Amide and Urea Ferrocene-Containing Macrocycles Capable of the Electrochemical Sensing of Anions

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Two novel macrocycles that incorporate the redox-active ferrocene motif have been synthesized. The amide-containing macrocycle is capable of sensing basic oxoanions such as dihydrogen phosphate and benzoate despite only exhibiting weak binding of these anions. The second macrocycle, which

Introduction

Anions have an immense impact on our world.^[1] They are of exceptional importance in biology, with enzyme substrates and cofactors being typically anionic, whereas the simple monoatomic chloride anion is found extensively in extracellular fluid. The misregulation of this particular anion in the human body is believed to cause the terminal genetic disease cystic fibrosis.^[2] Anions have also been found to have an adverse effect on the environment: the leaching of phosphates and nitrates into waterways through overuse of fertilizers leads to eutrophication.^[3] Pertechnetate (a radioactive byproduct of the nuclear industry)^[4] and perchlorate (which arises from the manufacture of explosives)^[5] are further examples of anionic pollutants.

The sensing of anions is therefore of significant research interest, and a large range of anion sensors that provide either optical or electrochemical responses have been reported.^[6] Among examples of electrochemical anion sensors, hydrogen-bond donor/receptor molecules that incorporate ferrocene have enjoyed considerable popularity. This may be explained by the readily accessible ferrocene/ferrocenium (Fc/Fc⁺) redox couple and the extensive chemistry of ferrocene that exists in the chemical literature.^[6c]

1,1'-Bis(aminocarbonyl)ferrocene (see Figure 1a) is a widely used motif in acyclic and macrocyclic anion-sensory receptors.^[7] Whilst exhibiting electrochemical recognition for anions, this motif has a rather positive Fc/Fc⁺ potential

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incorporates urea functionality, is capable of binding and sensing a greater range of anions with a maximum shift of the ferrocene/ferrocenium redox couple of -170 mV observed upon addition of an excess amount of dihydrogen phosphate.

value that may be responsible for the commonly encountered irreversible redox behaviour observed in the presence of excess amounts of anions. Reversing the amide as shown in Figure 1b should move the Fc/Fc⁺ redox couple to a less positive potential than the 1,1'-bis(aminocarbonyl)ferrocene motif. An alternative N–H hydrogen-bond donor is urea: examples of two 1,1'-ferrocene bis-urea motifs are depicted in Figure 1 (c and d).^[8,9] Of these, the latter has yet to be included in a macrocycle for anion sensing. Here in this paper we report the synthesis of novel ferrocenecontaining macrocycles that incorporate the motifs depicted in Figure 1 (b and d), and the subsequent investigations into their anion recognition and electrochemical sensing properties.



Figure 1. Ferrocene anion-recognition motifs: 1,1'-ferrocene bisamides (a) and (b) and 1,1'-ferrocene bis-ureas (c) and (d).

Results and Discussion

"Reverse amide" macrocycle **4** was synthesized as shown in Scheme 1. Dicarboxylic acid **1** was first activated with dicyclohexylcarbodiimide (DCC) and *N*-hydroxysuc-



Scheme 1. Synthesis of "reverse amide" macrocycles 4 and 5.

cinimide to produce bis-succinimide ester 2.^[10] Treatment of **2** with 1,1'-bis(aminomethyl)ferrocene (**3**)^[11] under high dilution conditions afforded macrocycle **4** in 41% yield after silica gel chromatographic purification. In addition, a dimeric macrocyclic species **5** was isolated in 15% yield. Both macrocycles were characterized by ¹H and ¹³C NMR spectroscopy and high-resolution mass spectrometry.

Single crystals of macrocycle **4** suitable for X-ray crystallography were grown from slow evaporation of a chloroform solution. The determined structure is shown in Figure 2 and confirms the constitution of the macrocycle. The ferrocene unit was found to be disordered in the crystal; it occupies one of two positions with a 1:1 ratio of occupancy of the two sites in the crystal.^[12]



Figure 2. X-ray crystal structure of macrocycle **4**. The ferrocene unit is disordered and occupies two positions with a 1:1 ratio of occupancy of the two sites.

Urea macrocycle **8** was synthesized as depicted in Scheme 2.^[13] In this case, lower-rim-substituted calix[4]-arene bis-amine $6^{[14]}$ was treated with 1,1'-ferrocene bis-carbamate **7** to furnish the desired macrocycle **8** in 37% yield. Once again, a dimeric macrocyclic species **9** was also isolated (in 6% yield); both macrocycles were characterized by ¹H and ¹³C NMR spectroscopy and high-resolution mass spectrometry.

To measure the strength of anion binding of macrocycles 4 and 8, ¹H NMR spectroscopic titration experiments were undertaken in CD₃CN.^[15] NMR spectroscopy samples of the two macrocycles were prepared, to which aliquots of tetrabutylammonium (TBA) salts of chloride, dihydrogen phosphate, benzoate and hydrogen sulfate were added. The chemical shifts of peaks that arose from the NH protons were monitored. Anion binding events were observed to be fast on the NMR spectroscopic timescale, thereby allowing the use of the computer program winEQNMR2^[16] to calculate association constants with data fitting to a 1:1 stoichiometric binding model (Table 1).

For macrocycle **4**, the addition of anions (apart from HSO_4^-) caused an appreciable downfield shift of the amide NH resonance. However, plots of the chemical shift of the NH peak against equivalents of anion are almost linear (see the Supporting Information), and values of K_a calculated by winEQNMR2 for all four anions were below 25 m^{-1} , thereby implying weak anion binding. For macrocycle **8**, all



Scheme 2. Synthesis of urea macrocycles 8 and 9.

Table 1. Shifts in NH resonances ($\Delta\delta$) and 1:1 anion association constants (K_a) of macrocycles 4 and 8.^[a]

	Macroc	ycle 4	Mac	rocycle 8
	$\Delta\delta$ [ppm]	$K_{\rm a} [{\rm M}^{-1}]$	$\Delta\delta$ [ppm]	$K_{\rm a} [{ m M}^{-1}]$
Cl-	+0.15	<25	+1.07	4.5×10^{2}
$H_2PO_4^-$	+0.35	<25	+1.53	1.1×10^{3}
BzO ⁻	+0.53	<25	+1.90	2.1×10^{3}
HSO_4^-	+0.02	<25	+0.23	<50

[a] Anions added as TBA salts. Shifts are for 10 equiv. of anions added. Association constants are calculated by winEQNMR2, with errors of experimental data fitting to the calculated binding isotherms <10%. Solvent: CD₃CN, concentration of macrocycles: 1.5 mM, T = 293 K, peaks monitored: amide NH (macrocycle 4) and urea NH (macrocycle 8). Values for macrocycle 8 are averages (see text).

four anions caused much greater downfield shifts of the urea NH resonances (see Figure 3). Apart from chloride, the two NH resonances rapidly merge, and as a consequence, the average of the chemical shifts of the two resonances was therefore used to calculate the association constants reported in Table 1.^[17] The observed increase in binding of all anions by macrocycle 8 compared to macrocycle 4 is attributed to the greater acidity of the urea protons



Figure 3. Plots of the average chemical shift of the urea NH resonances of macrocycle 8 versus equivalents of TBA salt added (solvent: CD₃CN, concentration of macrocycle 8: 1.5 mm, T = 293 K).

than the amide protons. The observed trend of anion binding, $BzO^- > H_2PO_4^- > Cl^- > HSO_4^-$, generally follows the basicity of the anion as expected for simple hydrogen-bond donor-acceptor systems. It is proposed that chloride is

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bound more strongly than hydrogen sulfate (which is more basic) due to a better geometric complementarity between chloride and the macrocycle cavity than for hydrogen sulfate.

The electrochemical properties of macrocycles **4** and **8** were investigated by cyclic and square-wave voltammetry (CV and SWV) in 0.1 M TBAPF₆ CH₃CN solution. Both macrocycles **4** and **8** exhibit quasi-reversible oxidation waves for the Fc/Fc⁺ redox couple, with $E_{1/2}$ = +18 and -12 mV (±5 mV) respectively, compared to $E_{1/2(\text{ferrocene})}$ =

Table 2. Shifts [mV] of the Fc/Fc⁺ redox couple ($\Delta E_{1/2}$) of macrocycles **4** and **8** upon the addition of anions^[a]

	Macrocycle 4	Macrocycle 8
Cl-	[b]	-45
$H_2PO_4^-$	-75 ^[c]	$-170^{[c]}$
BzO ⁻	[b,c,d]	-90
HSO_4^-	[b]	-25

[a] Anions added as TBA salts. Shifts are for 10 equiv. of anions added. Electrolyte: 0.1 M TBAPF₆ in CH₃CN. Concentration of macrocycles: 1.5 mM. Reference electrode: Ag/AgCl. Values reported to nearest 5 mV. T = 293 K. [b] Magnitiude of shifts are less than 10 mV. [c] Irreversible behaviour, values reported are pertubations of oxidation peak, $\Delta E_{\rm pa}$. [d] Appearance of a second quasireversible redox wave at more anodic potential.

0 V.^[18] Such a small deviation from that of ferrocene itself is attributed to the separation of the electron-withdrawing carbonyl functionalities from the cyclopentadienyl rings by the alkyl CH_2 linkers.

Aliquots of the same anions used in the ¹H NMR spectroscopic investigations were added to electrochemical solution samples of the macrocycles and voltammograms recorded. The shifts in $E_{1/2}$ observed upon the addition of 10 equiv. of anion (as calculated from the CVs) are summarized in Table 2.

A measurable negative shift in the potential of the Fc/Fc^+ redox couple (attributed to the stabilization of the ferrocenium oxidation state^[19]) was only observed with macrocycle **4** upon addition of dihydrogen phosphate (with a concomitant loss in reversibility; see Figure 4a).^[20] This illustrates that strong binding by the neutral receptor is *not* required for electrochemical sensing of this anion. However, the amide functionality *is* required for this electrochemical behaviour to occur: addition of TBAH₂PO₄ to ferrocene leads only to the development of a cathodic stripping peak,^[21] which is not observed with macrocycle **4**. Macrocycle **4** also demonstrates electrochemical recognition for benzoate: upon addition of this anion, the redox wave becomes irreversible^[20] but does not appreciably shift. Also of

Figure 4. CV of macrocycle 4 upon the addition of aliquots of (a) TBAH₂PO₄ and (b) TBABzO. Electrolyte: 0.1 M TBAPF₆/CH₃CN (concentration of macrocycle 4: 0.5 mm. T = 293 K, potential compared to Ag/AgCl reference).

(a) 1.0x10 8.0x10 6.0x10 4.0x10 Current / A 2.0x10⁻⁶ 0.0 0.2 0.6 0.8 -2.0x10⁻⁶ Potential / V -4.0x10⁻⁶ -6.0x10⁻⁶ -8.0x10⁻⁶ Macrocycle 8 8 + 2 eq TBACI 8 + 0.5 eq TBACI 8 + 5 eq TBACI • 8 + 1 eq TBACI 8 + 10 eq TBACI (b) 1.0x10⁻⁵ 8.0x10⁻⁶ 6.0x10⁻⁶ 4.0x10⁻⁶ 2.0x10⁻⁶ 0.0 Current / A -2.0x10⁻⁶ 0.6 0.8 -4.0x10⁻⁶ Potential / V -6.0x10⁻⁶ --8.0x10⁻⁶ --1.0x10⁻⁵ -1.2x10⁻⁵ -1.4x10⁻⁵ -1.6x10⁻⁵ 8 + 2 eq TBAH_PO, Macrocycle 8 8 + 0.5 eq TBAH, PO 8 + 5 eq TBAH,PO, -8 + 1 eq TBAH_PO 8 + 10 eq TBAH_PO,

Figure 5. CV of macrocycle **8** upon the addition of aliquots of (a) TBACl and (b) TBAH₂PO₄. Electrolyte: 0.1 M TBAPF₆/CH₃CN (concentration of macrocycle **8**: 0.5 mm. T = 293 K, potential compared to Ag/AgCl reference).

note is the appearance of a second quasi-reversible redox wave at a more positive potential (Figure 4b).^[22,23]

With macrocycle 8, after the addition of chloride, hydrogen sulfate and benzoate the Fc/Fc⁺ redox couple remained reversible and shifted to more negative potentials, indicative of anion sensing (see Figure 5a and the Supporting Information).^[19] Upon the addition of dihydrogen phosphate, somewhat different anion electrochemical sensing behaviour was observed (Figure 5b). At substoichiometric equivalents of this anion, a second quasi-reversible wave appears at a more negative potential, to the detriment of the original Fc/ Fc⁺ redox wave, which upon the addition of a full equivalent of anion disappears. Further addition of anion leads to no shift in potential of the new wave. This behaviour is believed to be due to the binding of the dihydrogen phosphate anion being kinetically slow on the timescale of the experiment.^[24] It should also be noted that between 0.5-2 equiv. of oxoanion there is a reductive stripping peak in the CV, which is lost upon addition of larger excess amounts of anion with the redox wave becoming irreversible. This is consistent with reversible adsorption on the working electrode.^[21]

Conclusion

Novel macrocycles containing amide and urea ferrocene have been synthesized and characterized by NMR spectroscopy, mass spectrometry, and in the case of the amide macrocycle 4 by X-ray crystallography. By means of ¹H NMR spectroscopic titration experiments, it was established that urea macrocycle 8 binds anions much more strongly in acetonitrile than amide macrocycle 4. This is attributed to the greater acidity of the urea protons of macrocycle 8 than the amide protons of 4. However, both macrocycles are able to exhibit electrochemical recognition of anions in acetonitrile, even though in the case of macrocycle 4 this is limited to the most basic oxoanions. Greater shifts of the Fc/Fc⁺ redox couple were observed with urea macrocycle 8, thereby reflecting the stronger anion binding affinity of this macrocycle compared to amide macrocycle 4.

Experimental Section

General Notes: Commercially available solvents and chemicals were used without further purification unless stated. Where dry solvents were used, they were degassed with nitrogen, dried with an MBraun MPSP-800 column and then used immediately. Deionized water was used in all cases. Triethylamine was distilled from and stored over potassium hydroxide. Ferrocene was recrystallized from pentane. NMR spectra were recorded with Varian Mercury 300, Varian Unity Plus 500 and Bruker AVII 500 (with ¹³C Cryoprobe) spectrometers. Mass spectra were carried out with Waters Micromass LCT, Waters GCT, Bruker micrOTOF and Bruker FT-ICR spectrometers. Melting points were recorded with a Gallenkamp capillary melting-point apparatus and are uncorrected.

Bis-acid $\mathbf{1}$,^[9] 1,1'-bis(aminomethyl)ferrocene $\mathbf{3}$ ^[10] and bis-amine $\mathbf{6}$ ^[13] were prepared by literature procedures.

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Amide Macrocycle 4: N-Hydroxysuccinimide (46 mg, 0.40 mmol) and DCC (76 mg, 0.37 mmol) were added to a suspension of bisacid 1 (83 mg, 0.17 mmol) in dry CH₃CN (10 mL), and the reaction mixture was then stirred under a N₂ atmosphere for 16 h. The resulting DCC urea was filtered, the solvent removed in vacuo and the isolated activated bis-ester 2, assumed to have been formed in quantitative yield, was used immediately in the next reaction step. Separate solutions of activated bis-ester 2 in dry CH₂Cl₂ (40 mL) and 1,1'-bis(aminomethyl)ferrocene (3) (41 mg, 0.167 mmol) were then added dropwise to NEt₃ (42 mg, 0.06 mL, 0.418 mmol) dissolved in dry CH₂Cl₂ (120 mL). The resulting reaction mixture was stirred under a N₂ atmosphere for 24 h. The volume was reduced to 25 mL and then washed with 10% citric acid (2×25 mL) and H_2O (1×25 mL). The organic layer was dried (MgSO₄) and the solvent was removed in vacuo. The crude material was purified by silica gel preparative TLC plate (97:3 CH₂Cl₂/CH₃OH) to give the amide macrocycle 4 as a yellow solid (48 mg, 41%); m.p. 152-154 °C. ¹H NMR (500 MHz, CDCl₃): δ = 6.79–6.84 (m, 10 H, NH and hydroquinone ArH), 4.44 [s, 4 H, C(O)CH₂O], 4.15 (br. s, 12 H, CH_2 and $2 \times CpH$), 3.97–3.99 (m, 4 H, CH_2), 3.79–3.81 (m, 4 H, CH₂), 3.65–3.70 (m, 8 H, $2 \times CH_2$) ppm. ¹³C NMR (75 MHz, 68.4, 68.2, 68.1, 37.7 (1×aliphatic C missing – coincidental) ppm. HRMS (ES, + mode): m/z calcd. for C₃₆H₄₂FeN₂NaO₉ 725.2133 $[M + Na]^+$; found 725.2131.

Amide Macrocycle 5: Isolated from the above reaction as a yellow solid (17 mg, 15%); m.p. 166 °C. ¹H NMR (500 MHz, CDCl₃): δ = 6.81–6.90 (m, 20 H, N*H* and hydroquinone Ar*H*), 4.42 [s, 8 H, C(O)C*H*₂O], 4.14 (br. s, 24 H, C*H*₂ and 2×Cp*H*), 4.02–4.04 (m, 8 H, C*H*₂), 3.79–3.81 (m, 8 H, C*H*₂), 3.65–3.70 (m, 16 H, 2×C*H*₂) ppm. ¹³C NMR (75 MHz, 1:1 CDCl₃/CD₃OD): δ = 169.2, 154.5, 152.1, 116.2, 116.2 [sic], 86.0, 71.2, 71.1, 70.2, 69.3, 69.1, 68.6, 68.4, 38.3 ppm. ESMS (ES, + mode): *m/z* calcd. for C₇₂H₈₄Fe₂N₄NaO₁₈ 1427.4377 [M + Na]⁺; found 1427.4372.

Urea Macrocycle 8: Separate solutions of bis-amine 5 (235 mg, 0.233 mol) in dry CH₂Cl₂ (100 mL) and ferrocene bis-carbamate 7 (134 mg, 0.233 mmol) in CH₂Cl₂ (100 mL) were added dropwise to NEt₃ (0.2 mL) and 4-(dimethylamino)pyridine (DMAP; cat.) dissolved in dry CH₂Cl₂ (50 mL). The resulting reaction mixture was stirred under an N2 atmosphere for 16 h. The solvent was reduced in volume (to 25 mL) and then washed with saturated NaHCO_{3(aq.)} until aqueous washes were colourless. The organic layer was dried (MgSO₄), the solvent removed in vacuo and crude material purified by silica gel preparative TLC (CH₂Cl₂/CH₃OH, 98:2) to give a pale yellow solid (112 mg, 39%); m.p. >148 °C (decomp.). ¹H NMR (500 MHz, [D₆]acetone): δ = 8.49 (s, 2 H, OH), 7.24 (s, 4 H, calix ArH), 7.22 (s, 4 H, calix ArH), 6.90-6.97 (m, 8 H, hydroquinone ArH), 6.37–6.41 (m, 4 H, $2 \times NH$), 4.49 (d, $^{2}J = 12.7$ Hz, 4 H, calix CH₂), 4.33–4.38 (m, 8 H, $2 \times CH_2$), 4.16 (d, ${}^{3}J$ = 6.0 Hz, 4 H, CpCH₂NH), 4.12–4.13 (m, 4H CpH), 4.09–4.10 (m, 4 H, CpH), 4.00 (t, ${}^{3}J$ = 6.0 Hz, 4 H, OCH₂CH₂NH), 3.56–3.59 (app. quartet, 4 H, OCH₂CH₂NH), 3.48 (d, ${}^{2}J$ = 12.7 Hz, 4 H, calix CH₂), 1.24 [s, 18 H, calix C(CH₃)₃], 1.06 [s, 18 H, calix C(CH₃)₃] ppm. ¹³C NMR (125.8 MHz, [D₆]acetone): δ = 159.9, 154.4, 154.1, 152.0, 151.1, 148.2, 142.3, 134.6, 128.5, 126.9, 126.4, 116.9, 116.5, 89.8, 75.3, 69.1, 69.1 [sic], 68.5, 68.2, 40.6, 39.4, 34.8, 34.5, 32.7, 32.1, 31.5 $(2 \times \text{aliphatic } C \text{ peaks missing})$ ppm. HRMS (ES, + mode): m/zcalcd. for C₇₈H₉₄N₄NaO₁₀ 1325.6214 [M + Na]⁺; found 1325.6177.

Urea Macrocycle 9: Isolated pure from the above reaction after a second silica gel preparative TLC plate (CH₂Cl₂/CH₃OH, 98:2) as a pale yellow solid (18 mg, 6%); m.p. >160 °C (decomp.). ¹H NMR (500 MHz, [D₆]acetone): δ = 8.53 (s, 4 H, OH), 7.22 (s, 8 H, calix

Ar*H*), 7.21 (s, 8 H, calix Ar*H*), 6.92–6.96 (m, 16 H, hydroquinone Ar*H*), 6.58 (t, ${}^{3}J$ = 5.6 Hz, 4 H, N*H*), 6.43 (t, ${}^{3}J$ = 6.1 Hz, 4 H, N*H*), 4.47 (d, ${}^{2}J$ = 12.5 Hz, 8 H, calix C*H*₂), 4.25–4.27 (m, 8 H, OC*H*₂), 4.20–4.21 (m, 8 H, OC*H*₂), 4.11–4.12 (m, 16 H, C*H*₂Cp and Cp*H*), 4.06–4.07 (m, 8 H, Cp*H*), 4.02 (t, ${}^{3}J$ = 5.4 Hz, 8 H, OC*H*₂CH₂NH), 3.57–3.60 (app. quartet, 8 H, OCH₂C*H*₂NH), 3.44 (d, ${}^{2}J$ = 12.5 Hz, 8 H, calix C*H*₂), 1.23 [s, 36 H, calix C(C*H*₃)₃], 1.05 [s, 36 H, calix C(C*H*₃)₃] ppm. 13 C NMR (125.8 MHz, [D₆]-acetone): δ = 160.0, 154.4, 154.1, 152.0, 151.0, 148.2, 142.2, 134.7, 128.5, 126.8, 126.4, 117.0, 116.4, 89.4, 75.2, 69.2, 69.1, 68.5, 68.4, 40.6, 39.6, 34.8, 34.5, 32.7, 32.1, 31.5 (2 × aliphatic *C* peaks missing) ppm. HRMS (ES, + mode): *m*/*z* calcd. for C₁₅₆H₁₈₈Fe₂N₈-Na₂O₂₀ 1325.6221 [M + 2Na]²⁺; found 1325.6239.

Supporting Information (see footnote on the first page of this article): Syntheses of compounds **3** and **7**; spectral characterization of macrocycles **4**, **5**, **8** and **9**; crystallographic information for structure of macrocycle **4**; protocols and further data from ¹H NMR spectroscopy and electrochemistry experiments.

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- [18] See the Supporting Information for details of the assessment of the reversibility of macrocycles **4** and **8**.
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- [23] See the Supporting Information for further CVs and SWVs of electrochemical anion titration experiments of macrocycle 4.
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