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Estelle Métay, Marie-Christine Duclos, S Pellet-Rostaing, Marc Lemaire, Jürgen Schulz, et al.. Conformational analysis and anion binding properties of ferrocenyl- calixarene receptors. *Supramolecular Chemistry*, 2009, 21 (01-02), pp.68-80. 10.1080/10610270802527036 . hal-00513547

HAL Id: hal-00513547

<https://hal.science/hal-00513547>

Submitted on 1 Sep 2010

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Conformational analysis and anion binding properties of ferrocenyl- calixarene receptors

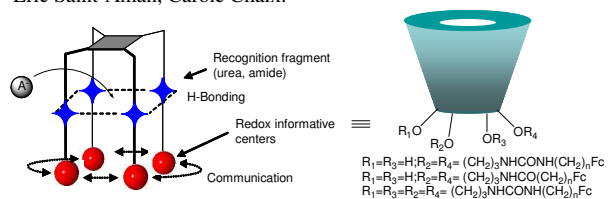
Journal:	<i>Supramolecular Chemistry</i>
Manuscript ID:	GSCH-2008-0081.R1
Manuscript Type:	Special Issue Paper
Date Submitted by the Author:	29-Sep-2008
Complete List of Authors:	Métay, Estelle; université Claude Bernard Lyon 1, ICBMS-UMR 5246 Duclos, Marie-Christine; université Claude Bernard Lyon 1, ICBMS-UMR 5246 Pellet-Rostaing, stéphane; Université Claude Bernard Lyon 1, ICBMS-UMR 5246 Lemaire, Marc; Université Claude Bernard Lyon 1, ICBMS-UMR 5246 Schulz, Jürgen; Université Claude Bernard Lyon 1, ICBMS-UMR 5246 Kannappan, Ramu; Université joseph Fourier, DCM-CIRE-UMR 5250 Bucher, Christophe; Université joseph Fourier, DCM-CIRE-UMR 5250 saint-Aman, Eric; Université joseph fourier Chaix, Carole; Université Claude Bernard Lyon 1, Sciences analytiques-UMR 5180
Keywords:	calixarene, ferrocene, intramolecular H-bonding, anion recognition, cyclic voltammetry



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Synthesis and anion binding properties of novel redox-active calixarene receptors

Estelle Métaý, Marie Christine Duclos, Stéphane Pellet-Rostaing,
Marc Lemaire, Jürgen Schulz, Ramu Kannappan, Christophe Bucher,
Eric Saint-Aman, Carole Chaix.



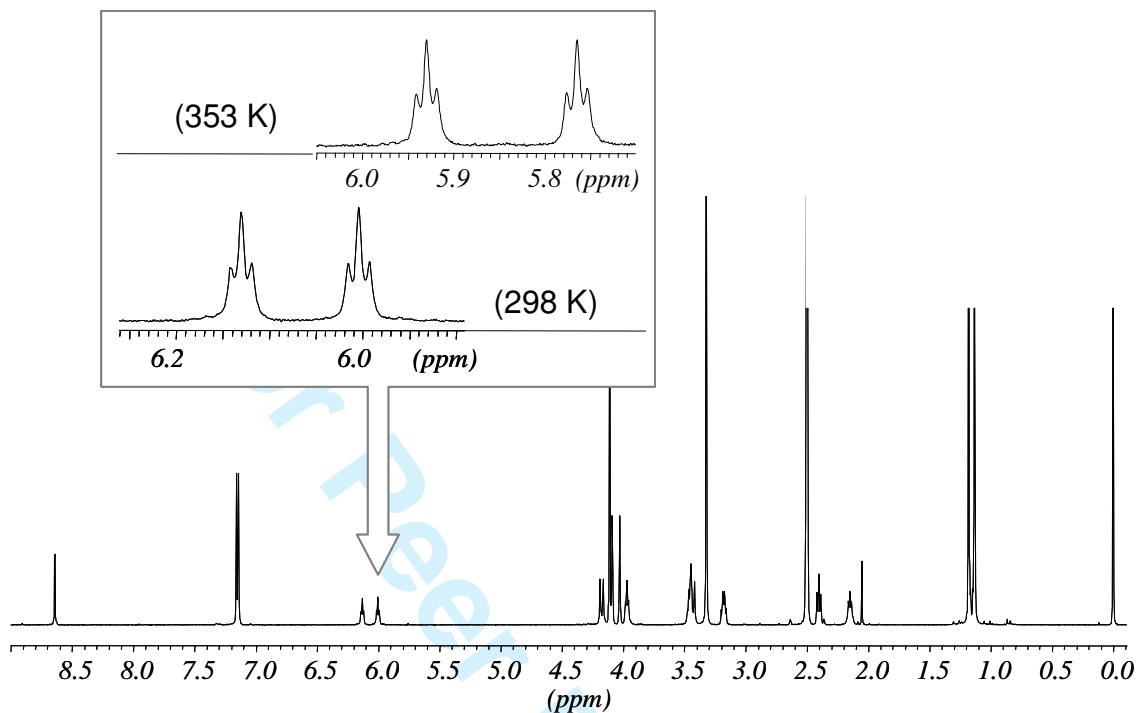


Fig. 1: ^1H NMR spectra of **15** in $\text{DMSO}-d_6$ (500MHz) at 298 K. Enlargement showing the effect of temperature on both NH of the urea's chemical shifts.

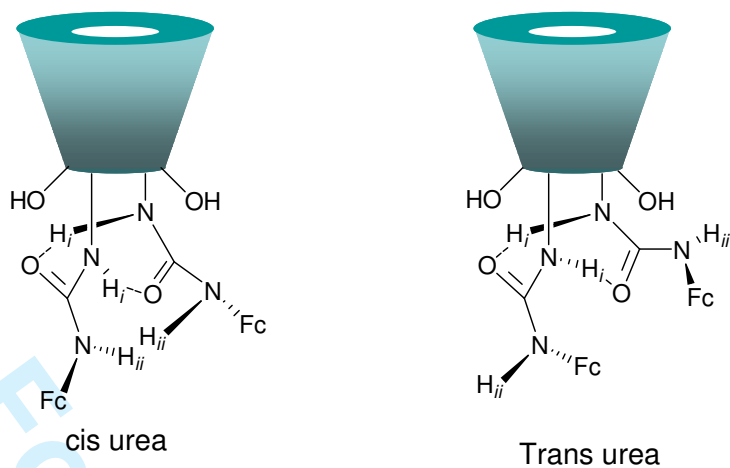


Fig. 2 : expected H-bonding in compound 15

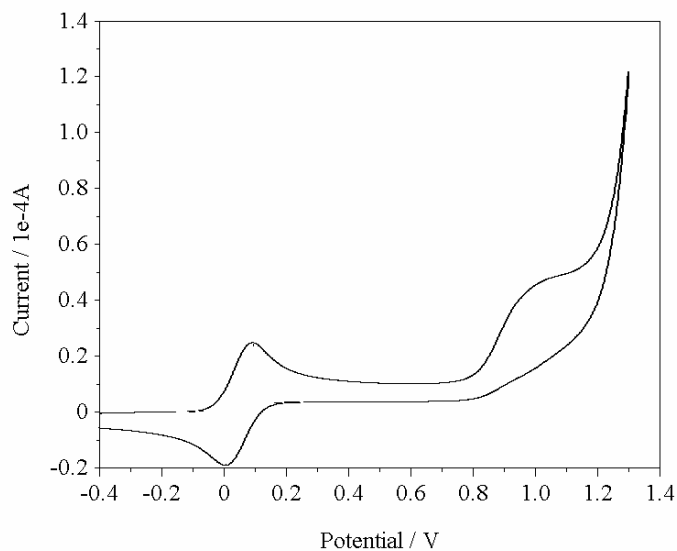


Fig. 3: Cyclic voltammogram of **14** (10^{-3} M) recorded in DMF (0.1 M TBAP) at a glassy carbon electrode. ($\varnothing = 3$ mm, $\nu = 100$ mVs $^{-1}$).

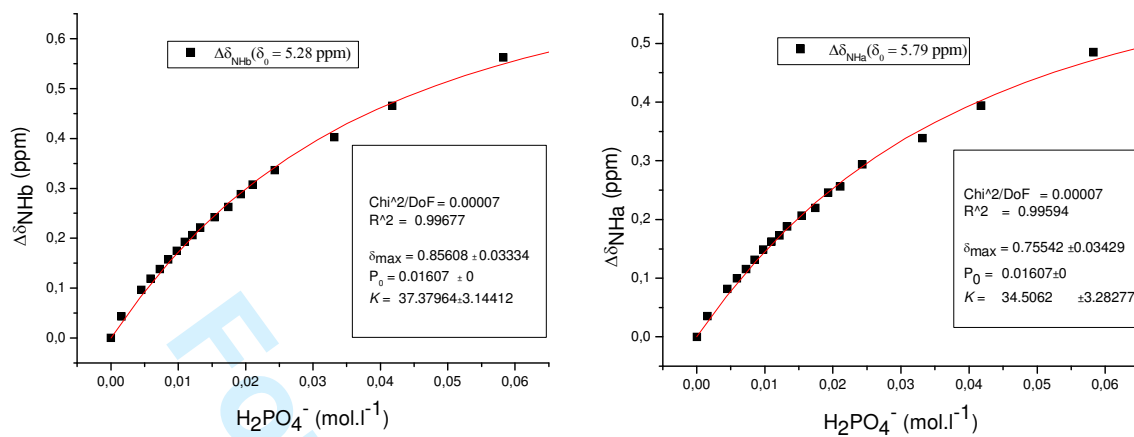
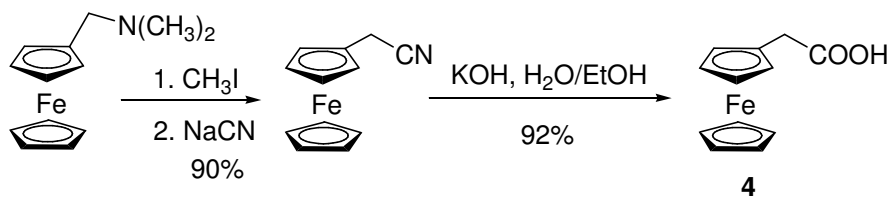
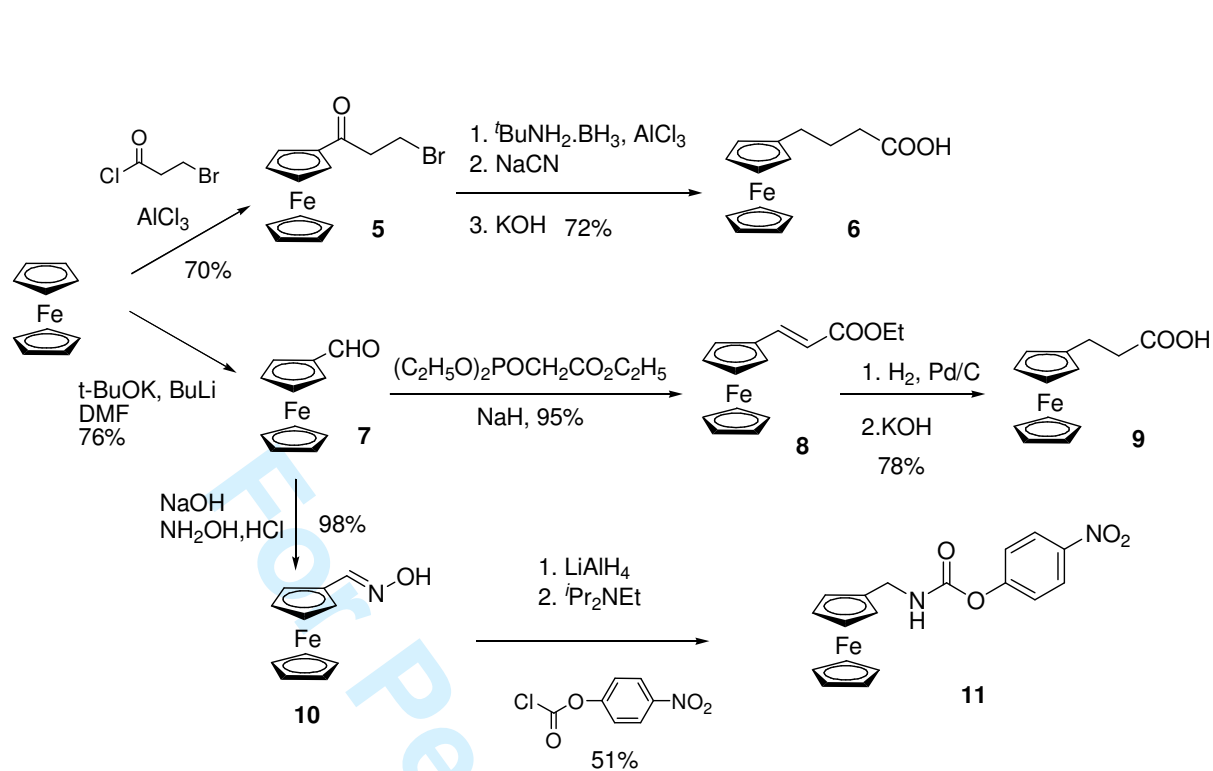


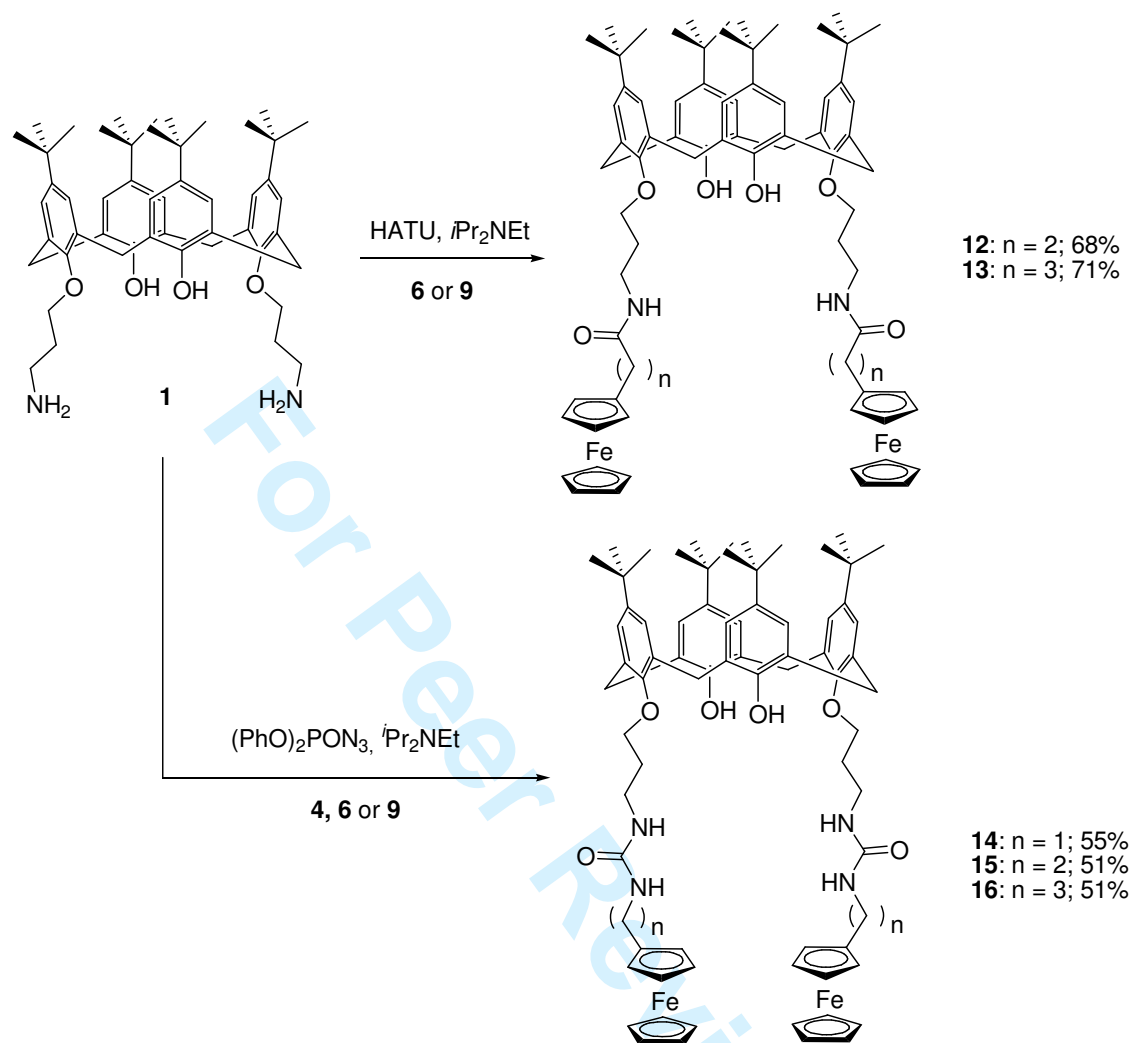
Fig. 5: $\Delta\delta_{\text{NH}_i}$ and $\Delta\delta_{\text{NH}_{ii}}$ as a function of $[\text{H}_2\text{PO}_4^-]$ for 14



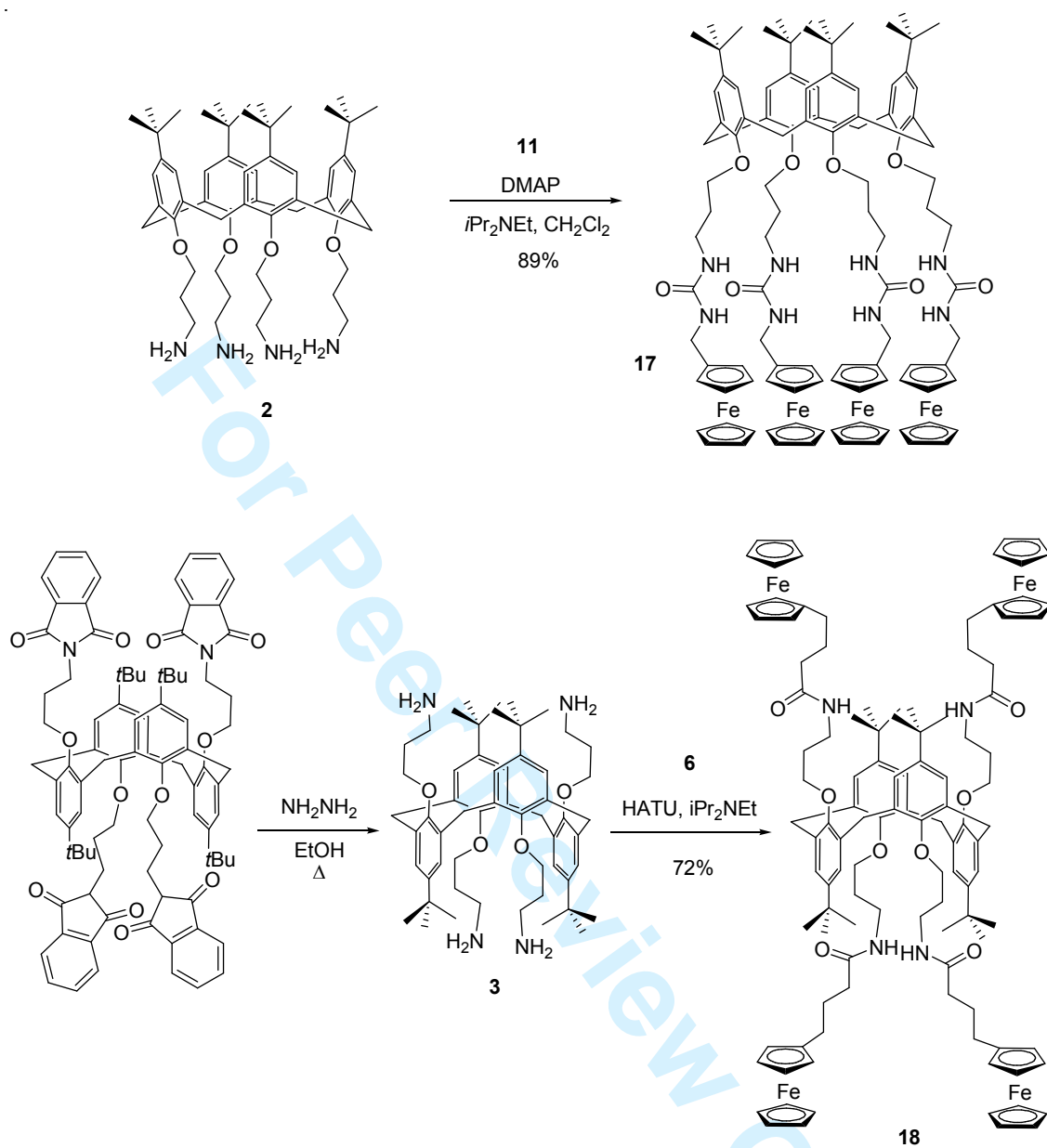
10 **Scheme 1.** Synthesis of the ferrocene -acetic acid **4** from *N,N*-dimethylaminomethyl-
11 ferrocene.³²
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Scheme 2. Synthesis of the ferrocenyl derivatives **6**, **9** and **11** from ferrocene.



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



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

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

	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

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Table 2: Experimental $E_{1/2}$ and ΔE_p values (mV)*

	CH ₂ Cl ₂		DMF		CH ₃ CN		DMSO	
	$E_{1/2}$	ΔE_p	$E_{1/2}$	ΔE_p	$E_{1/2}$	ΔE_p	$E_{1/2}$	ΔE_p
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	-	-

* $E_{1/2} = (E_{pa} + E_{pc})/2$; $\Delta E_p = E_{pa} - E_{pc}$. Data recorded for **12-18** (10^{-3} M) on glassy carbon electrodes ($\varnothing = 3\text{mm}$) at 100 mVs^{-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·H₂PO₄ to dichloromethane (0.1M TBAP) solutions of **14**, **16** and **13** ($5 \cdot 10^{-4}$ M, $v = 100$ mVs⁻¹, glassy carbon electrode $\varnothing = 3$ mm).

	13	13 ·(H ₂ PO ₄ ⁻) ₂	14	14 ·(H ₂ PO ₄ ⁻) ₂	16	16 ·(H ₂ PO ₄ ⁻) ₂
ΔE (mV)	92	108	98	100	92	98
$\Delta E_{1/2}$ (mV)	94		155		135	

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

Conformational analysis and anion binding properties of ferrocenyl-calixarene receptors

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Abstract

Novel synthetic approaches toward redox active calixarene-based receptors is described wherein ferrocene fragments have been introduced at the lower rim through anion-binding urea or amide connections. A thorough ¹H 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.

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 synthesize complex host molecules allowing multi-point recognitions of anionic targets. In the present study we

1
2 synthesized and investigated the anion binding properties of novel artificial receptors
3 associating calixarene as modular platform, urea units as anion binding moieties and
4 ferrocene redox active reporters. Urea fragments have already been introduced into *p*-
5 positions of calixarene skeleton mostly through direct linkage to elaborate supramolecular
6 capsular materials⁴⁻⁹ and anions or ditopic receptors.¹⁰⁻²²

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11 The incorporation of metallocene fragments, usually cobaltocene or ferrocene, in such
12 systems has been pursued essentially to sense or activate molecular level processes. Kaifer
13 and coworkers reported a redox controlled dissociation of a self assembled dimer²³ whereas
14 Beer took advantage of the receptor's electrochemical activity as a signal of a recognition
15 event.^{24,25} The latter has been pioneered in making metallocene appended calixarenes for
16 analytic purposes or to investigate electrochemical interactions between multi redox
17 architectures.²⁶ Among the most relevant examples, one find an hetero ditopic ferrocene
18 receptors containing two ethyl ester calix[4]arene units bridged by a ferrocene amide moiety²⁷
19 or a tetraferrocenyl-calixarene in which metallocenes have been directly introduced on
20 aniline-like fragments.²⁸

21
22 In this paper, we report the synthesis and the characterization of novel redox active
23 calixarene-based receptors wherein ferrocene fragments have been introduced at the lower rim
24 through anion-binding urea or amide connections. We performed a thorough ¹H NMR
25 investigation on a series of calixarene-ferrocene receptors to estimate their hydrogen bonding-
26 driven self-association properties and improve our understanding of the correlation between
27 molecular structures and redox properties. Their anion binding properties have especially
28 been investigated by electrochemical methods and NMR spectroscopy.
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43 **Experimental Section**

44 *Electrochemical analysis*

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46 All electrochemical experiments were carried out using a CH-Instrument potentiostat. A
47 standard three-electrode cell was used for analytical experiments. Potentials are referred to the
48 Ag|Ag⁺10⁻² M in CH₃CN + 0.1 M TBAP. Glassy carbon disc electrodes (3 mm diameter,
49 from CH Instruments) were polished with 1- μ m diamond paste. All experiments were run at
50 room temperature under an argon atmosphere. An automatic iR compensation was performed
51 before each cyclic voltammetry experiments conducted in homogeneous media Acetonitrile
52 (HPLC grade) was purchased from Rathburn chemicals; DMF (99.8 % extra dry) was
53 purchased from Acros chemicals and Anhydrous dichloromethane was purchased from SDS.
54 *n*-tetrabutylammonium perchlorate (99 %) was purchased from Fluka.
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*¹H NMR titration of calixarene **14** with n-tetrabutylammonium dihydrogenphosphate*

Titration experiments were conducted in CD₂Cl₂ keeping the total concentration in **14** constant during the experiment ($[\mathbf{14}]_{\text{tot}} = [\mathbf{14}] + [\mathbf{14} \cdot (\text{H}_2\text{PO}_4)_n]^{n-} = 16.07 \text{ mM}$). Aliquots of a CD₂Cl₂ solution made up of n-TBA.H₂PO₄ (79 mM ou 645 mM) and **14** (16.07 mM) were added into an NMR tube containing **14** (16.07 mM) in CD₂Cl₂ at 293 K. The chemical shifts of both signals (δH_i and δNH_{ii}) were followed and recorded upon adding increasing amounts of n-TBAH₂PO₄. Fit of experimental data were achieved considering a 1/1 stoichiometry corresponding to the following equation:

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

with $\Delta\delta = \delta_x - \delta_{\text{initial}}$; $\delta_{\text{max}} = \delta_{\text{final}} - \delta_{\text{initial}}$; P₀: concentration of **14**; S₀: concentration of anion; 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 DRX500 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 electrospray at the Mass Spectrometry centre.

The synthesis of compound **4**,³² **11**²⁴ and **7**⁵⁰ was realized according to the literature procedure.

(3-bromopropyl)ferrocene **5**:

3-Bromopropanoyl chloride (2.17 mL, 21.5 mmol) in CH₂Cl₂ (8 mL) was added dropwise to a suspension of aluminium chloride (3 g, 22.5 mmol) in CH₂Cl₂ (8 mL) at room temperature and stirred for 2 hours. After cooling (-10 °C), the homogenous solution was added to a solution of ferrocene (4 g, 21.5 mmol) in CH₂Cl₂ (50 mL) cooled to 0 °C. The resulting purple solution was allowed to warm to room temperature and stirred for 16 hours. This solution was then diluted with CH₂Cl₂ and poured over ice-H₂O. The product was extracted with CH₂Cl₂ and the organic phase was washed with saturated aqueous solution of NaHCO₃, brine, dried over MgSO₄, filtered and concentrated. After purification by flash chromatography (silica gel CH₂Cl₂), the desired product was obtained in 70% yield (4.85 g). ¹H NMR (300 MHz, CDCl₃): 4.78 (t, 2H, *J*=1.88 Hz, *H*Fc), 4.23 (s, 5H, *H*Fc), 3.72 (t, 2H, *J*=6.60 Hz, CH₂), 3.29 (t, 2H, *J*=6.60 Hz, CH₂). ¹³C NMR (75 MHz, CDCl₃): 200.6, 78.3, 72.6, 70.0, 69.3, 42.4, 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 hours 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 1M and extracted with diethyl ether. The organic phase was dried over MgSO₄, filtered and concentrated under vacuum. The desired product was obtained in 84% yields (4.28 g) Mp = 85-86 °C ¹H NMR (300 MHz, CDCl₃): 4.12 (s, 5H, HFc), 4.07 (s, 4H, HFc), 2.37-2.42 (m, 4H, CH₂), 1.75-1.80 (m, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃): 179.9, 87.8, 68.5, 68.1, 67.2, 33.6, 28.8, 25.9. HRMS calculated for C₁₄H₁₆FeO₂: 272.04997 found: 272.05044.

Ethyl ferrocenylacrylate 8⁵¹ :

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 hour. Saturated aqueous ammonium chloride was then added to the mixture. Diethyl ether was added and the combined layers were washed with water, dried (MgSO₄) and the solvent removed under vacuum. Purification by column chromatography (silica gel dichloromethane) affords compound **8** in 98% yields (6.5 g). ¹H NMR (300 MHz, CDCl₃): 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, CH₂), 4.15 (s, 5H, HFc), 1.32 (t, *J* = 7.2 Hz, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃): 167.4, 145.7, 115.1, 78.8, 70.9, 69.7, 68.7, 60.3, 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. ¹H NMR (300 MHz, CDCl₃): 4.31 (s, 9H, HFc), 2.45 (s, 4H, CH₂), 4.39 (q, 2H, *J* = 7 Hz, CH₂), 1.21 (t, 3H, *J* = 7 Hz, CH₃).

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 hours 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 1M and extracted with diethyl ether. The organic phase was dried over MgSO₄, filtered and concentrated under vacuum. Ferroceneproponic acid **9** was obtained in 83% yields (1.5 g). ¹H NMR (300 MHz, CDCl₃): 11.03 (s br, 1H), 4.02-4.08 (m, 9H, HFc), 2.49-2.63 (m, 4H, CH₂). ¹³C NMR (75 MHz, CDCl₃): 180.1, 87.6, 68.9, 68.3, 67.9, 67.0, 35.9, 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 CHCl₃, washed with water, dried (MgSO₄) 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**: ¹H NMR (300 MHz, CDCl₃): 6.92 (s, 8H, ArH), 3.74 (s, 8H, ArCH₂Ar), 3.34-3.42 (m, 8H, CH₂O), 2.39-2.46 (m, 8H, CH₂NH), 1.20-1.24 (m, 44H, CH₂CH₂CH₂, *t*-Bu). ¹³C NMR (75 MHz, CDCl₃): 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. HRMS calculated for C₅₆H₈₄N₄O₄: 877.6571 found: 877.6566.

Amide Synthesis:

HATU (1.2 mmol, 450 mg) and diisopropylethylamine (1.2 mmol, 0.2 mL) was 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 hours, 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**: 68% Mp = 223-225 °C; ¹H NMR (300 MHz, CDCl₃): 7.63 (s, 2H, OH), 7.10 (s, 4H, ArH), 6.85 (s, 4H, ArH), 3.96-4.17 (m, 26H, ArCH₂Ar, HFc, CH₂O), 3.62-3.67 (m, 4H, CH₂NH), 3.34 (d, 4H, *J*=12.9 Hz, ArCH₂Ar), 2.61-2.69 (m, 4H, CH₂CO), 2.41-2.44 (m, 4H, CH₂Fc), 2.05-2.14 (m, 4H, CH₂CH₂CH₂), 1.29 (s, 18H, *t*-Bu), 0.98 (s, 18H, *t*-Bu). ¹³C NMR (75 MHz, CDCl₃): 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, 1635. Elem. Anal. Calculated 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; ¹H NMR (300 MHz, CDCl₃): 7.56 (s, 2H, OH), 7.09 (s, 4H, ArH), 6.84 (s, 4H, ArH), 4.29-4.45 (m, 18H, HFc), 4.19 (d, 4H, *J*=13 Hz, ArCH₂Ar), 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 , $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.66-1.69 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 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 calculated for $\text{C}_{78}\text{H}_{98}\text{Fe}_2\text{N}_2\text{O}_6$: 1270.61237 found: 1270.61244.

Compound **18**: 72%; Mp = 139-143°C; ^1H NMR (300 MHz, CDCl_3): 6.99 (s, 8H, *ArH*), 6.03 (m, 4H, *NH*), 4.14 (m, 20H, *HFc*), 4.10 (m, 16H, *HFc*), 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, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.25-1.36 (m, 44H, $\text{CH}_2\text{CH}_2\text{CH}_2$, *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, 27.3. IR: KBr pellets cm^{-1} : 3299, 2951, 2866, 1643. HRMS calculated for $\text{C}_{112}\text{H}_{141}\text{Fe}_4\text{N}_4\text{O}_8$: 1893.81416 found: 1893.81435.

General procedure for Curtius reaction:

diisopropylethylamine (9 mmol) and diphenylphosphoryl azide (4.4 mmol) were added to a solution ferrocenecarboxylic acid (2.2 mmol) was dissolved in toluene (15 mL). The reaction mixture was heated at 70 °C for 2 hours then the 5,11,17,23-tetra(*tert*-butyl)-25,27-bis(3-aminopropoxy)-26,28-dihydroxycalix[4]arene (1 mmoles) was added. After 2 hours 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**: 55%; Mp: 143-146 °C; ^1H NMR (500 MHz, CDCl_3): 7.71 (s, 2H, *OH*), 7.04 (s, 4H, *ArH*), 6.83 (s, 4H, *ArH*), 5.94 (s br, 2H, *NH*), 5.40 (s br, 2H, *NH*), 4.11 (s, 10H, *HFc*), 4.02-4.08 (m, 16H, ArCH_2Ar , *HFc*, 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, $\text{CH}_2\text{CH}_2\text{CH}_2$), 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, 30.1. IR: KBr pellets cm^{-1} : 3364, 2956, 2867, 1632. HRMS calculated for $\text{C}_{74}\text{H}_{92}\text{Fe}_2\text{N}_4\text{O}_6$: 1244.57157 found: 1244.57163.

Compound **15**: 51%; Mp = 159-162 °C; ^1H NMR (300 MHz, CDCl_3): 7.87 (s, 2H, *OH*), 7.09 (s, 4H, *ArH*), 6.91 (s, 4H, *ArH*), 5.81 (s br, 2H, *NH*), 5.26 (s br, 2H, *NH*), 4.08-4.22 (m, 26H, ArCH_2Ar , *HFc*, 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, $\text{CH}_2\text{CH}_2\text{Fc}$), 2.14-2.19 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 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,

30.5. IR: KBr pellets cm^{-1} : 3370, 2959, 2869, 1651. HRMS calculated for $\text{C}_{76}\text{H}_{97}\text{Fe}_2\text{N}_4\text{O}_6$: 1273.6112 found: 1273.612.

Compound **16**: 51%; Mp: 125-130 °C; ^1H NMR (300 MHz, CDCl_3): 7.73 (s, 2H, OH), 7.09 (s, 4H, ArH), 6.87 (s, 4H, ArH), 5.91 (s br, 2H, NH), 5.39 (s br, 2H, NH), 4.19 (d, 4H, $J = 13.2$ Hz, ArCH_2Ar) 4.08 (s, 10H, HFc), 3.99-4.06 (m, 12H, HFc, 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, $\text{CH}_2\text{CH}_2\text{Fc}$), 2.16-2.20 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.61-1.67 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 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, 27.0. IR: KBr pellets cm^{-1} : 3376, 2961, 2867, 1634. HRMS calculated for $\text{C}_{78}\text{H}_{100}\text{Fe}_2\text{N}_4\text{O}_6$: 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 then the organic fraction was dried over magnesium sulfate, filtered, and the solvent 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; ^1H NMR (500 MHz, $\text{DMSO}-d_6$): 6.78 (s, 8H, ArH), 6.22 (s br, 4H, NH), 6.02 (s br, 4H, NH), 4.27 (d, 8H, $J = 12.3$ Hz, ArCH_2Ar), 4.13-4.16 (m, 28H, HFc), 4.05-4.07 (m, 12H, HFc), 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, $\text{CH}_2\text{CH}_2\text{CH}_2$), 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, 31.2. IR: KBr pellets cm^{-1} : 3376, 2961, 2867, 1634. HRMS calculated for $\text{C}_{106}\text{H}_{137}\text{Fe}_4\text{N}_8\text{O}_8$: 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**,²⁹ 5,11,17,23-tetra(*tert*-butyl)-25,26,27,26-tetra(3-aminopropoxy)-calix[4]arene in cone conformation **2**³⁰ 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 Bhömer et al.³¹ The ferrocene-acetic acid starting material **4** (scheme 1) was prepared as described in literature

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2 from the *N,N*-dimethylaminomethylferrocene in good yield (83%).³² The methyl iodide
3 intermediate was treated with potassium cyanide to afford the ferrocenylacetonitrile which
4 was then converted to the corresponding carboxylic acid **4**.
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7 The ferrocenebutyric acid **6** was previously prepared by reaction of the ferrocene with
8 succinic anhydride followed by a Clemmensen reduction.³³ We report here an alternative
9 approach from the ferrocene in four steps and 50% overall yield (scheme 2). After a Friedel-
10 Craft acylation, the ketone was reduced to affording the (3-bromopropyl)-ferrocene **5**. The
11 last steps are identical to those detailed for the ferrocene-acetic acid **4**, cyanide formation then
12 hydrolysis. The ferrocene propanoic acid **9**³⁴ was prepared from the ferrocene carboxaldehyde
13 **7** via a Horner-Wardsworth-Emmons olefination in quantitative yield. The last steps are the
14 double bond hydrogenation of **8** followed by a saponification of the ester function to afford **9**
15 in 78 % yields. Finally, **11** was obtained in three steps as already described in the literature²⁸
16 from the ferrocene carboxaldehyde **7** previously transformed into the corresponding oxime **10**
17 followed by the reductive amination and condensation with the 4-nitrophenyl chloroformate.
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19 Metallocene redox-active fragments were introduced onto a calixarene framework using the
20 the ferrocene acids **6** or **9** and HATU (2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl
21 uronium hexafluorophosphate) as coupling reagent. This straightforward peptide-based
22 strategy allowed us to isolate the bis(amido)-calixarenes **12** and **14** respectively in 68% and
23 71 % yield (scheme 3).
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25 Ferrocene acids **4**, **6** or **9** and aminocalixarene **1** were also linked via an urea connection
26 through a Curtius rearrangement.³⁵ A variety of approaches towards calixarene-ureas have
27 already been investigated. Most of them were based on the use of commercially available
28 isocyanates³⁶⁻³⁸ or isocyanate derivatives of calixarenes.^{39,40} In this study, the targeted redox
29 active receptors **14**, **15** and **16** were prepared in one pot procedure without isolating the
30 isocyanate intermediate by reacting the calixarene amine with ferrocene carboxylic acid in the
31 presence of diphenylphosphoryl azide and diisopropylethylamine
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33 The tetra-ureaferrocenyl derivative **17** was obtained in relatively low yield (15%) through a
34 Curtius rearrangement between **9** and a tetra(amino)calix[4]arene **2** (scheme 4). However, this
35 yield was improved up to nearly 90 % using the Paul Beer's strategy upon using **11** as
36 ferrocene-urea precursor.²⁸ Finally, the peptide coupling from **3** with **6** in the presence of
37 HATU gave the corresponding tetra(amidoferrocenyl) macrocycle **18** in 72% yield with a
38 1,3-alternate conformation.
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48 NMR analysis

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2 The structures of **12-18** were clearly established by NMR spectroscopy and electrospray mass
3 spectrometry. The cone conformations adopted in solution by the calixarene frameworks of
4 calixarenes **12-17** were deduced from the ^{13}C NMR experiments with the presence of
5 resonance signals observed between 31 and 32 ppm corresponding to the ArCH_2Ar
6 fragments.⁴¹ Moreover, these compounds are present in symmetrical cone conformation as
7 proved by the low value of $\Delta\delta$ between the signals of the two sets of aromatic protons ($\Delta\delta$
8 lower than 0.016 in DMSO-d_6) and *tert*-butyl groups ($\Delta\delta$ close to 0.05 ppm in DMSO-d_6) as
9 already observed by Ungaro et al with peptidocali[4]arene bisureas.⁴² The resonance signal
10 located at 39.6 ppm which corresponds to the ArCH_2Ar of **18** confirmed the 1,3-alternate
11 conformation of the macrocycle.
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21 Information about the solvent accessibility of all NH protons in **12-18** and their level of
22 engagement in H-bonding could be obtained from temperature coefficients. The relative
23 change in chemical shifts recorded as temperature is changed by 1 K ($\Delta\delta/\Delta T$) is indeed an
24 accurate probe to estimate the level of hydrogen bonding in molecular systems.^{42,43} The
25 temperature dependence ($\Delta\delta/\Delta T$) of the ^1H NMR chemical shifts attributed to the NH signals
26 in compounds **12-18** was evaluated in DMSO-d_6 . A typical displacement observed with **15**
27 between 298 and 353 K is depicted on Figure 1. In this polar and H-bond acceptor media,
28 intermolecular hydrogen bonds and those established with solvent molecules are known to be
29 readily cleaved by increasing temperature. We moreover known from literature that $\Delta\delta/\Delta T$
30 values found below -4.0 ppb/K for amide protons unambiguously reveal the absence of
31 intramolecular hydrogen bonding processes.⁴³ Temperature coefficients were measured for
32 compounds **12-18** upon recording seven ^1H NMR spectra between 298 K and 353 K. These
33 analyses were performed on 3.0 mM solutions to ensure the absence of significant molecular
34 aggregation. The recorded and calculated results are summarized in Table 1.
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46 Full NMR characterizations and exhaustive proton assignments were achieved, for all
47 receptors, from ^1H NMR and 2D-COSY spectra. From the low $\Delta\delta/\Delta T$ values calculated for
48 the bis-amide derivative **12**, **13** and tetramide **18**, we readily inferred the absence of
49 interactions between amide arms. Surprisingly, both NHs of the urea linked ferrocene-
50 calixarenes **14**, **15** and **17** turned out to exhibit significantly different $\Delta\delta/\Delta T$ values.
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53 Whereas NHs on the calixarene side ($\Delta\delta/\Delta T = -3.6$ ppm/K) are clearly involved in
54 intramolecular H-bonding, lower value ($\Delta\delta/\Delta T = -4.4$ ppm/K) calculated for NH's on the
55 ferrocene side suggest simple solvent effects. The most positive $\Delta\delta/\Delta T$ values were found for
56 the tetra urea-linked ferrocene calixarene **17**. In contrast to what was found with **15**, both
57 NH's in **17** exhibit similar values strongly suggesting the existence of an intramolecular
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2 hydrogen bonding network between all four urea groups. In view of these results, ROESY
3 analysis was carried on compound **15** and **17** to obtain more information. Selective
4 irradiation of each NH for compound **17** revealed a correlation between NH_i (stands for NH's
5 on the calixarene side) and O-CH₂-CH₂-CH₂, NH_b (stands for NH's on the ferrocene side) and
6 between NH_{ii} and NH_i, CH₂-HFc. Concerning compounds **14** and **15**, the same type of
7 correlation was observed for NH_i than for compound **17**. With a limit $\Delta\delta/\Delta T$ value of -4.0 ppb
8 concerning the NH_{ii} of **14**, a weak H-bonding interaction could be expected. However NH_b
9 correlated only with NH_i. Based on these results which suppose that only NH_i are engaged in
10 a H-bonding, we assume that the urea was in *trans* configuration and/or the bottom part of the
11 molecule was outside the cavity (figure 2).
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21 Electrochemical analysis

22 Depending of their solubility, the electrochemical signatures of compounds **12-18** were
23 investigated by cyclic voltammetry, RDE and square wave voltammetry on glassy carbon
24 electrodes in dichloromethane, DMF, acetonitrile and DMSO using *n*-tetrabutylammonium
25 perchlorate as electrolyte (TBAP, 0.1 M). All cyclic voltammograms featured one single
26 wave corresponding to the simultaneous oxidation of both ferrocene fragments, highlighting
27 the limited or non-existent communication between the iron centres. As proved by the
28 experimental data reported in table 2, the ferrocene half wave potential significantly shifts
29 towards less positive values when the number of atoms between the metallocene and urea
30 fragments increases (see compounds **14** and **16** in CH₂Cl₂). This significant displacement can
31 be unambiguously attributed to the electron-withdrawing effect of the urea and amide
32 fragments on the metallocene probe which logically strengthens as their linker shortens.
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42 Whatever the macrocycle, the redox signatures did not reveal strong interactions between
43 ferrocenes, as proved by the observation of one single wave on their cyclic voltammograms
44 corresponding to the simultaneous oxidation of all iron centres. The weak "interaction level"
45 between redox moieties could nevertheless subtly be appraised upon measuring and
46 comparing the difference between oxidation and reduction peak potentials (ΔE_p), assuming
47 that hints of "communication" between redox centers should bring about inequivalence
48 signalled by larger ΔE_p values. The experimental values reported in Table 2 are interestingly
49 in full agreement with the outcomes of NMR spectroscopy establishing that **14**, **15** and **17**
50 exhibit stronger intramolecular hydrogen bonding. Albeit numerous physico-chemical
51 parameters might contribute to these deviation in electrochemical activities (number of redox
52 centers, adsorption processes, kinetics...), the changes in ΔE_p and $\Delta\delta/\Delta T$ values, calculated in
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2 DMSO for a series of structurally related receptors, are consistent and led to similar
3 conclusions.
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6 As mentioned above, the observation of one single ferrocene centered oxidation wave results
7 from the lack of communication between both centres. The expected intra-molecular
8 association between urea fragments hence does not bring both metallocene in sufficient
9 proximity to bring about significant electrochemically promoted electrostatic effects. It is now
10 well established that the level of electrochemical connection in multi-redox architectures can
11 be accurately estimated upon measuring discrepancies between experimental results and
12 theoretical modeling. The electrochemical behaviour of molecules with multiple redox centres
13 has indeed been the subject of numerous studies.^{43,44} It has been especially demonstrated⁴⁵
14 that electron transfers to or from molecules containing identical, non interacting, electroactive
15 centres should yield a single current-potential curve similar to that observed with single
16 electroactive centre ($\Delta E_p = 58$ mV at 25 °C) but with a magnitude determined by the total
17 number of redox centres. When each centre is characterized by the same standard potential
18 E_m° , and adheres to the Nernst equation independently of the oxidation state of any of the
19 other centres in the molecule, it is possible to calculate the formal potentials corresponding to
20 each pair of successive oxidation states of the multi-centres molecules. Considering fully non
21 interacting centres, the theoretical shift between both ferrocene based formal oxidation
22 potentials in **13**, **14** and **16** (E_1° and E_2°) should thus equal $\Delta E = E_1^\circ - E_2^\circ = 35.6$ mV, although
23 both redox processes are expected to appear as a single wave with peak potentials satisfying
24 $\Delta E_p = 58$ mV.⁴⁶ Formal potentials E_1° and E_2° can not be determined in a straightforward
25 manner but the easily measured difference between oxidation and reduction peak potentials
26 (ΔE_p) gives reliable leads on the “communication level” between multiple redox centres. The
27 experimental values reported in table 2 especially reveal the discrepancy in ΔE_p values
28 ranging from 98 to 126 mV in dichloromethane. Such deviation from theoretical prediction
29 can be attributed to different factors, involving electron transfer kinetics, adsorption processes
30 or ohmic drop contributions but also to non negligible interactions between electrogenerated
31 ferricinium species. Such assumption especially relies on the fact that the largest ΔE_p value
32 was observed with **14**, wherein intramolecular hydrogen bonds between urea groups
33 expectedly lead to the shortest distance between both metallocene centres. This ΔE_p
34 differences measured in apolar dichloromethane however turned out to be concentration
35 dependent since a significantly smaller value was measured at $5 \cdot 10^{-4}$ M (table 3). Such feature
36 thus clearly suggested the absence of communication effect which should thus not be
37 considered to account for the large ΔE value. All studied receptors exhibit a second
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2 irreversible oxidation process, at $E \geq 800$ mV, centred on both phenol subunits of the
3 calixarene skeleton.⁴⁷ A typical voltammogram showing the ferrocene and phenol centred
4 redox systems is depicted on figure 3. As discussed above, **14**, **16** and **13** exhibit structural
5 and chemical features fully suited to achieve an efficient complexation/sensing of anionic
6 species. Urea and phenol groups are indeed among the most widely used binding fragments to
7 trap or transport negatively charged species in biological systems.⁴⁸ The calixarene's
8 lipophilic character and structuring effect associated to the anion binding properties of urea
9 or amide and phenol are expedient complementary features defining **14**, **16** and **13** as artificial
10 anion receptors with great potential. In addition to these favourable chemical and structural
11 aspects, both metallocene moieties can be easily activated, *ie* oxidized at low potential, to
12 further improve the receptor anion binding ability through electrochemically triggered ion
13 pairing effects between anionic targets and *in situ* mono or bis-positively charged receptors.¹
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25 Anion binding

26 The anion binding ability of these receptors could be quickly confirmed upon studying the
27 effects of added anionic substrates on the chemical shifts of selected fragments. Addition of
28 *n*-tetrabutylammonium dihydrogenphosphate to a CDCl₃ solution of **14** especially led to
29 significant low field shifts of singlets attributed to the urea groups (◦, figure 4) and to a lesser
30 extent to the phenol moieties (•, figure 4). Such perturbations could be observed with all of
31 the studied receptors which were soluble in CDCl₃ (**13**, **14** and **16**) and clearly result from
32 interactions between hydrogen-bond donors and electron rich anionic species. In agreement
33 with previously reported studies,⁴⁴ these receptors exhibit however, at least in their reduced
34 forms, relatively low binding constants with anionic species, especially in the case of **13** and
35 **16** for which the binding constants could not be precisely determined.
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45 On the other hand, titration of **14** conducted in CD₂Cl₂ with dihydrogenphosphate anion, since
46 the affinity for this anion is higher, yielded for instance curves which could be fitted
47 according to a 1/1 calixarene/anion stoichiometry with an estimated binding constant of $36 \pm$
48 4 M^{-1} (figure 5). The 1:1 stoichiometry was confirmed by job plot with ¹H NMR experiment
49 in CD₂Cl₂ (figure 6). A symmetrical bell-shaped curve centered at a 0.5 molar fraction was
50 observed, thus confirming the presence only of the 1:1 host/guest complex.
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55 The ability of **13**, **14**, and **16** to complex anionic species and their potential in molecular
56 electrochemical recognition were also investigated by cyclic voltammetry in dichloromethane
57 electrolyte. The addition of increasing amounts *n*-tetrabutylammonium nitrate, sulphate,
58 chloride or acetate to a 10⁻³ M solution of these receptors did not induce measurable changes
59 in the ferrocene centred oxidation wave. This lack of electrochemical response can be
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1 attributed to weak associations between these anions and the phenol/amide/urea binding
2 fragments and/or to limited interaction of the complexed anion with the neutral and/or
3 oxidized metallocenes redox probes.
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7 However, an effective electrochemical response was observed in presence of hydrogen
8 phosphate anions (figure 7). Addition of the latter indeed resulted in a clear two wave
9 behaviour wherein the intensity of the initial ferrocene based wave progressively decreases at
10 the expense of a novel signal at a much less positive potential (figure 7A and 7B). After
11 adding one molar equivalent of anion, the intensity of both signals appeared comparable and
12 full disappearance of the original wave was only observed when the anion/receptor ratio
13 reached about two. Such evolution is fully compatible with a strong binding of one H_2PO_4^-
14 anion per urea fragment leading, *in fine*, to a bis(hydrogenophosphate) complex. This 2/1
15 binding stoichiometry, while differing from that found from NMR experiments, can be easily
16 explained upon considering that two positive charges are being electrochemically generated
17 onto the calixarene receptors. These results are furthermore in agreement with previously
18 reported studies conducted on similar receptors.⁴⁸ It needs to be stressed out that both waves
19 remained fully reversible through the titration experiment and that the maximal potential shift
20 ($\Delta E_{1/2}$) between the uncomplexed and complexed receptors electrochemical activities reached
21 155 mV. The addition of H_2PO_4^- anions to a solution of **14** did moreover not significantly
22 modify the shift between oxidation and reduction peak potentials (ΔE , table 3). This
23 observation is another clear indication that the “large” ΔE value measured in dichloromethane
24 does not result from urea-driven intramolecular redox communication which would logically
25 be disrupted upon adding hydrogen-phosphates.
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28 Several interactions and effects can potentially be considered to account for the observed
29 changes. The hydrogen bonding ability of urea and phenol groups is obviously of great
30 importance but the influence of ferricinium and effect of complexation on ferrocene are also
31 key elements to achieve such efficient molecular electrochemical sensing. A short linkage
32 between urea and ferrocene was initially considered to be essential to optimize the
33 transduction of any recognition process. In order to estimate the importance of the urea-
34 phosphate bonds in the wave's displacement, which arises from an overall increase of electron
35 density around the metallocene fragments, we studied the response of **16** and **13** in which
36 ferrocene and binding fragments are fully disconnected, through a long alkyl chain,
37 prohibiting any through bonds effects on the electrochemical recognition process. Addition of
38 increasing amounts of $\text{TBA}\cdot\text{H}_2\text{PO}_4$ to a dichloromethane solution of the free receptors **16** and
39 **13** surprisingly led to similar “two wave” responses only distinguished by the half waves
40 potential shifts amplitudes ($\Delta E_{1/2}$, table 3). The $\Delta E_{1/2}$ values reported in table 3 indeed clearly
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1 highlight the beneficial effects of intimately connecting the recognition and signalling
2 fragments. The interaction of the urea groups in **14** with H_2PO_4^- species has indeed an
3 unambiguous electronic, through bonds, effect on the ferrocene's final oxidation potential.
4 Although the most important perturbation is observed in the latter case, **16** and **13** still allow
5 an effective sensing through important displacements of the ferrocene oxidation potential.
6 This result shows the utmost importance of ion pairing effects in electrochemical recognition
7 process. When the ferrocene groups are far away from the hydrogen binding fragments, as in
8 **16** and **13**, the strong selective electrostatic interaction between hydrogen phosphate and the
9 electrogenerated ferricinium species is almost enough to ensure an efficient transduction. This
10 assumption is further demonstrated upon studying the electrochemical activity of simple
11 ferrocene and $\text{TBA}\cdot\text{H}_2\text{PO}_4$ in dichloromethane. The initial reversible Fc/Fc^+ couple quickly
12 evolve towards a broad irreversible system in presence of phosphate presumably resulting
13 from the formation of poorly soluble ion pairs. The organic receptors used in this study have
14 thus two main effects, besides introducing selectivity and affinity associated to the specific
15 binding fragments, they also greatly help stabilizing and solubilizing the oxidized forms of the
16 calixarene-anion complexes. The difference in $\Delta E_{1/2}$ (ca. 40 mV, Table 3)) observed between
17 **16** $\cdot(\text{H}_2\text{PO}_4^-)_2$ and **13** $\cdot(\text{H}_2\text{PO}_4^-)_2$ is tentatively attributed to distinct coordination modes setting
18 the complexed anion closer to the redox probe in **16** than in **13**. This shift is furthermore
19 correlated to the number of atoms separating the ferrocene fragment from the amide hydrogen
20 bond donor in both receptors.
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39 Conclusion

40 In conclusion, we have described the synthesis of original calix[4]arenes wherein ferrocene
41 fragments have been introduced at the lower rim through urea or amide connections. We
42 especially assessed the presence and/or the lack of intramolecular hydrogen bonds by NMR
43 spectroscopy. The anion binding properties of these artificial receptors have been revealed by
44 NMR spectroscopy and thoroughly investigated by electrochemical methods. We especially
45 assessed the importance of the urea-phosphate bonds in the observed electrochemical
46 response upon studying receptors wherein ferrocene and binding fragments are intimately
47 associated or fully disconnected through a long alkyl chain. Although similar selective
48 phosphate sensing properties have been previously reported with intimately connected
49 ferrocene-amide-calixarene receptors,^{26,49} our experimental results clearly show the utmost
50 importance of ion pairing effects in this electrochemical recognition process which accounts
51 for more than 85 % of the transduction signal.
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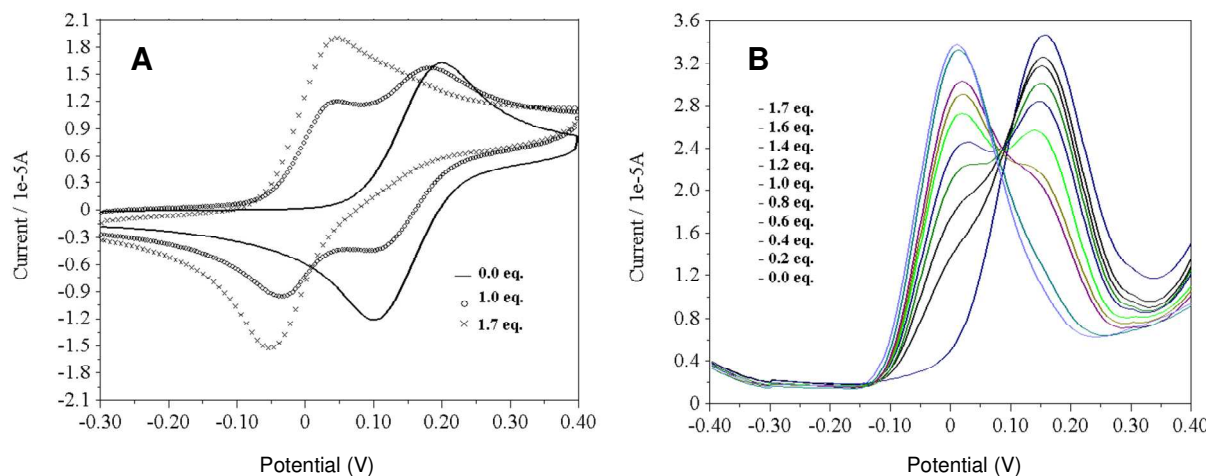


Fig. 7: (A) Cyclic ($v=100 \text{ mV}\cdot\text{s}^{-1}$) and (B) square wave voltammograms of **14** ($5\cdot 10^{-4} \text{ M}$) recorded in dichloromethane (0.1 M TBAP) upon adding increasing amounts of TBA•H₂PO₄ (glassy carbon electrode, $\varnothing = 3 \text{ mm}$).

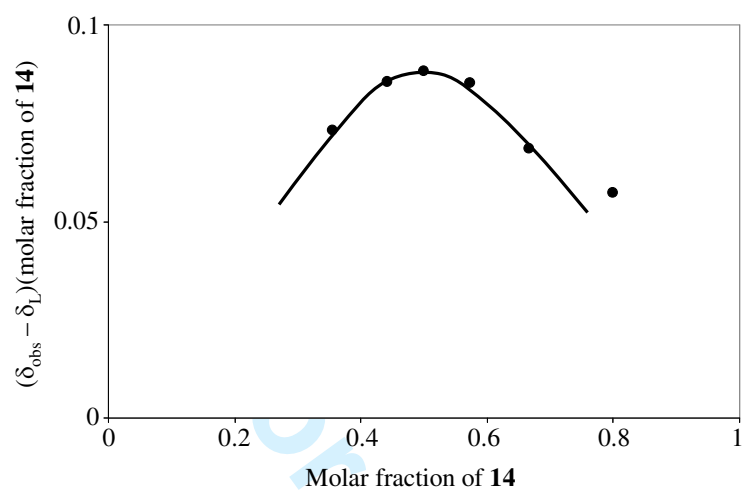


Fig. 6 : job plot of the titration of $\text{Bu}_4\text{NH}_2\text{PO}_4$ with 14 in CD_2Cl_2