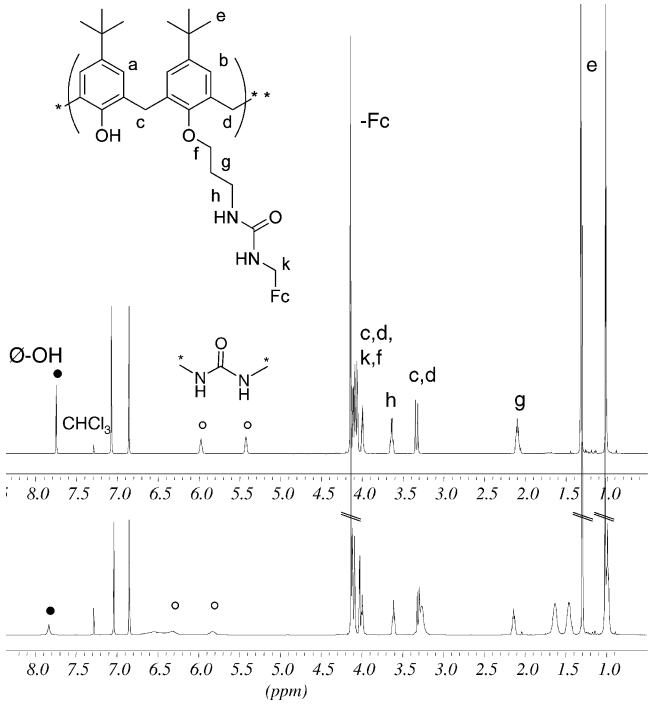


Figure 1. ^1H NMR spectra of **8** recorded in $CDCl_3$ (300 MHz) before (top) and after (bottom) the addition of an excess of $TBA{\cdot}H_2PO_4$.

NMR Analysis

The ferrocene-appended calixarene derivatives **8**, **9** and **10** were characterized by ^1H NMR spectroscopy in deuteriated chloroform. The corresponding spectra showed no evidence of intra- or intermolecular hydrogen-bonding, which would lead to capsular materials. Such association is frequently observed with tetraurea–calixarenes and clearly revealed by NMR spectroscopy through an overall symmetry loss and downfield shifts of the signals of the urea protons.[5] The NMR spectrum of **8** shown in Figure 1 features signals and chemical shifts in accordance with a non-self-assembled module.

The anion-binding ability of these receptors could be quickly confirmed by studying the effects of added anionic substrates on the chemical shifts of selected fragments. Addition of *n*-tetrabutylammonium dihydrogenphosphate to a $CDCl_3$ solution of **8** in particular led to significant downfield shifts of singlets attributed to the urea groups (Figure 1) and to a lesser extent to those of the phenol moieties (Figure 1). Such perturbations could be observed with all the synthesized receptors and clearly result from interactions between hydrogen-bonding donors and electron-rich anionic species. However, in agreement with previously reported studies,[40] these receptors exhibit, at least in their

reduced forms, relatively low-binding constants with anionic species. Titration of **8** conducted in CD_2Cl_2 with dihydrogenphosphate anions yielded, for instance, curves that could be fitted to a 1:1 calixarene/anion stoichiometry with an estimated binding constant of 36 ± 4 M^{-1}.[41]

Electrochemical Analysis

The electrochemical signatures of **8**, **9** and **10** were investigated by cyclic voltammetry, rotating disc electrode (RDE) and square-wave voltammetry on glassy carbon electrodes in dichloromethane, DMF and acetonitrile by using *n*-tetrabutylammonium perchlorate as the electrolyte (TBAP, 0.1 M). All cyclic voltammograms featured one single wave corresponding to the simultaneous oxidation of both ferrocene fragments, which highlights the limited or non-existent communication between the iron centres. As proven by the experimental data reported in Table 1, the ferrocene half-wave potential shifts significantly towards less positive values when the number of atoms between the metallocene and urea fragments increases. This significant displacement can be unambiguously attributed to the electron-withdrawing effect of the urea fragments on the metallocene probe which logically strengthens as their linker shortens.

Table 1. Experimental $E_{1/2}$ and ΔE_p values.[a]

	CH_2Cl_2		DMF		CH_3CN	
	$E_{1/2}$ [mV]	ΔE_p [mV]	$E_{1/2}$ [mV]	ΔE_p [mV]	$E_{1/2}$ [mV]	ΔE_p [mV]
8	175	126	49	86	[b]	[b]
9	139	106	25	78	39	70
10	153	98	36	84	42	77

[a] $E_{1/2} = (E_{pa} + E_{pc})/2$; $\Delta E_p = E_{pa} - E_{pc}$. Data recorded for **8**, **9** and **10** (10^{-3} M) on glassy carbon electrodes (3 mm diameter) at 100 mV s^{-1} by using TBAP (0.1 M) as the electrolyte. *E* vs. Ag/Ag^+ (10^{-2} M). [b] Not soluble in CH_3CN.

As mentioned above, the observation of one single ferrocene-centred oxidation wave results from the lack of communication between the two centres. The expected intramolecular association between urea fragments hence does not bring the two metallocenes into sufficient proximity to bring about significant electrochemically promoted electrostatic effects. It is now well established that the level of electrochemical connection in multi-redox architectures can be accurately estimated by measuring discrepancies between experimental results and theoretical modelling. The electrochemical behaviour of molecules with multiple redox centres has indeed been the subject of numerous studies.[42,43] It has been demonstrated[44] that electron transfers to or from molecules containing identical, non-interacting, electroactive centres should yield a single current–potential curve similar to that observed with a single electroactive centre (ΔE_p = 58 mV at 25 °C) but with a magnitude determined by the total number of redox centres. When each centre is characterized by the same standard potential $E_m°$ and adheres to the Nernst equation independently of the oxidation state of any of the other centres in the molecule, it is possible to calculate formal potentials for each pair of successive oxidation states of the multi-centre molecules. Considering fully non-interacting centres, the theoretical shift between the two ferrocene-based formal oxidation potentials for **8**, **9** and **10** ($E_1°$ and $E_2°$) should thus equal $\Delta E = E_1° - E_2° = 35.6$ mV, although both redox processes are expected to appear as a single wave with peak potentials satisfying $\Delta E_p = 58$ mV.[44] Formal potentials $E_1°$ and $E_2°$ cannot be determined in a straightforward manner, but the easily measured difference between oxidation and reduction peak potentials (ΔE_p) gives reliable leads on the "communication level" between multiple redox centres. The experimental values reported in Table 1 reveal the discrepancies in ΔE_p values, which range from 98 to 126 mV in dichloromethane. Such deviation from theoretical predictions can be attributed to different factors, including electron-transfer kinetics, adsorption processes or ohmic drop contributions, but also to non-negligible interactions between electrogenerated ferricinium species. Such assumptions especially rely on the fact that the largest ΔE_p value was observed for **8** in which intramolecular hydrogen bonds between urea groups expectedly lead to the shortest distance between the two metallocene centres. The differences in the ΔE_p values measured in apolar dichloromethane, however, turned out to be concentration-dependent as a significantly smaller value was measured at 5×10^{-4} M (Table 2). Such a feature clearly suggests the absence of a communication effect which therefore should not be considered to account for the large ΔE value. All the receptors studied exhibit a second irreversible oxidation process at $E \geq 800$ mV centred on both phenol subunits of the calixarene skeleton.[41] A typical voltammogram showing the ferrocene- and phenol-centred redox systems is depicted in Figure 2. As discussed above, **8**, **9** and **10** exhibit structural and chemical features fully suited to achieving an efficient complexation/sensing of anionic species. Urea and phenol

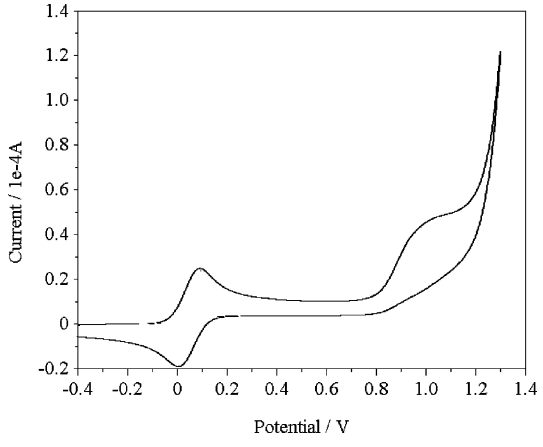


Figure 2. Cyclic voltammogram of **8** (10^{-3} M) recorded in DMF (0.1 M TBAP) at a glassy carbon electrode (3 mm diameter, ν = 100 mV s^{-1}).

groups are indeed among the most widely used binding fragments to trap or transport negatively charged species in biological systems.[45] The calixarene's lipophilic character and the structuring effect associated with the anion-binding properties of urea or amide and phenol are complementary expedient features that define **8**, **9** and **10** as artificial anion receptors with great potential. In addition to these favourable chemical and structural aspects, both metallocene moieties can be easily activated, that is, oxidized at low potential, to further improve the receptor anion-binding ability through electrochemically triggered ion-pairing effects between anionic targets and in situ singly or doubly positively charged receptors.[1]

The ability of **8**, **9** and **10** to complex anionic species and their potential in molecular electrochemical recognition were first investigated by cyclic voltammetry in dichloromethane electrolyte. The addition of increasing amounts *n*-tetrabutylammonium nitrate, sulfate, chloride or acetate to a 5×10^{-4} M solution of these receptors did not induce measurable changes in the ferrocene-centred oxidation wave. This lack of electrochemical response can be attributed to weak associations between these anions and the phenol/amide binding fragments and/or to limited interaction of the complexed anion with the neutral and/or oxidized metallocene redox probes. Completely different behaviour was, however, observed with fluoride. The addition of *n*-tetrabutylammonium fluoride (TBA·F) under the same conditions indeed prompted the development of a new irreversible oxidation wave at a less positive potential as well as an overall current increase (Figure 3). Fluoride is the hardest Lewis base of the halides due to its well-known limited size, weakly polarizable nature and high electronegativity. This species hence has the ability to form unusually strong non-covalent interactions with hydrogen-bonding donors. It has even been demonstrated that fluoride is basic enough to remove protons from amide-like-containing receptors, the properties of which are consequently drastically modified.[46–48] In order to establish whether the observed changes could be imputable to simple non-covalent interactions or to proton transfer, the same experiment was conducted by replacing fluoride by a non-anionic base. As shown in Figure 3B, addition of triethylamine in excess led to the growth of an intense irreversible signal centred at 550 mV, which corresponds to the oxidation of the tertiary amine, whereas the ferrocene-based signal was totally unaffected. The overall changes observed in Figure 3A are not yet fully understood but could be attributed to numerous factors including coupled chemical reactions or the adsorption of strong ion pairs formed between electrogenerated ferricinium and fluoride.[49,50] Similar behaviour and electrochemical responses were observed with **9** and **10** in the presence of fluoride.

An effective electrochemical response was also observed in the presence of hydrogenphosphate anions. The addition of these anions indeed resulted in a clear two-wave behaviour in which the intensity of the initial ferrocene-based wave progressively decreases at the expense of a novel signal at a much less positive potential (Figure 4A and B). After addition of 1 mol-equiv of anion, the intensity of both signals appeared comparable, and full disappearance of the original wave was only observed when the anion/receptor ratio reached about two. Such an evolution is fully compatible with the strong binding of one $H_2PO_4^-$ anion per urea fragment leading, in the end, to a bis(hydrogenphosphate) complex. This 2:1 binding stoichiometry, although different to that found in NMR experiments, can be easily explained by considering that two positive charges are electrochemically generated on the calixarene receptors. These results are furthermore in agreement with previously reported studies conducted on similar receptors.[40] It needs to be stressed that both waves remained fully reversible throughout the titration experiment and that the maximal potential shift ($\Delta E_{1/2}$) between the uncomplexed and complexed receptors reached 155 mV. The addition of $H_2PO_4^-$ anions to a solution of **8** did moreover not significantly modify the shift between oxidation and reduction peak potentials (ΔE, Table 2). This observation is another clear indication that the "large" ΔE value measured in dichloromethane does

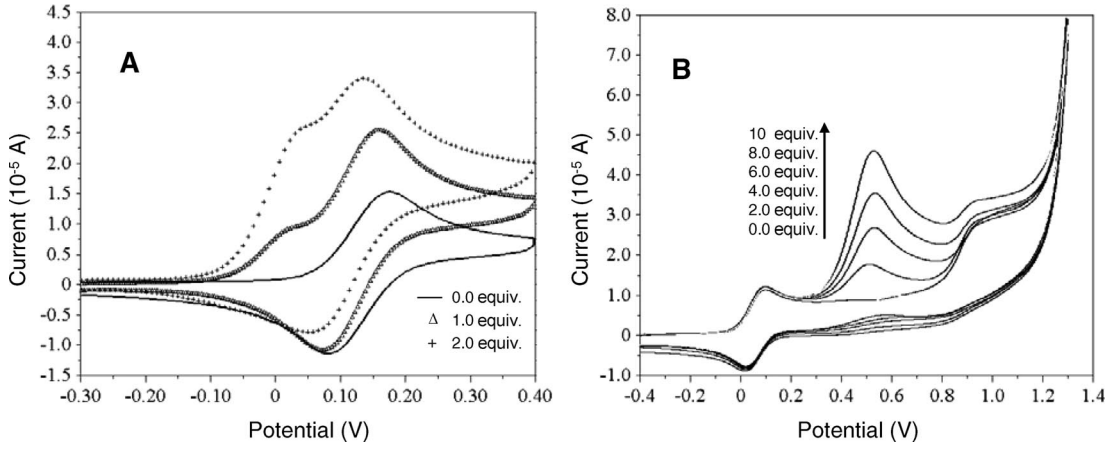


Figure 3. Cyclic voltammograms of **8** (5×10^{-4} M) recorded in dichloromethane (0.1 M TBAP) after the addition of increasing amounts of (A) TBAF and (B) triethylamine (glassy carbon electrode, 3 mm diameter, v = 100 mV s^{-1}).

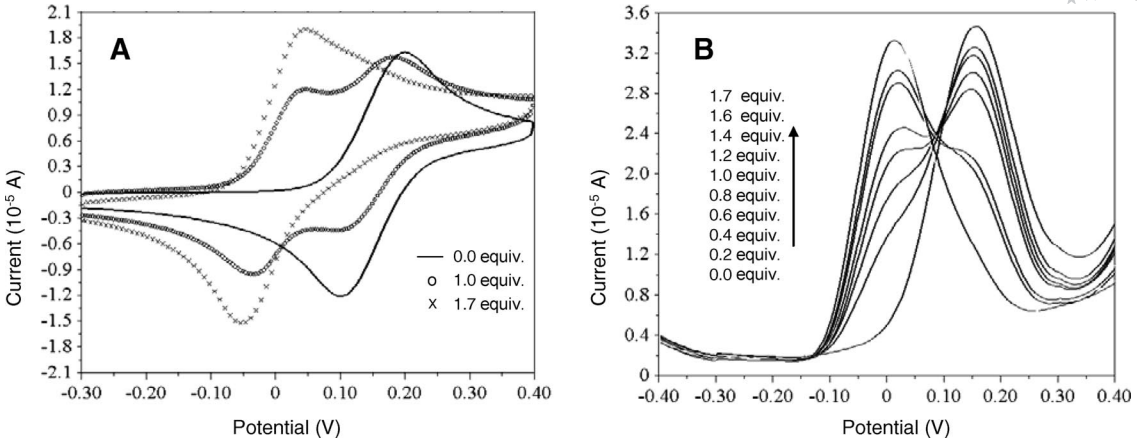


Figure 4. (A) Cyclic (v = 100 mV s^{-1}) and (B) square-wave voltammograms of **8** (5×10^{-4} M) recorded in dichloromethane (0.1 M TBAP) upon the addition of increasing amounts of TBA·H_2PO_4 (glassy carbon electrode, 3 mm diameter).

not result from urea-driven intramolecular redox communication which would logically be disrupted upon the addition of hydrogenphosphates.

Table 2. Electrochemical data (ΔE, $\Delta E_{1/2}$)[a] measured by cyclic voltammetry before and after the addition of 2 mol-equiv. of TBA·H_2PO_4 to dichloromethane (0.1 M TBAP) solutions of **8**, **9** and **10** (5×10^{-4} M, v = 100 mV s^{-1}, glassy carbon electrode, 3 mm diameter).

	ΔE [mV]	$\Delta E_{1/2}$ [mV]
8	98	155
8·($H_2PO_4^-$)$_2$	100	
9	92	135
9·($H_2PO_4^-$)$_2$	98	
10	92	94
10·($H_2PO_4^-$)$_2$	108	

[a] $\Delta E = (E_{pa} + E_{pc})/2$; $\Delta E_{1/2} = (E_{1/2})_{\mathbf{L}} - (E_{1/2})_{[\mathbf{L}\cdot(H_2PO_4^-)_2]}$ (**L** = **8**–**10**).

Several interactions and effects can potentially be considered to account for the observed changes. The hydrogen-bonding ability of the urea and phenol groups is clearly of great importance, but the influence of ferricinium and the effect of complexation on ferrocene are also key elements to achieving such efficient molecular electrochemical sensing. A short linkage between urea and ferrocene was initially considered to be essential to optimize the transduction of any recognition process. In order to estimate the importance of the urea–phosphate bonds in the wave's displacement, which arises from an overall increase of electron density around the metallocene fragments, we studied the response of **9** and **10** in which the ferrocene and the binding fragments are fully disconnected through a long alkyl chain, which prohibits any through-bond effects on the electrochemical recognition process. Addition of increasing amounts of TBA·H_2PO_4 to a dichloromethane solution of the free receptors **9** and **10** surprisingly led to similar "two-wave" responses distinguished only by the half-wave potential shift amplitudes ($\Delta E_{1/2}$, Table 2). The $\Delta E_{1/2}$ values reported in Table 2 indeed clearly highlight the beneficial effects of closely connecting the recognition and signalling fragments. The interaction of the urea groups in **8** with $H_2PO_4^-$ species has indeed an unambiguous electronic through-bond effect on the ferrocene's final oxidation potential. Although the most important perturbation is observed in the case of **8**, calixarenes **9** and **10** still allow effective sensing through important displacements of the ferrocene oxidation potential. This result shows that the ion-pairing effects on the electrochemical recognition process are of the utmost importance. When the ferrocene groups are far away from the hydrogen-binding fragments, as in **9** and **10**, the strong selective electrostatic interaction between hydrogen phosphate and the electrogenerated ferricinium species is almost enough to ensure an efficient transduction. This assumption has been further demonstrated by studying the electrochemical activity of ferrocene and TBA·H_2PO_4 in dichloromethane. The initial reversible Fc/Fc$^+$ couple quickly evolves towards a broad irreversible system in the presence of phosphate, which presumably results from the formation of poorly soluble ion pairs.[41] The organic receptors used in this study have thus two main effects; in addition to introducing selectivity and affinity towards the specific binding fragments, they also greatly help to stabilize and solubilize the oxidized forms of the calixarene anion complexes. The difference in $\Delta E_{1/2}$ (ca. 40 mV, Table 2) observed between **9**·($H_2PO_4^-$)$_2$ and **10**·($H_2PO_4^-$)$_2$ has tentatively been attributed to distinct coordination modes that set the complexed anion closer to the redox probe in **9** than in **10**. This shift is furthermore correlated to the number of atoms separating the ferrocene fragment from the amide hydrogen-bond donor in both receptors.

Conclusions

We have described herein a novel synthetic approach towards redox-active calixarene-based receptors in which ferrocene fragments have been introduced at the lower rim through anion-binding urea or amide connections. These derivatives were prepared in one pot by treating an amine-containing calixarene precursor with ferrocenyl–carboxylic acid in the presence of diphenylphosphoryl azide and diisopropylethylamine. This method allows a convergent ap-

proach to the receptors and is readily adaptable to the introduction of other more complex urea substituents. The anion-binding properties of these artificial receptors have been revealed by NMR spectroscopy and thoroughly investigated by electrochemical methods. We have assessed the importance of the urea–phosphate bonds in the observed electrochemical response by studying receptors in which the ferrocene and binding fragments are closely associated or fully disconnected through a long alkyl chain. Although similar selective phosphate-sensing properties have previously been reported with closely connected ferrocene–amide–calixarene receptors,[27,51] our experimental results clearly show that ion-pairing effects in this electrochemical recognition process, which account for more than 85% of the transduction signal, are of the utmost importance.

Experimental Section

Electrochemical Analysis: All electrochemical experiments were carried out by using a CH Instrument potentiostat. A standard three-electrode cell was used for analytical experiments. Potentials are referenced to $Ag|Ag^+$ (10^{-2} M in CH_3CN + 0.1 M TBAP). Glassy carbon disc electrodes (3 mm diameter, from CH Instruments) were polished with 1 μm diamond paste. All experiments were performed at room temperature under argon. An automatic *iR* compensation was performed before each cyclic voltammetric experiment conducted in homogeneous media. Acetonitrile (HPLC grade) was purchased from Rathburn chemicals, DMF (99.8% extra dry) was purchased from Acros chemicals and anhydrous dichloromethane was purchased from SDS. *n*-Tetrabutylammonium perchlorate (99%) was purchased from Fluka.

Synthesis: Starting materials and solvents were obtained from commercial suppliers and used without further purification. TLC was performed on silica gel 60 F254. NMR spectra were recorded with DRX300 or DRX500 Bruker FT spectrometers. Multiplicities are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quadruplet), quint (quintuplet), m (multiplet) and br. (broad). Mass spectra were recorded at the ECP Mass Spectrometry Centre by electrospray ionization. Compounds **3** and **4** were synthesized according to literature procedures.[31,52]

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(phthalimidopropoxy)calix[4]-arene-26,28-diol (1): *p-tert*-Butylcalix[4]arene (10 g, 15.4 mmol) and K_2CO_3 (2.34 g, 17 mmol) were heated in acetonitrile (380 mL) at reflux for 1 h. *N*-(3-Bromopropyl)phthalimide (9.1 g, 33.9 mmol) was added and the mixture heated at reflux for an additional 48 h. The solvent was evaporated in vacuo and the residue dissolved in $CHCl_3$. The solution was washed twice with water and brine and then dried. Evaporation of the solvent followed by precipitation from chloroform/methanol gave the desired compound as a white solid. Yield: 86%, 10.1 g. M.p. 261–264 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72–7.75 (m, 4 H, Pht*H*), 7.56–7.60 (m, 4 H, Pht*H*), 7.44 (s, 2 H, O*H*), 7.02 (s, 4 H, Ar*H*), 6.77 (s, 4 H, Ar*H*), 4.30 (d, J = 13.0 Hz, 4 H, ArCH_2Ar), 4.09 (m, 8 H, CH_2N, OCH_2), 3.31 (d, J = 13.0 Hz, 4 H, ArCH_2Ar), 2.43 (quint, J = 7.2 Hz, 4 H, CH_2CH$_2$N), 1.27 (s, 18 H, *t*Bu), 0.93 (s, 18 H, *t*Bu) ppm. HRMS: calcd. for $C_{66}H_{74}N_2O_8Na$ [MNa] 1045.5343; found 1045.53358.

25,27-Bis(3-aminopropoxy)-5,11,17,23-tetra-*tert*-butyl-26,28-dihydroxycalix[4]arene (2): A solution of **1** (5 g, 4.9 mmol) in EtOH (100 mL) was heated at reflux in the presence of hydrazine (5 mL). After 8 h, the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ (150 mL), washed with water (2 × 50 mL), dried ($MgSO_4$) and the solvent was evaporated. Addition of $CHCl_3$ (20 mL) followed by precipitation with hexane (40 mL) afforded the pure diamine as a white powder. Yield: 87%, 3.74 g. M.p. 207–210 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.06 (s, 4 H, Ar*H*), 6.75 (s, 4 H, Ar*H*), 4.12 (d, J = 13 Hz, 4 H, ArCH_2Ar), 4.07 (t, J = 5.8 Hz, 4 H, OCH_2), 3.21–3.30 (m, 8 H, ArCH_2Ar), 2.13 (m, J = 6.2 Hz, 4 H, CH$_2$CH_2CH$_2$), 1.23 (s, 18 H, *t*Bu), 0.90 (s, 18 H, *t*Bu) ppm. HRMS: calcd. for $C_{50}H_{71}N_2O_4$ [MH] 763.5414; found 763.5410.

(3-Bromo-1-oxopropyl)ferrocene (5): 3-Bromopropanoyl chloride (2.17 mL, 21.5 mmol) in CH_2Cl_2 (8 mL) was added dropwise to a suspension of aluminium chloride (3 g, 22.5 mmol) in CH_2Cl_2 (8 mL) at room temperature and stirred for 2 h. After cooling (–10 °C), the homogeneous solution was added to a solution of ferrocene (4 g, 21.5 mmol) in CH_2Cl_2 (50 mL) cooled to 0 °C. The resulting purple solution was warmed to room temperature and stirred for 16 h. This solution was then diluted with CH_2Cl_2 and poured over ice/H_2O. The product was extracted with CH_2Cl_2, and the organic phase was washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried with $MgSO_4$, filtered and concentrated. After purification by flash chromatography (silica gel; CH_2Cl_2), the desired product was obtained in 70% yield (4.85 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.78 (t, J = 1.88 Hz, 2 H, *H*Fc), 4.23 (s, 5 H, *H*Fc), 3.72 (t, J = 6.60 Hz, 2 H, CH$_2$), 3.29 (t, J = 6.60 Hz, 2 H, CH$_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.6, 78.3, 72.6, 70.0, 69.3, 42.2, 26.1 ppm.

(3-Bromopropyl)ferrocene (6) [CA 129467-15-8]: Borane–*tert*-butylamine complex (7.32 g, 84 mmol) in CH_2Cl_2 (200 mL) was added at 0 °C to a suspension of aluminium chloride (5.6 g, 42 mmol) in CH_2Cl_2 (200 mL). After 1 h, **5** (4.5 g, 14 mmol) in CH_2Cl_2 (100 mL) was added through a cannula. After stirring for 8 h, the reaction mixture was hydrolyzed with water and extracted with CH_2Cl_2. The crude product was purified by flash chromatography (silica gel; CH_2Cl_2) to afford 12.5 g (97%) of **6**. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.12 (s, 5 H, *H*Fc), 4.06 (s, 4 H, *H*Fc), 3.42 (t, J = 6.50 Hz, 2 H, CH$_2$), 2.50 (t, J = 7.50 Hz, 2 H, CH$_2$), 2.04 (tt, J = 6.50, J = 7.50 Hz, CH$_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 87.4, 68.7, 68.3, 67.5, 34.1, 33.7, 28.1 ppm. HRMS: calcd. for $C_{13}H_{15}BrFe$ 305.97066; found 305.97057.

(3-Cyanopropyl)ferrocene [CA 125848-67-1]: Sodium cyanide (1.2 g, 24.5 mmol) was added to a solution of **6** (2.5 g, 8.1 mmol) in DMSO (50 mL). After 8 h at 90 °C, 100 mL of brine was added, and the reaction mixture was extracted with ethyl acetate. The crude product was purified by flash chromatography (silica gel; cyclohexane/CH_2Cl_2, 5:5) to afford 1.8 g (88%) of the desired product. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.11 (s, 5 H, *H*Fc), 4.07 (s, 4 H, *H*Fc), 2.52 (t, J = 7.5 Hz, 2 H, CH$_2$), 2.33 (t, J = 7.0 Hz, 2 H, CH$_2$), 1.83 (tt, J = 7.5, J = 7.0 Hz, CH$_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 119.8, 86.5, 68.7, 68.3, 67.7, 28.6, 27.0, 16.8 ppm.

4-Ferrocenylbutyric Acid (7) [CA 1291-76-5]: Potassium hydroxide (3.92 g, 70 mmol) in water (10 mL) was added to a solution of (3-cyanopropyl)ferrocene (1.77 g, 7 mmol) in ethanol (60 mL). After 8 h at reflux, the reaction mixture was concentrated in vacuo and then diluted with water and washed with diethyl ether. The aqueous phase was acidified with 1 M HCl and extracted with diethyl ether. The organic phase was dried with $MgSO_4$, filtered, and concentrated under vacuum to afford 1.6 g (84%). M.p. 85–86 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.12 (s, 5 H, *H*Fc), 4.07 (s, 4 H, *H*Fc), 2.37–2.42 (m, 4 H, CH$_2$), 1.75–1.80 (m, 2 H, CH$_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.9, 87.8, 68.5, 68.1, 67.2, 33.6,

28.8, 25.9 ppm. HRMS: calcd. for $C_{14}H_{16}FeO_2$ 272.04997; found 272.05044.

General Procedure for the Curtius Reaction: Diisopropylethylamine (9 mmol) and diphenylphosphoryl azide (4.4 mmol) were added to a solution ferrocenyl–carboxylic acid (2.2 mmol) dissolved in toluene (15 mL). The reaction mixture was heated at 70 °C for 2 h, and then **2** (1 mmol) was added. After 2 h at 70 °C, the reaction mixture was concentrated under vacuum and purified by flash chromatography (silica gel; ethyl acetate/cyclohexane, 6:4) to afford the desired product.

Compound 8: Yield: 55%, 685 mg. M.p. 143–146 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71 (s, 2 H, O*H*), 7.04 (s, 4 H, Ar*H*), 6.83 (s, 4 H, Ar*H*), 5.94 (br. s, 2 H, N*H*), 5.40 (br. s, 2 H, N*H*), 4.11 (s, 10 H, *H*Fc), 4.02–4.08 (m, 16 H, ArCH_2Ar, *H*Fc, FcCH_2NH), 3.95–3.97 (m, 4 H, CH_2O), 3.59–3.63 (m, 4 H, CH_2NH), 3.30 (d, J = 13 Hz, 2 H, ArCH_2Ar), 2.05–2.08 (m, 4 H, $CH_2CH_2CH_2$), 1.29 (s, 18 H, *t*Bu), 0.98 (s, 18 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.0, 149.7, 149.6, 147.8, 142.9, 132.6, 128.0, 126.1, 125.7, 86.1, 76.1, 68.9, 68.7, 68.3, 39.9, 39.2, 34.3, 34.2, 32.4, 31.9, 31.3, 30.1 ppm. IR: (KBr pellets): $\tilde{\nu}$ = 3364, 2956, 2867, 1632 cm^{-1}. HRMS: calcd. for $C_{74}H_{92}Fe_2N_4O_6$ 1244.57157; found 1244.57163.

Compound 9: Yield: 51%, 664 mg. M.p. 125–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (s, 2 H, O*H*), 7.09 (s, 4 H, Ar*H*), 6.87 (s, 4 H, Ar*H*), 5.91 (br. s, 2 H, N*H*), 5.39 (br. s, 2 H, N*H*), 4.19 (d, J = 13.2 Hz, 4 H, ArCH_2Ar) 4.08 (s, 10 H, *H*Fc), 3.99–4.06 (m, 12 H, *H*Fc, CH_2O), 3.64–3.70 (m, 4 H, CH_2NH), 3.39 (d, J = 13.2 Hz, ArCH_2Ar), 3.19–3.26 (m, 4 H, CH_2NH), 2.27–2.31 (m, 4 H, CH_2CH_2Fc), 2.16–2.20 (m, 4 H, $CH_2CH_2CH_2$), 1.61–1.67 (m, 4 H, $CH_2CH_2CH_2$), 1.31 (s, 18 H, *t*Bu), 1.00 (s, 18 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.5, 149.9, 149.6, 147.7, 142.9, 132.6, 128.0, 126.1, 125.7, 88.8, 75.8, 68.7, 68.2, 67.4, 40.4, 38.9, 34.3, 34.7, 32.2, 31.9, 31.7, 31.3, 30.4, 27.0 ppm. IR: (KBr pellets): $\tilde{\nu}$ = 3376, 2961, 2867, 1634 cm^{-1}. HRMS: calcd. for $C_{78}H_{100}Fe_2N_4O_6$ 1300.63417; found 1300.63419.

Compound 10: HATU (1.2 mmol, 450 mg) and diisopropylethylamine (1.2 mmol, 0.2 mL) were added to a solution of **7** (1.2 mmol, 320 mg) in DMF (3 mL), and the mixture was stirred at 25 °C for 15 min. This solution was then transferred into a suspension of **2** (0.49 mmol, 370 mg) in DMF (5 mL) through a cannula. After 2 h, the reaction mixture was concentrated and purified by flash chromatography (silica gel; cyclohexane/ethyl acetate, 6:4) to afford compound **10** in 71% yield (443 mg). M.p. 105–109 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (s, 2 H, O*H*), 7.09 (s, 4 H, Ar*H*), 6.84 (s, 4 H, Ar*H*), 4.29–4.45 (m, 18 H, *H*Fc), 4.19 (d, J = 13 Hz, 4 H, ArCH_2Ar), 4.01–4.05 (m, 4 H, CH_2O), 3.67–3.69 (m, 4 H, CH_2NH), 3.36 (d, J = 13 Hz, 2 H, ArCH_2Ar), 2.13–2.25 (m, 16 H, CH_2Fc, CH_2CO,CH_2CH_2CH$_2$), 1.66–1.69 (m, 4 H, $CH_2CH_2CH_2$), 1.32 (s, 18 H, *t*Bu), 0.99 (s, 18 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.0, 150.4, 149.7, 147.7, 142.6, 132.7, 127.9, 126.0, 125.7, 88.9, 74.5, 69.0, 68.6, 67.7, 37.3, 36.5, 34.3, 34.2, 32.2, 32.0, 31.3, 30.5, 29.7, 29.2, 27.2 ppm. IR: (KBr pellets): $\tilde{\nu}$ = 3299, 2954, 2866, 1643 cm^{-1}. HRMS: calcd. for $C_{78}H_{98}Fe_2N_2O_6$ 1270.61237; found 1270.61244.

Supporting Information (see footnote on the first page of this article): ^{1}H NMR spectroscopic and analytical data for **8**, **9** and **10**.

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