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Conformational analysis and anion-binding properties of ferrocenyl-calixarene receptors

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Novel synthetic approaches toward redox active calixarene-based receptors are described wherein ferrocene fragments have been introduced at the lower rim through anion-binding urea or amide connections. A thorough ^{1}H NMR investigation on macrocycles was performed in order to estimate their hydrogen bonding-driven self-association properties and improve our understanding of the correlation between molecular structures and redox properties. The anion-binding properties of these artificial receptors have also been revealed by NMR spectroscopy and thoroughly investigated by electrochemical methods. We especially assessed the importance of the urea–phosphate bonds in the observed electrochemical response upon studying receptors wherein the ferrocene reporters and binding fragments are intimately associated or fully disconnected through a long alkyl chain. The experimental results clearly showed the utmost importance of ion pairing effects in the electrochemical recognition process accounting for most of the transduction signal in organic apolar media.

Keywords: calixarene; ferrocene; intramolecular H-bonding; anion recognition; cyclic voltammetry

Introduction

Anion recognition and sensing are increasingly important research topics in supramolecular chemistry due to the entanglement of various anions in biological and environmental subjects (*1*, *2*). Chemists usually take advantage of a wide range of recognition fragments introduced on 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 to build on artificial anion-binding architectures (*3*). Their dynamic properties, hydrophobic bowl-shape structures and well-known chemical versatility are indeed fully suited to straightforwardly synthesise complex host molecules allowing multi-point recognitions of anionic targets. In the present study we synthesised and investigated the anion-binding properties of novel artificial receptors associating calixarene as modular platform, urea units as anion-binding moieties and ferrocene redox–active reporters. Urea fragments have already been introduced into *p*-positions of calixarene skeleton mostly through direct linkage to elaborate supramolecular capsular materials (*4–9*) and anions or ditopic receptors (*10–22*).

The incorporation of metallocene fragments, usually cobaltocene or ferrocene, in such systems has been pursued essentially to sense or activate molecular level processes. Moon and Kaifer (*23*) reported a redox-controlled dissociation of a self-assembled dimer, whereas Beer took advantage of the receptor's electrochemical activity as a signal of a recognition event (*24*, *25*). The latter has been pioneered in making metallocene appended calixarenes for analytic purposes or to investigate electrochemical interactions between multi redox architectures (*26*). Among the most relevant examples, one finds hetero ditopic ferrocene receptors containing two ethyl ester calix[4]arene units bridged by a ferrocene amide moiety (*27*) or a tetraferrocenyl-calixarene in which metallocenes have been directly introduced on aniline-like fragments (*28*).

In this paper, we report the synthesis and the characterisation of novel redox active calixarene-based receptors wherein ferrocene fragments have been introduced at the lower rim through anion-binding urea or amide connections. We performed a thorough ^{1}H NMR investigation on a series of calixarene–ferrocene receptors to estimate their hydrogen bonding-driven self-association properties and improve our understanding of the correlation between molecular structures and redox properties. Their anion-binding properties have especially been investigated by electrochemical methods and NMR spectroscopy.

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Experimental section

Electrochemical analysis

All electrochemical experiments were carried out using a CH-Instrument potentiostat. A standard three-electrode cell was used for analytical experiments. Potentials are referred to the $Ag|Ag^{+}10^{-2}M$ 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 run at room temperature under an argon atmosphere. An automatic iR compensation was performed before each cyclic voltammetry experiment conducted in homogeneous media. Acetonitrile (HPLC grade) was purchased from Rathburn chemicals; dimethylformamide (DMF) (99.8% extra dry) and Anhydrous dichloromethane were purchased from Acros Chemicals. (Z.I. de Valdone 13124 Peypin). *n*-Tetrabutylammonium perchlorate (99%) was purchased from Fluka (St Quentin Fallavier (France)).

^{1}H NMR titration of calixarene 14 with n-tetrabutylammonium dihydrogenphosphate

Titrations were conducted in CD_2Cl_2 keeping the total concentration in **14** constant during the experiment ($[\mathbf{14}]tot = [\mathbf{14}] + [\mathbf{14}\cdot(H_2PO_4)_n]^{n-} = 16.07$ mM. Aliquots of a CD_2Cl_2 solution made up of *n*-TBA·H_2PO_4 (79 ou 645 mM) and 14 (16.07 mM) were added into an NMR tube containing **14** (16.07 mM) in CD_2Cl_2 at 293 K. The chemical shifts of both signals (δH_i and δNH_{ii}) were followed and recorded upon adding increasing amounts of *n*-TBAH_2PO_4. Fit of experimental data were achieved considering a 1/1 stoechiometry corresponding to the following equation:

$$\Delta\delta = (\delta_{max}/2P_0)[(P_0 + S_0 + 1/K) - [(P_0 + S_0 + 1/K)^2 - 4P_0S_0]^{1/2}]$$

with $\Delta\delta = \delta_x - \delta_{initial}$; $\delta_{max} = \delta_{final} - \delta_{initial}$; P_0, concentration of **14**; S_0, concentration of anion and K, binding constant.

Synthesis

General considerations

Starting materials and solvents were obtained from commercial suppliers and used without further purification. TLC: silica gel 60 F254. NMR spectra were recorded on DRX 300 or DRX 500 Brücker FT spectrometers. Abbreviation was used as: s (singlet), d (doublet), dd (divided doublet), t (triplet), q (quadruplet), m (multiplet) and l (large). Mass spectra were recorded by electrospay at the Mass Spectrometry Centre.

The synthesis of compound **4** (*29*), **11** (*24*) and **7** (*30*) was realised according to the literature procedure.

*(3-Bromopropyl)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 homogenous 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 allowed to warm 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 saturated aqueous solution of $NaHCO_3$, brine, dried over $MgSO_4$, 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, $CDCl_3$): 4.78 (t, 2H, J = 1.88 Hz, *H*Fc), 4.23 (s, 5H, *H*Fc), 3.72 (t, 2H, J = 6.60 Hz, CH_2), 3.29 (t, 2H, J = 6.60 Hz, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): 200.6, 78.3, 72.6, 70.0, 69.3, 42.4 and 26.1.

*Ferrocenebutyric acid **6***

Potassium hydroxide (3.92 g, 70 mmol) in 10 mL of water 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 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 over $MgSO_4$, filtered and concentrated under vacuum. The desired product was obtained in 84% yields (4.28 g) Mp = 85–86°C ^{1}H NMR (300 MHz, $CDCl_3$): 4.12 (s, 5H, HFc), 4.07 (s, 4H, HFc), 2.37–2.42 (m, 4H, CH_2), 1.75–1.80 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): 179.9, 87.8, 68.5, 68.1, 67.2, 33.6, 28.8, 25.9. HRMS calcd for $C_{14}H_{16}FeO_2$, 272.04997; found, 272.05044.

*Ethyl ferrocenylacrylate **8** (31)*

Triethyl phosphonoacetate (5.2 mL, 30 mmol) was added to a stirred suspension of sodium hydride (1.16 g, 31 mmol) in THF (50 mL) at 0°C to give white foam. The mixture was allowed to warm to room temperature for 30 min, then cooled in an ice bath and compound **7** (5 g, 23.3 mmol) was added as a solution in THF (50 mL). After 20 min the reaction mixture was allowed to warm to room temperature and stirred for 1 h. Saturated aqueous ammonium chloride was then added to the mixture. Diethyl ether was added and the combined layers were washed with water, dried ($MgSO_4$) and the solvent was removed under vacuum. Purification by column chromatography (silica gel dichloromethane) affords compound **8** in 98% yields (6.5 g). ^{1}H NMR (300 MHz, $CDCl_3$): 7.56

(d, $J = 15.8$ Hz, 1H, CH), 6.03 (d, $J = 15.8$ Hz, 1H, CH), 4.48 (m, 2H, HFc), 4.39 (m, 2H, HFc), 4.22 (q, $J = 7.2$ Hz, 2H, CH_2), 4.15 (s, 5H, HFc), 1.32 (t, $J = 7.2$ Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 167.4, 145.7, 115.1, 78.8, 70.9, 69.7, 68.7, 60.3 and 14.5.

Ferroceneproponic acid ***9***

A solution of 1 g (3.52 mmol) of ethyl ferrocenylacrylate **8** and 0.10 g (1 mmol) of palladium-on-charcoal in 50 ml of ethanol was degassed under argon for 30 min before saturated with hydrogen. The mixture was vigorously stirred for 24 h. The filtration and the concentration under reduced pressure gave 1 g (95%) of yellow crystals corresponding to ethyl 3-ferrocenylpropanoate. ^{1}H NMR (300 MHz, $CDCl_3$): 4.31 (s, 9H, HFc), 2.45 (s, 4H, CH_2), 4.39 (q, 2H, $J = 7$ Hz, CH_2), 1.21 (t, 3H, $J = 7$ Hz, CH_3).

Potassium hydroxide (3.92 g, 70 mmol) in 10 mL of water was added to a solution of ethyl 3-ferrocenylpropanoate (2.0 g, 7 mmol) in ethanol (60 mL). After 8 h at reflux the reaction mixture was concentrated in vacuo then diluted with water and washed with diethyl ether. The aqueous phase was acidified with HCl 1 M and extracted with diethyl ether. The organic phase was dried over $MgSO_4$, filtered and concentrated under vacuum. Ferroceneproponic acid **9** was obtained in 83% yields (1.5 g). ^{1}H NMR (300 MHz, $CDCl_3$): 11.03 (s br, 1H), 4.02–4.08 (m, 9H, HFc), 2.49–2.63 (m, 4H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): 180.1, 87.6, 68.9, 68.3, 67.9, 67.0, 35.9 and 25.0.

1,3-Alternate tetraaminocalixarene ***3***

A solution of tetraphthalimidopropoxy-*p-tert*-butylcalix[4]arene (6.9 g, 5 mmol) in ethanol (100 ml) was refluxed with hydrazine (5 ml). After 8 h the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$, washed with water, dried ($MgSO_4$) and the solvent was evaporated. The formed powder was dissolved in chloroform and precipitated with hexane to give the pure compound in 90% yields (3.9 g). Compound **3**: ^{1}H NMR (300 MHz, $CDCl_3$): 6.92 (s, 8H, Ar*H*), 3.74 (s, 8H, ArCH_2Ar), 3.34–3.42 (m, 8H, CH_2O), 2.39–2.46 (m, 8H, CH_2NH), 1.20–1.24 (m, 44H, $CH_2CH_2CH_2$, *t*-Bu). ^{13}C NMR (75 MHz, $CDCl_3$): 155.3, 144.0, 126.3, 69.1, 39.9, 39.6, 34.4, 33.8, 32.1. IR: KBr pellets cm^{-1}: 3369, 2958, 2901, 1482 and HRMS calcd for $C_{56}H_{84}N_4O_4$, 877.6571; found, 877.6566.

Amide synthesis

HATU (1.2 mmol, 450 mg) and diisopropylethylamine (1.2 mmol, 0.2 mL) were added to a solution of ferrocenebutyric acid (1.2 mmol, 320 mg) in DMF (3 mL) and stirred for 15 min at 25°C. This solution was then transferred to a suspension of 5,11,17,23-tetra (*tert*-butyl)-25,27-bis(3-aminopropoxy)-26,28-dihydroxycalix[4]arene (0.49 mmol, 370 mg) in DMF (5 mL) via a cannula. After 2 h, the reaction mixture was concentrated and purified by flash chromatography (silica gel cyclohexane-ethyl acetate 6/4) to afford the compound **13** in 71% yields (443 mg).

Compound ***12***. Sixty-eight percentage (mp) = 223–225°C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.63 (s, 2H, O*H*), 7.10 (s, 4H, Ar*H*), 6.85 (s, 4H, Ar*H*), 3.96–4.17 (m, 26H, ArCH_2Ar, *H*Fc, CH_2O), 3.62–3.67 (m, 4H, CH_2NH), 3.34 (d, 4H, $J = 12.9$ Hz, ArCH_2Ar), 2.61–2.69 (m, 4H, CH_2CO), 2.41–2.44 (m, 4H, CH_2Fc), 2.05–2.14 (m, 4H, $CH_2CH_2CH_2$), 1.29 (s, 18H, *t*-Bu), 0.98 (s, 18H, *t*-Bu). ^{13}C NMR (75 MHz, $CDCl_3$): 173.5, 150.4, 149.7, 147.7, 142.7, 132.8, 128.0, 126.1, 125.7, 88.3, 77.6, 74.4, 69.2, 68.7, 67.8, 38.7, 37.2, 34.4, 34.3, 32.3, 32.0, 31.4, 29.5, 26.2. IR: KBr pellets cm^{-1}: 3333, 2954, 2869 and 1635. Elem. Anal. Calcd for C: 73.42, H: 7.62, N: 2.25; found, C: 73.19, H: 7.55, N: 2.13.

Compound ***13***. Mp 105–109°C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.56 (s, 2H, O*H*), 7.09 (s, 4H, Ar*H*), 6.84 (s, 4H, Ar*H*), 4.29–4.45 (m, 18H, *H*Fc), 4.19 (d, 4H, $J = 13$ Hz, ArCH_2Ar), 4.01–4.05 (m, 4H, CH_2O), 3.67–3.69 (m, 4H, CH_2NH), 3.36 (d, 2H, $J = 13$ Hz, ArCH_2Ar), 2.13–2.25 (m, 16H, CH_2Fc, CH_2CO,$CH_2CH_2CH_2$), 1.66–1.69 (m, 4H, $CH_2CH_2CH_2$), 1.32 (s, 18H, *t*-Bu), 0.99 (s, 18H, *t*-Bu). ^{13}C NMR (75 MHz, $CDCl_3$): 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. IR: KBr pellets cm^{-1}: 3299, 2954, 2866, 1643. HRMS calcd for $C_{78}H_{98}Fe_2N_2O_6$, 1270.61237; found, 1270.61244.

Compound ***18***. Seventy-two percentage mp = 139–143°C; ^{1}H NMR (300 MHz, $CDCl_3$): 6.99 (s, 8H, Ar*H*), 6.03 (m, 4H, NH), 4.14 (m, 20H, *H*Fc), 4.10 (m, 16H, *H*Fc), 3.78–3.90 (m, 8H, ArCH_2Ar), 3.13–3.30 (m, 8H), 2.90–3.03 (m, 8H), 2.08–2.45 (m, 8H), 2.07–2.21 (m, 8H), 1.72–1.88 (m, 8H, $CH_2CH_2CH_2$), 1.25–1.36 (m, 44H, $CH_2CH_2CH_2$, *t*-Bu). ^{13}C NMR (75 MHz, $CDCl_3$): 173.2, 155.1, 144.5, 133.8, 126.4, 88.7, 68.9, 68.8, 68.5, 67.7, 39.7, 37.6, 36.45, 34.3, 32.1, 30.5, 30.1, 39.6, 27.5 and 27.3. IR: KBr pellets cm^{-1}: 3299, 2951, 2866 and 1643. HRMS calcd for $C_{112}H_{141}Fe_4N_4O_8$, 1893.81416; found, 1893.81435.

General procedure for Curtius reaction

Diisopropylethylamine (9 mmol) and diphenylphosphoryl azide (4.4 mmol) were added to a solution of ferrocenecarboxylic acid (2.2 mmol) and was dissolved in toluene (15 mL). The reaction mixture was heated at 70°C for 2 h, and then the 5,11,17,23-tetra(*tert*-butyl)-25,27-bis(3-aminopropoxy)-26,28-dihydroxycalix[4]arene (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 ***14***. Fifty-five percentage mp: 143–146°C; ^{1}H NMR (500 MHz, $CDCl_3$): 7.71 (s, 2H, O*H*), 7.04 (s, 4H, Ar*H*), 6.83 (s, 4H, Ar*H*), 5.94 (s br, 2H, N*H*), 5.40 (s br, 2H, N*H*), 4.11 (s, 10H, *H*Fc), 4.02–4.08 (m, 16H, ArCH_2Ar, *H*Fc, FcCH_2NH), 3.95–3.97 (m, 4H, CH_2O), 3.59–3.63 (m, 4H, CH_2NH), 3.30 (d, 2H, $J = 13$ Hz, ArCH_2Ar), 2.05–2.08 (m, 4H, CH_2CH_2-CH_2), 1.29 (s, 18H, *t*-Bu), 0.98 (s, 18H, *t*-Bu). ^{13}C NMR (125 MHz, $CDCl_3$): 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 and 30.1. IR: KBr pellets cm^{-1}: 3364, 2956, 2867 and 1632. HRMS calcd for $C_{74}H_{92}Fe_2N_4O_6$, 1244.57157; found, 1244.57163.

Compound ***15***. Fifty-one percentage mp = 159–162°C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.87 (s, 2H, O*H*), 7.09 (s, 4H, Ar*H*), 6.91 (s, 4H, Ar*H*), 5.81 (s br, 2H, N*H*), 5.26 (s br, 2H, N*H*), 4.08–4.22 (m, 26H, ArCH_2Ar, *H*Fc, CH_2O), 3.64–3.70 (m, 4H, CH_2NH), 3.20–3.34 (m, 8H, ArCH_2Ar, CH_2NH), 2.39–2.42 (m, 4H, CH_2CH_2Fc), 2.14–2.19 (m, 4H, $CH_2CH_2CH_2$), 1.30 (s, 18H, *t*-Bu), 1.03 (s, 18H, *t*-Bu). ^{13}C NMR (75 MHz, $CDCl_3$): 159.4, 149.9, 149.7, 148.1, 143.2, 132.9, 128.2, 126.2, 125.8, 77.7, 75.7, 69.6, 69.1, 68.7, 68.2, 41.8, 38.8, 34.5, 34.3, 32.4, 32.0, 31.4, 30.7 and 30.5. IR: KBr pellets cm^{-1}: 3370, 2959, 2869 and 1651. HRMS calcd for $C_{76}H_{97}Fe_2N_4O_6$, 1273.6112; found, 1273.612.

Compound ***16***. Fifty-one percentage mp: 125–130°C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.73 (s, 2H, O*H*), 7.09 (s, 4H, Ar*H*), 6.87 (s, 4H, Ar*H*), 5.91 (s br, 2H, N*H*), 5.39 (s br, 2H, N*H*), 4.19 (d, 4H, $J = 13.2$ Hz, ArCH_2Ar) 4.08 (s, 10H, *H*Fc), 3.99–4.06 (m, 12H, *H*Fc, CH_2O), 3.64–3.70 (m, 4H, CH_2NH), 3.39 (d, $J = 13.2$ Hz, ArCH_2Ar), 3.19–3.26 (m, 4H, CH_2NH), 2.27–2.31 (m, 4H, CH_2CH_2Fc), 2.16–2.20 (m, 4H, $CH_2CH_2CH_2$), 1.61–1.67 (m, 4H, $CH_2CH_2CH_2$), 1.31 (s, 18H, *t*-Bu), 1.00 (s, 18H, *t*-Bu). ^{13}C NMR (75 MHz, $CDCl_3$): 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 and 27.0. IR: KBr pellets cm^{-1}: 3376, 2961, 2867 and 1634. HRMS calcd for $C_{78}H_{100}Fe_2N_4O_6$, 1300.63417; found, 1300.63419.

Tetra-ferrocene–urea functionalised calix[4]arene receptor ***17***

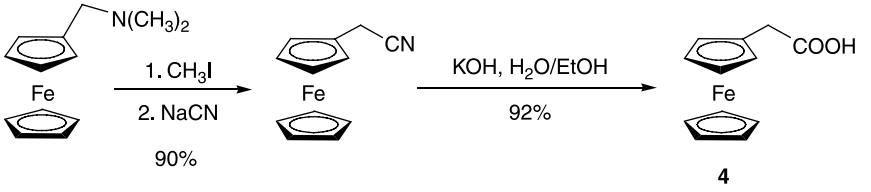
Tetra-aminocalix[4]arene derivative **2** (480 mg, 0.55 mmol) in CH_2Cl_2 (20 ml) was added dropwise to a stirred solution of **11** (878 mg, 2.31 mmol), ethyldiisopropylamine (1.5 ml, excess) and DMAP (catalytic) in CH_2Cl_2 (20 ml) and the mixture was stirred for 24 h under argon. The reaction mixture was washed with sodium carbonate solution and then the organic fraction was dried over magnesium sulphate, filtered and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel ethyl acetate). The desired product was obtained in 89% yields (0.916 g). Mp > 300°C; ^{1}H NMR (500 MHz, DMSO-d_6): 6.78 (s, 8H, Ar*H*), 6.22 (s br, 4H, N*H*), 6.02 (s br, 4H, N*H*), 4.27 (d, 8H, $J = 12.3$ Hz, ArCH_2Ar), 4.13–4.16 (m, 28H, *H*Fc), 4.05–4.07 (m, 12H, *H*Fc), 3.95–3.97 (m, 8H, CH_2NH), 3.76–3.82 (m, 4H, CH_2O), 3.21–3.29 (m, 8H, CH_2NH), 3.11 (d, 8H, $J = 13.2$ Hz, ArCH_2Ar), 2.08–2.11 (m, 8H, $CH_2CH_2CH_2$), 1.00 (s, 36H, *t*-Bu). ^{13}C NMR (75 MHz, $CDCl_3$): 159.0, 154.1, 144.5, 134.2, 125.5, 88.2, 73.8, 69.2, 68.3, 68.09, 39.6, 39.3, 37.5, 34.3, 32.0, 31.8 and 31.2. IR: KBr pellets cm^{-1}: 3376, 2961, 2867 and 1634. HRMS calcd for $C_{106}H_{137}Fe_4N_8O_8$, 1873.79516; found, 1873.79483.

Results and discussion

Synthesis

The 5,11,17,23-tetra(*tert*-butyl)-25,27-bis(3-aminopropoxy)-26,28-dihydroxycalix[4]arene **1** (*32*), 5,11,17,23-tetra(*tert*-butyl)-25,26,27,26-tetra(3-aminopropoxy)-calix[4]arene in cone conformation **2**(*33*) were prepared in two steps from *p-tert*-butylcalix[4]arene as described in literature. Calixarene **3** in 1,3-alternate conformation was obtained by reduction of the tetra(phthalimide) analogue preliminary prepared as described by Danila et al. (*34*). The ferrocene–acetic acid starting material **4** (Scheme 1) was prepared as described in literature from the *N*,*N*-dimethylaminomethylferrocene in good yield (83%) (*35*). The methyliodide intermediate was treated with potassium cyanide to afford the ferrocenylacetonitrile, which was then converted to the corresponding carboxylic acid **4**.

The ferrocenebutyric acid **6** was previously prepared by reaction of the ferrocene with succinic anhydride



Scheme 1. Synthesis of the ferrocene–acetic acid **4** from *N*,*N*-dimethylaminomethyl-ferrocene (*32*).

followed by a Clemmensen reduction (*36*). We report here an alternative approach from the ferrocene in four steps and 50% overall yield (Scheme 2). After a Friedel–Craft acylation, the ketone was reduced to affording the (3-bromopropyl)-ferrocene **5**. The last steps are identical to those detailed for the ferrocene–acetic acid **4**, cyanide formation and then hydrolysis. The ferrocene propanoic acid **9** (*37*) was prepared from the ferrocene carboxaldehyde **7** via a Horner–Wardsworth–Emmons olefination in quantitative yield. The last steps are the double bond hydrogenation of **8** followed by a saponification of the ester function to afford **9** in 78% yields. Finally, **11** was obtained in three steps as already described in the literature (*28*) from the ferrocene carboxaldehyde **7** previously transformed into the corresponding oxime **10**, followed by the reductive amination and condensation with the 4-nitrophenyl chloroformate.

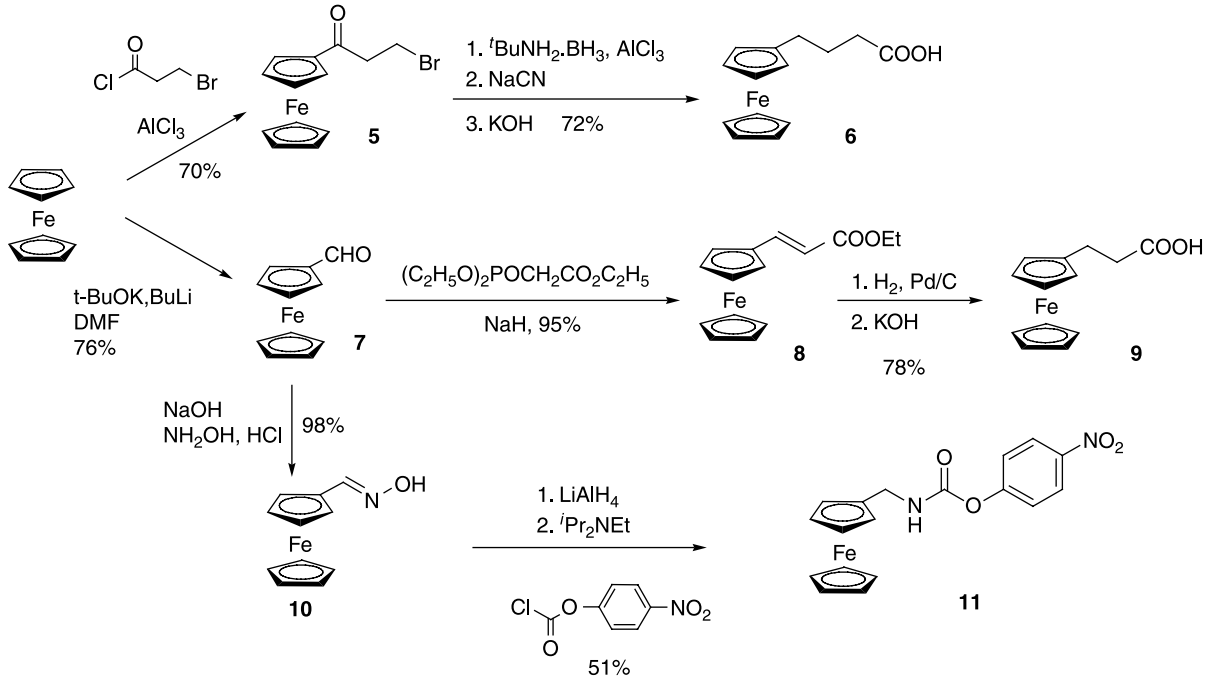
Metallocene redox–active fragments were introduced onto a calixarene framework using the the ferrocene acids **6** or **9** and HATU (2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate) as coupling reagent. This straightforward peptide-based strategy allowed us to isolate the bis(amido)-calixarenes **12** and **14**, respectively, in 68% and 71% yield (Scheme 3).

Ferrocene acids **4**, **6** or **9** and aminocalixarene **1** were also linked via a urea connection through a Curtius rearrangement (*37*). A variety of approaches towards calixarene–ureas have already been investigated. Most of them were based on the use of commercially available isocyanates (*38–40*) or isocyanate derivatives of calixarenes (*41*, *42*). In this study, the targeted redox active receptors **14**, **15** and **16** were prepared in one pot procedure without isolating the isocyanate intermediate by reacting the calixarene amine with ferrocene carboxylic acid in the presence of diphenylphosphoryl azide and diisopropylethylamine.

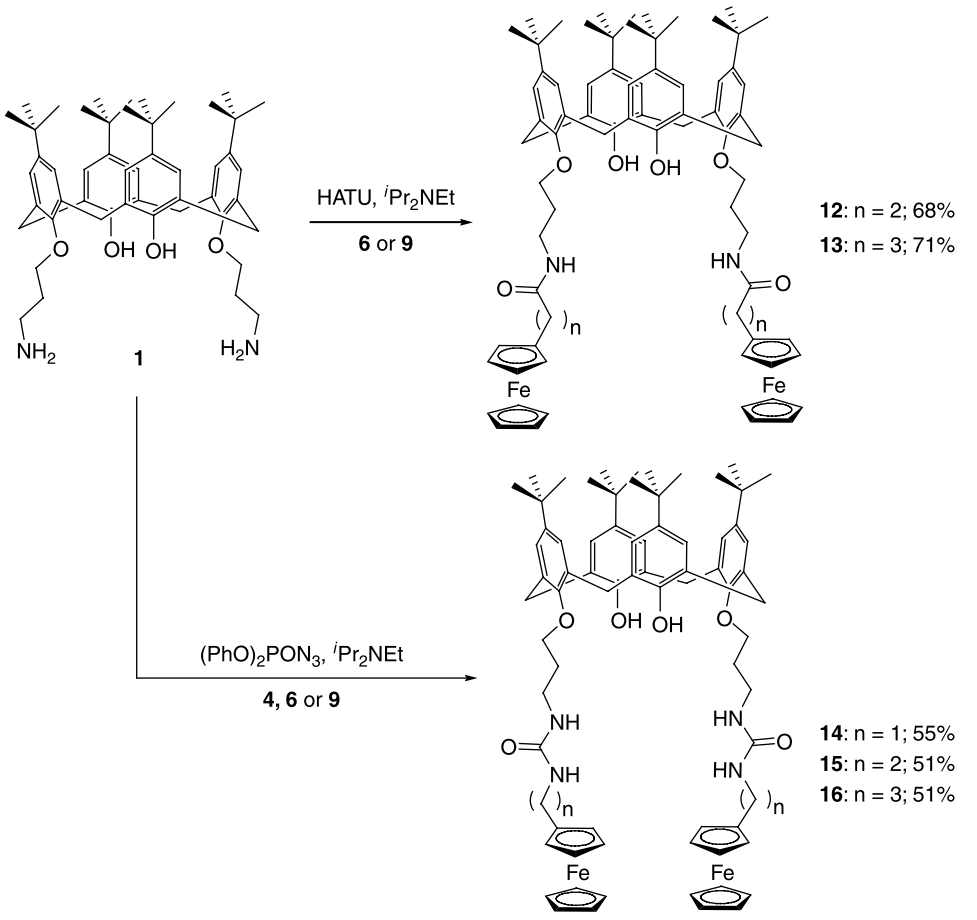
The tetra-urea ferrocenyl derivative **17** was obtained in relatively low yield (15%) through a Curtius rearrangement between **9** and a tetra(amino)calix[4]arene **2** (Scheme 4). However, this yield was improved up to nearly 90% using the Paul Beer's strategy upon using **11** as ferrocene–urea precursor (*28*). Finally, the peptide coupling from **3** with **6** in the presence of HATU gave the corresponding tetra(amidoferrocenyl) macrocycle **18** in 72% yield with a 1,3-alternate conformation.

NMR analysis

The structures of **12–18** were clearly established by NMR spectroscopy and electrospray mass spectrometry. The cone conformations adopted in solution by the calixarene frameworks of calixarenes **12–17** were deduced from the ^{13}C NMR experiments with the presence of resonance signals observed between 31 and 32 ppm corresponding to the ArCH_2Ar fragments (*43*). Moreover, these compounds are present in symmetrical cone conformation as proved by the low value of $\Delta\delta$ between the signals of the two sets of aromatic protons ($\Delta\delta$ lower than 0.016 in DMSO-d_6)



Scheme 2. Synthesis of the ferrocenyl derivatives **6**, **9** and **11** from ferrocene.



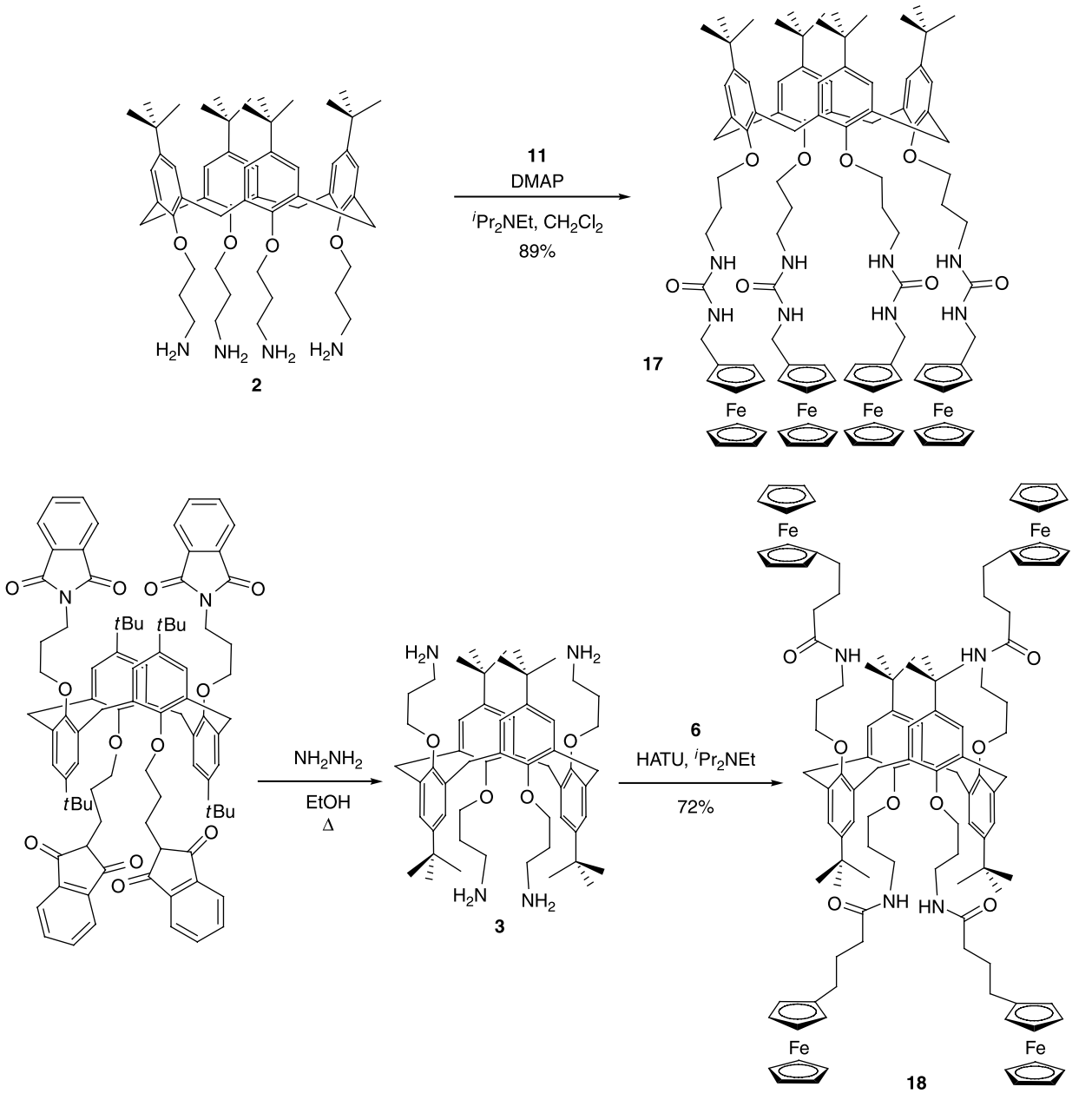
Scheme 3. Synthesis of redox–active bis-1,3-(amido)calixarenes **12**, **13** and bis-1,3-(urea)calixarenes **14**, **15** and **16**.

and *tert*-butyl groups ($\Delta\delta$ close to 0.05 ppm in DMSO-d_6) as already observed by Ungaro and co-workers (*44*) with peptidocali[4]arene bisureas. The resonance signal located at 39.6 ppm, which corresponds to the ArCH_2Ar of **18**, confirmed the 1,3-alternate conformation of the macrocycle.

Information about the solvent accessibility of all NH protons in **12**–**18** and their level of engagement in H-bonding could be obtained from temperature coefficients. The relative change in chemical shifts recorded as temperature is changed by 1 K ($\Delta\delta/\Delta T$) and is indeed an accurate probe to estimate the level of hydrogen bonding in molecular systems (*44*, *45*). The temperature dependence ($\Delta\delta/\Delta T$) of the ^{1}H NMR chemical shifts attributed to the NH signals in compounds **12**–**18** was evaluated in DMSO-d_6. A typical displacement observed with **15** between 298 and 353 K is depicted on Figure 1. In this polar and H-bond acceptor media, intermolecular hydrogen bonds and those established with solvent molecules are known to be readily cleaved by increasing temperature. We moreover know from literature that $\Delta\delta/\Delta T$ values found below -4.0 ppb/K for amide protons unambiguously reveal the absence of intramolecular hydrogen bonding processes (*45*). Temperature coefficients were measured for compounds **12**–**18** upon recording seven ^{1}H NMR spectra between 298 and 353 K. These analyses were performed on 3.0 mM solutions to ensure the absence of significant molecular aggregation. The recorded and calculated results are summarised in Table 1.

Full NMR characterisations and exhaustive proton assignments were achieved, for all receptors, from ^{1}H NMR and 2D-COSY spectra. From the low $\Delta\delta/\Delta T$ values calculated for the bis-amide derivative **12**, **13** and tetramide **18**, we readily inferred the absence of interactions between amide arms. Surprisingly, both NHs of the urea-linked ferrocene–calixarenes **14**, **15** and **17** turned out to exhibit significantly different $\Delta\delta/\Delta T$ values.

Whereas NHs on the calixarene side ($\Delta\delta/\Delta T = -3.6$ ppm/K) are clearly involved in intramolecular H-bonding, lower value ($\Delta\delta/\Delta T = -4.4$ ppm/K) calculated for NH's on the ferrocene side suggest simple solvent effects. The most positive $\Delta\delta/\Delta T$ values were found for the tetra urea-linked ferrocene calixarene **17**. In contrast to what was found with **15**, both NH's in **17** exhibit similar values strongly, suggesting the existence of an intramolecular hydrogen bonding network between all four urea groups.



Scheme 4. Synthesis of terafunctionalised calix[4]arenes **17** and **18**.

In view of these results, ROESY analysis was carried on compounds **15** and **17** to obtain more information. Selective irradiation of each NH for compound **17** revealed a correlation between NH_i (stands for NH's on the calixarene side) and $O-CH_2-CH_2-CH_2$, NH_b (stands for NH's on the ferrocene side) and between NH_{ii} and NH_i, CH_2-HFc. Concerning compounds **14** and **15**, the same type of correlation was observed for NH_i than for compound **17.** With a limit $\Delta\delta/\Delta T$ value of -4.0 ppb concerning the NH_{ii} of **14**, a weak H-bonding interaction could be expected. However, NH_b correlated only with NH_i. Based on these results that suppose that only NH_i are engaged in a H-bonding, we assume that the urea was in *trans*-configuration and/or the bottom part of the molecule was outside the cavity (Figure 2).

Electrochemical analysis

Depending of their solubility, the electrochemical signatures of compounds **12**–**18** were investigated by cyclic voltammetry, RDE and square wave voltammetry on glassy carbon electrodes in dichloromethane, DMF, acetonitrile and DMSO using *n*-tetrabutylammonium perchlorate as electrolyte (TBAP, 0.1 M). All cyclic

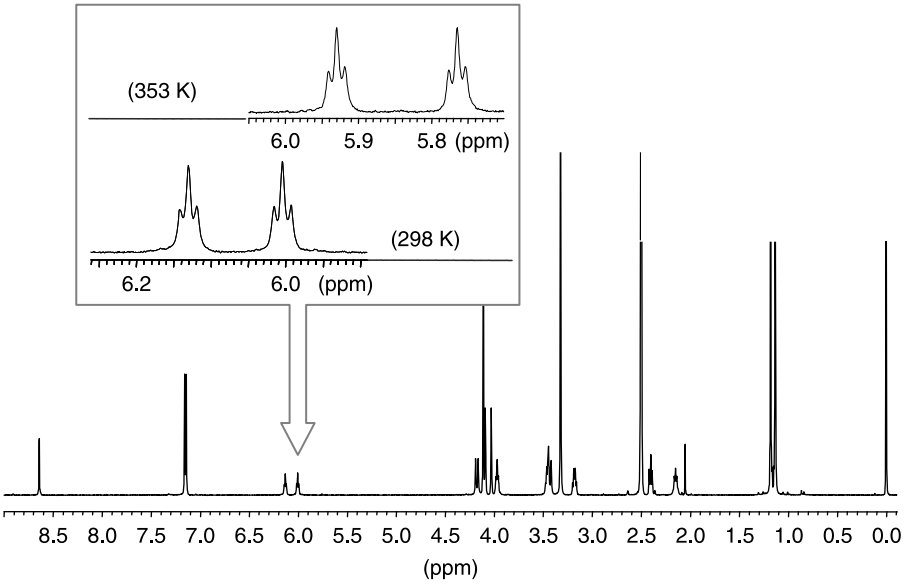


Figure 1. ^{1}H NMR spectra of **15** in DMSO-d_6 (500 MHz) at 298 K. Enlargement showing the effect off temperature on both NH of the urea's chemical shifts.

voltammograms featured one single wave corresponding to the simultaneous oxidation of both ferrocene fragments, highlighting the limited or non-existent communication between the iron centres. As proved by the experimental data reported in Table 2, the ferrocene half wave potential significantly shifts towards less positive values when the number of atoms between the metallocene and urea fragments increases (see compounds **14** and **16** in CH_2Cl_2). This significant displacement can be unambiguously attributed to the electron-withdrawing effect of the urea and amide fragments on the metallocene probe which logically strengthens as their linker shortens.

Whatever the macrocycle, the redox signatures did not reveal strong interactions between ferrocenes, as proved by the observation of one single wave on their cyclic voltammograms corresponding to the simultaneous oxidation of all iron centres. The weak 'interaction level' between redox moieties could nevertheless subtly be appraised upon measuring and comparing the difference between oxidation and reduction peak potentials (ΔE_p), assuming that hints of 'communication' between redox centers should bring about inequivalence signalled by larger ΔE_p values. The experimental values reported in Table 2 are interestingly in full agreement with the outcomes of NMR spectroscopy establishing that **14**, **15** and **17** exhibit stronger intramolecular hydrogen bonding. Albeit numerous physico-chemical parameters might

Table 1. $\Delta\delta/\Delta T$ (ppb/K) **12**–**17** (DMSO-d_6, 500 MHz).

	Amides			Ureas		
	12	**13**	**18**	**14**	**15**	**17**
NH_i	−5.9	−5.5	−5.9	−3.7	−3.6	−3.4
NH_{ii}	–	–	–	−4.0	−4.4	−3.2

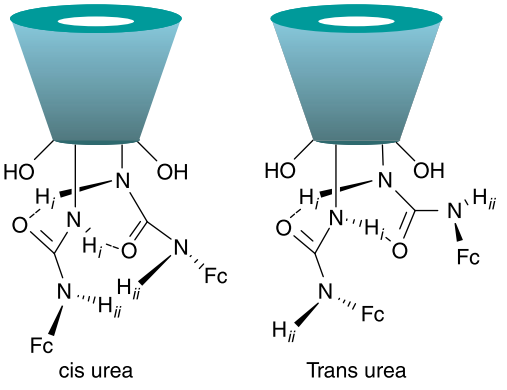


Figure 2. Expected H-bonding in compound **15**.

Table 2. Experimental $E_{1/2}$ and ΔEp values (mV)*.

	CH_2Cl_2		DMF		CH_3CN		DMSO	
	$E_{1/2}$	ΔEp	$E_{1/2}$	ΔEp	$E_{1/2}$	ΔEp	$E_{1/2}$	ΔEp
14	175	126	49	86	–	–	–	–
15	–	–	–	–	–	–	−5	86
16	139	106	25	78	39	70	–	–
17	–	–	–	–	–	–	16	100
12	–	–	–	–	56	68	−12	76
13	153	98	36	84	42	77	–	–
18	–	–	–	–	53	62	–	–

* $E_{1/2} = (E_{pa} + E_{pc})/2$; ΔEp $= E_{pa} - E_{pc}$. Data recorded for **12**–**18** (10^{-3} M) on glassy carbon electrodes ($\varnothing = 3$ mm) at 100 mV s^{-1} using TBAP (0.1 M) as electrolyte. *E vs.* Ag/Ag^+(10^{-2} M).

Table 3. Electrochemical data (ΔE, $\Delta E_{1/2}$) measured by cyclic voltammetry before and after adding two molar equivalents of $TBA \cdot H_2PO_4$ to dichloromethane (0.1 M TBAP) solutions of **14**, **16** and **13** (5×10^{-4} M, $\nu = 100\,mV\,s^{-1}$, glassy carbon electrode $\varnothing = 3$ mm).

	13	**13** $\cdot (H_2PO_4^-)_2$	**14**	**14** $\cdot (H_2PO_4^-)_2$	**16**	**16** $\cdot (H_2PO_4^-)_2$
ΔE (mV)	92	108	98	100	92	98
$\Delta E_{1/2}$ (mV)	94	–	155	–	135	–

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

contribute to these deviation in electrochemical activities (number of redox centres, adsorbtion processes, kinetics, etc.), the changes in ΔE_p and $\Delta\delta/\Delta T$ values, calculated in DMSO for a series of structurally related receptors, are consistent and led to similar conclusions.

As mentioned above, the observation of one single ferrocene centred oxidation wave results from the lack of communication between both centres. The expected intramolecular association between urea fragments hence does not bring both metallocene in 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 upon 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 (*45*, *46*). It has been especially demonstrated (*47*) 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 single electroactive centre ($\Delta E_p = 58$ mV at 25°C) but with a magnitude determined by the total number of redox centres. When each centre is characterised 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 the formal potentials corresponding to each pair of successive oxidation states of the multi-centres molecules. Considering fully non interacting centres, the theoretical shift between both ferrocene based formal oxidation potentials in **13**, **14** and **16** (E°_1 and E°_2) should thus equal $\Delta E = E^\circ_1 - E^\circ_2 = 35.6$ mV, although both redox processes are expected to appear as a single wave with peak potentials satisfying $\Delta E_p = 58$ mV (*48*). 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 2 especially reveal the discrepancy in ΔE_p values ranging from 98 to 126 mV in dichloromethane. Such deviation from theoretical prediction can be attributed to different factors, involving electron transfer kinetics, adsorption processes or ohmic drop contributions but also to non-negligible interactions between electrogenerated ferricinium species. Such assumption especially relies on the fact that the largest ΔE_p value was observed with **14**, wherein intramolecular hydrogen bonds between urea groups expectedly lead to the shortest distance between both metallocene centres. This ΔEp differences measured in apolar dichloromethane, however, turned out to be concentration-dependent since a significantly smaller value was measured at 5×10^{-4} M (Table 3). Such feature thus clearly suggested the absence of communication effect which should thus not be considered to account for the large ΔE value. All studied receptors exhibit a second irreversible oxidation process, at $E \geq 800$ mV, centred on both phenol subunits of the calixarene skeleton (*49*). A typical voltammogram showing the ferrocene and phenol centred redox systems is depicted in Figure 3. As discussed above, **14**, **16** and **13** exhibit structural and chemical features fully suited to achieve an efficient complexation/sensing of anionic species. Urea and phenol groups are indeed among the most widely used binding fragments to trap or transport negatively charged species in biological systems (*50*). The calixarene's lipophilic character and structurating effect associated to the anion-binding properties of urea or amide and phenol are expedient complementary features defining

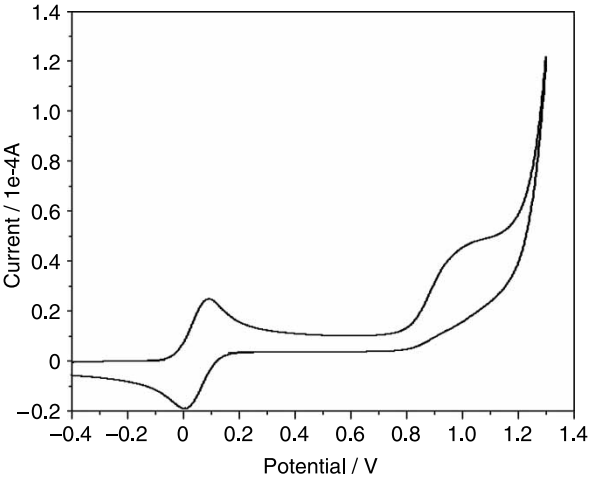


Figure 3. Cyclic voltammogram of **14** (10^{-3} M) recorded in DMF (0.1 M TBAP) at a glassy carbon electrode. ($\varnothing = 3$ mm, $\nu = 100\,mV\,s^{-1}$).

14, **16** and **13** as artificial anion receptors with great potential. In addition, to these favourable chemical and structural aspects, both metallocene moieties can be easily activated, i.e. oxidised at low potential, to further improve the receptor anion-binding ability through electrochemically triggered ion pairing effects between anionic targets and *in situ* mono or bis-positively charged receptors (*1*).

Anion binding

The anion-binding ability of these receptors could be quickly confirmed upon 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 **14** especially led to significant low field shifts of singlets attributed to the urea groups (○, Figure 4) and to a lesser extent to the phenol moieties (●, Figure 4). Such perturbations could be observed with all of the studied receptors which were soluble in $CDCl_3$ (**13**, **14** and **16**) and clearly result from interactions between hydrogen-bond donors and electron rich anionic species. In agreement with previously reported studies (*46*), these receptors exhibit however, at least in their reduced forms, relatively low binding constants with anionic species, especially in the case of **13** and **16** for which the binding constants could not be precisely determined.

On the other hand, titration of **14** conducted in CD_2Cl_2 with dihydrogenphosphate anion, since the affinity for this anion is higher, yielded, for instance, curves that could be fitted according to a 1/1 calixarene/anion stoechiometry with an estimated binding constant of $36 \pm 4\,M^{-1}$ (Figure 5). The 1:1 stoechiometry was confirmed by job plot with ^1H NMR experiment in CD_2Cl_2 (Figure 6). A symmetrical bell-shaped curve centred at a 0.5 M fraction was observed, thus confirming the presence only of the 1:1 host/guest complex.

The ability of **13**, **14** and **16** to complex anionic species and their potential in molecular electrochemical recognition

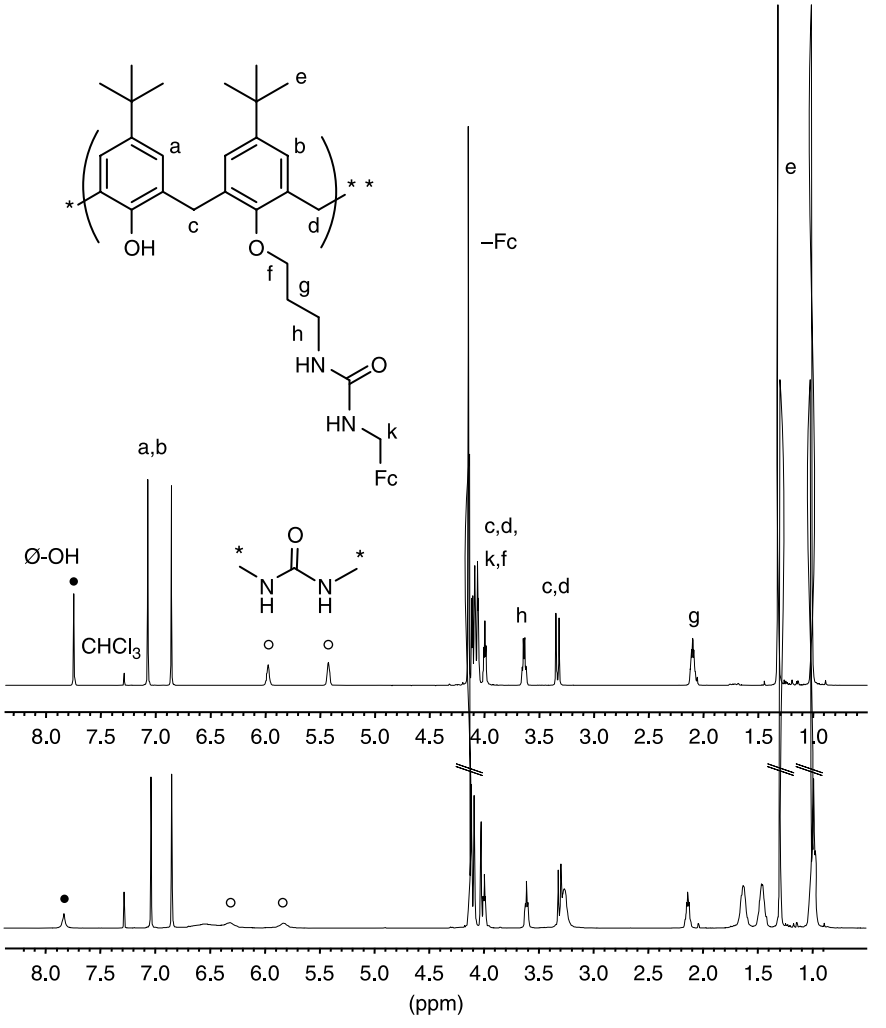


Figure 4. ^1H NMR spectra of **14** recorded in $CDCl_3$ (300 MHz) before (top) and after (bottom) adding $TBA \cdot H_2PO_4$ in excess.

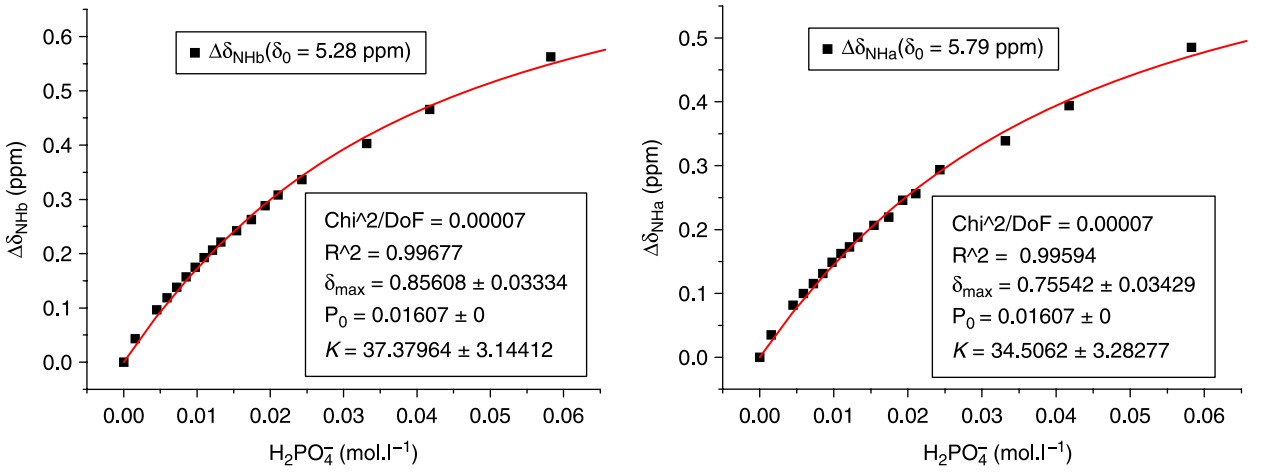


Figure 5. $\Delta\delta NH_i$ and $\Delta\delta NH_{ii}$ as a function of $[H_2PO_4^-]$ for **14**.

were also investigated by cyclic voltammetry in dichloromethane electrolyte. The addition of increasing amounts *n*-tetrabutylammonium nitrate, sulphate, chloride or acetate to a 10^{-3} 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/urea-binding fragments and/or to limited interaction of the complexed anion with the neutral and/or oxidised metallocenes redox probes.

However, an effective electrochemical response was observed in presence of hydrogen phosphate anions (Figure 7). Addition of the latter indeed resulted in a clear two-wave behaviour wherein the intensity of the initial ferrocene-based wave progressively decreases at the expense of a novel signal at a much less positive potential (Figure 7(A) and (B)). After adding 1 M equivalent 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 evolution is fully compatible with a strong binding

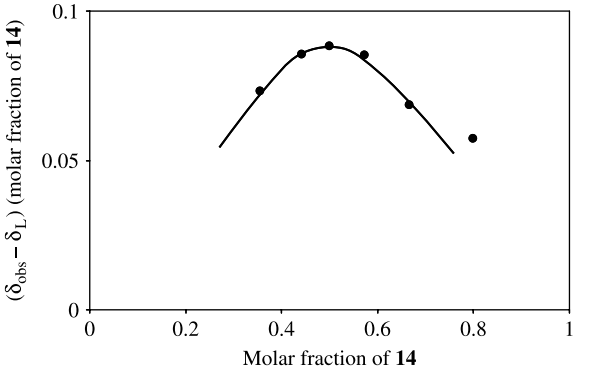


Figure 6. Job plot of the titration of $Bu_4NH_2PO_4$ with **14** in CD_2Cl_2.

of one $H_2PO_4^-$ anion per urea fragment leading, *in fine*, to a bis(hydrogenophosphate) complex. This 2/1 binding stoechiometry, while differing from that found from NMR experiments, can be easily explained upon considering that two positive charges are being electrochemically generated onto the calixarene receptors. These results are furthermore in agreement with previously reported studies conducted on similar receptors (*50*). It needs to be stressed that both waves remained fully reversible through the titration experiment and that the maximal potential shift ($\Delta E_{1/2}$) between the uncomplexed and complexed receptors electrochemical activities reached 155 mV. The addition of $H_2PO_4^-$ anions to a solution of **14** did not significantly modify the shift between oxidation and reduction peak potentials (ΔE, Table 3). This observation is another clear indication that the 'large' ΔE value measured in dichloromethane does not result from urea-driven intramolecular redox communication which would logically be disrupted upon adding hydrogen-phosphates.

Several interactions and effects can potentially be considered to account for the observed changes. The hydrogen bonding ability of urea and phenol groups is obviously of great importance, but the influence of ferricinium and effect of complexation on ferrocene are also key elements to achieve such efficient molecular electrochemical sensing. A short linkage between urea and ferrocene was initially considered to be essential to optimise 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 **16** and **13** in which ferrocene and binding fragments are fully disconnected, through a long alkyl chain, prohibiting any through bonds effects on the electrochemical recognition process. Addition of increasing amounts of $TBA \cdot H_2PO_4$

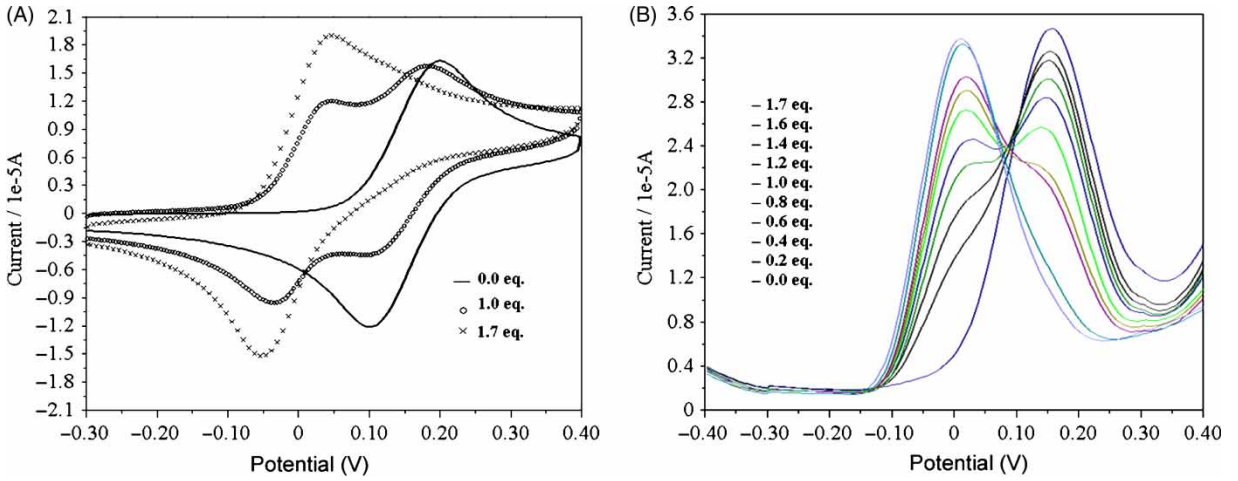


Figure 7. (A) Cyclic ($\nu = 100$ mV s^{-1}) and (B) square wave voltammograms of **14** (5×10^{-4} M) recorded in dichloromethane (0.1 M TBAP) upon adding increasing amounts of TBA · H_2PO_4 (glassy carbon electrode, $\varnothing = 3$ mm).

to a dichloromethane solution of the free receptors **16** and **13** surprisingly led to similar 'two-wave' responses only distinguished by the half waves potential shifts amplitudes ($\Delta E_{1/2}$, Table 3). The $\Delta E_{1/2}$ values reported in Table 3 indeed clearly highlight the beneficial effects of intimately connecting the recognition and signalling fragments. The interaction of the urea groups in **14** with $H_2PO_4^-$ species has indeed an unambiguous electronic, through bonds, effect on the ferrocene's final oxidation potential. Although the most important perturbation is observed in the latter case, **16** and **13** still allow an effective sensing through important displacements of the ferrocene oxidation potential. This result shows the utmost importance of ion pairing effects in electrochemical recognition process. When the ferrocene groups are far away from the hydrogen-binding fragments, as in **16** and **13**, the strong selective electrostatic interaction between hydrogen phosphate and the electrogenerated ferricinium species is almost enough to ensure an efficient transduction. This assumption is further demonstrated upon studying the electrochemical activity of simple ferrocene and TBA · H_2PO_4 in dichloromethane. The initial reversible Fc/Fc^+ couple quickly evolve towards a broad irreversible system in presence of phosphate presumably resulting from the formation of poorly soluble ion pairs. The organic receptors used in this study have thus two main effects, besides introducing selectivity and affinity associated to the specific binding fragments, they also greatly help stabilizing and solubilizing the oxidised forms of the calixarene–anion complexes. The difference in $\Delta E_{1/2}$ (*ca.* 40 mV, Table 3) observed between **16** · $(H_2PO_4^-)_2$ and **13** · $(H_2PO_4^-)_2$ is tentatively attributed to distinct coordination modes setting the complexed anion closer to the redox probe in **16** than in **13**. This shift is furthermore correlated to the number of atoms separating the ferrocene fragment from the amide hydrogen bond donor in both receptors.

Conclusion

In conclusion, we have described the synthesis of original calix[4]arenes wherein ferrocene fragments have been introduced at the lower rim through urea or amide connections. We especially assessed the presence and/or the lack of intramolecular hydrogen bonds by NMR spectroscopy. The anion-binding properties of these artificial receptors have been revealed by NMR spectroscopy and thoroughly investigated by electrochemical methods. We especially assessed the importance of the urea–phosphate bonds in the observed electrochemical response upon studying receptors wherein ferrocene and binding fragments are intimately associated or fully disconnected through a long alkyl chain. Although similar selective phosphate sensing properties have been previously reported with intimately connected ferrocene–amide–calixarene receptors (*26*, *51*), our experimental results clearly show the utmost importance of ion pairing effects in this electrochemical recognition process that accounts for more than 85% of the transduction signal.

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