Selective electrochemical magnesium and calcium sensors based on non-macrocyclic nitrogen-containing ferrocene ligands

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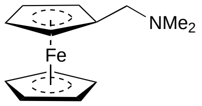
Ferrocene derivatives 1, 2a, 2b and 5 act as electrochemical sensors of Mg^{2+} and Ca^{2+} ions in acetonitrile solution in concentrations as low as 10 mol%: a new redox peak appears in the cyclic voltammogram, anodically shifted by 160–360 mV, with no interference from a large excess of several other metal salts; the single crystal X-ray structure of ligand 5 is reported.

The study of redox-active ligands in which a change in electrochemical behaviour can be used to monitor complexation of guest species is an increasingly important area of molecular recognition.[1] Ferrocene derivatives, most of which are substituted with macrocyclic ligands, have proved successful as ion sensors.[2] However, no selectivity towards magnesium or calcium ions has been reported for these systems: representative derivatives[3,4] show strong affinities for group 1 metals in solution (typically Li, Na or K) and selectivity for Li^+ has been observed for systems which are insensitive to Na^+ or K^+.[5] The electrochemical sensing of Mg^{2+} has been demonstrated in molten alloys[6] and in ferret ventricular muscle tissue,[7] and both fluorescent[8] and fibre-optical[9] devices have proved useful. However, no solution studies on efficient redox-active Mg^{2+} or Ca^{2+} sensors have been reported.



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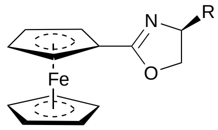


2a R = H
b R = Pr^i

We now report the metal-binding properties of nitrogen-containing, non-macrocyclic derivatives of ferrocene. Commercially available (dimethylamino)methylferrocene **1** was employed initially. Titration studies using cyclic voltammetry (CV)† in acetonitrile indicated that compound **1** could detect the presence of Mg^{2+} and Ca^{2+} ions in concentrations as low as 10 mol%: on addition of $Mg(ClO_4)_2$ or $Mg(CF_3SO_3)_2$ a second redox peak appeared in the CV, anodically shifted by *ca.* 230 mV. The observation of approximately equal peak currents for the two redox waves after addition of 0.2 equiv. of $Mg(ClO_4)_2$ (Fig. 1) or $Mg(CF_3SO_3)_2$ suggests the formation of a complex with a ligand : metal ratio of *ca.* 2 : 1. Addition of $Ca(ClO_4)_2$, instead of $Mg(ClO_4)_2$, led to an anodic drift in the redox wave with no clearly defined new peak. Remarkably, the presence of a range of other metal ions in solution [$LiClO_4$, $NaClO_4$, $KClO_4$, $CsClO_4$, $Ba(ClO_4)_2$ and $AgClO_4$] had no effect on the CV, even in concentrations as high as 2500 mol%.‡

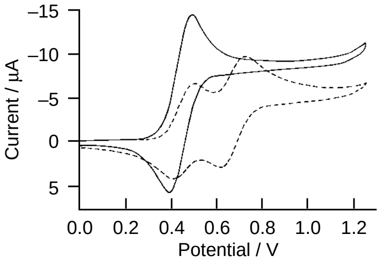
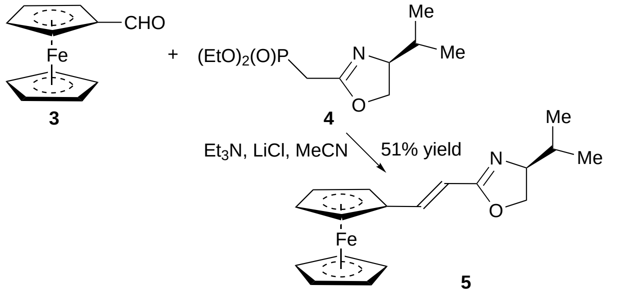


Fig. 1 Cyclic voltammogram of **1** in MeCN (———) and after the addition of $Mg(ClO_4)_2$ (0.2 equiv.) (- - - -)

We next studied the known oxazolines **2a** and **2b**.[10] The oxygen atom of **2a** and **2b** could act as an alternative chelation site, and **2b** also possesses a potentially sterically demanding isopropyl group α to the nitrogen. Additionally, to assess the importance of the proximity of the binding site to the ferrocene core on the selectivity and strength of binding, the extended oxazoline ligand **5** was prepared from aldehyde **3** according to Scheme 1, utilising reagent **4**, prepared by analogy with the literature procedure.[11] X-Ray crystal structure analysis§ of **5** confirmed the expected *trans* configuration of the alkene bridge (in agreement with ^1H NMR data) and the (*S*)-configuration of the chiral centre at C(4) (Fig. 2).



Scheme 1

Ligands **2a**, **2b** and **5** all demonstrated a selectivity towards Mg^{2+} and Ca^{2+} over other metal ions, similar to that observed for amine **1** and Mg^{2+} with a second redox peak emerging in the CV arising from ligand–metal complexation. This 'two-wave' behaviour is diagnostic of a large value ($>10^4$) for the equilibrium constant for cation binding by the neutral (electrochemically unaltered) ligand.[12] Data comparing the redox behaviour of these systems in the presence of Mg^{2+} and Ca^{2+} ions are collated in Table 1. These ligands showed a significant binding enhancement[12] in the presence of Mg^{2+} and Ca^{2+} ions‡ and these data are quantitatively similar to those reported by Beer for the interaction of cations (Na^+, Li^+) with a macrocycle,

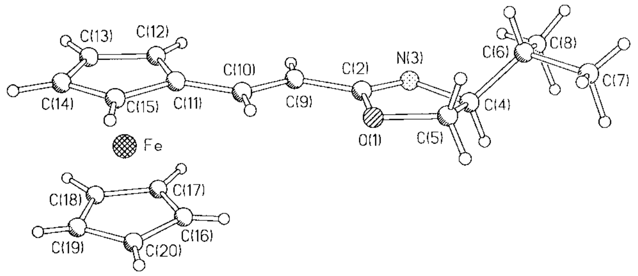


Fig. 2 X-Ray molecular structure of **5**

Table 1 Cyclic voltammetric data

Ligand/ M	$E_{\frac{1}{2}\mathrm{free}}$/ mV	$E_{\frac{1}{2}\mathrm{complex}}$/ mV	ΔE/ mV	min. equiv. $M^{2+\,a}$	max. equiv. $M^{2+\,b}$	$K_1/K_2{}^c$
1/Ca	490	—[d]		0.1	0.5	
1/Mg	490	720	230	0.1	3	3.8×10^5
2a/Ca	670	980	310	0.1	1	1.7×10^5
2a/Mg	670	1000	330	0.1	3	3.8×10^5
2b/Ca	680	1040	360	0.1	3	1.2×10^6
2b/Mg	680	1040	360	1	5	1.2×10^6
5/Ca	650	810	160	0.1	3	5.0×10^3
5/Mg	650	840	190	1	15	1.6×10^3

[a] Minimum equiv. of metal ClO_4^- salt required to produce a detectable second redox peak. [b] Equiv. of metal salt required for complete disappearance of original ligand redox peak (E free). [c] Binding enhancement for the complexation of a metal cation calculated using the equation in 12(*b*). The equilibrium constants K_1 and K_2 correspond to the complexation processes by the neutral and oxidised forms of the ligand. [d] A second redox peak was not observed; instead, an anodic drift occurred upon addition of Ca^{2+} which ceased when *ca.* 0.5 equiv. had been added. This behaviour is diagnostic of weak binding of the metal and the neutral ligand[12] and prevented the calculation of a binding enhancement.

monitored by changes in the cathodic electrochemistry of an appended anthraquinone substituent, although such systems do not often exhibit significant selectivity in the presence of other metals.[2a] Notably, compounds **1** and **2a** showed an identical affinity for Mg^{2+}, whereas only **2a** showed a strong affinity for Ca^{2+}. The presence of the isopropyl group in **2b** slightly increased the strength of binding of both Mg^{2+} and Ca^{2+} still further, presumably for electronic rather than steric reasons, whilst the amount of Mg^{2+} required to achieve a response was increased by a factor of 10 over that observed for **2a**: recognition of Ca^{2+}, however, suffered no such problem. For compound **5**, there was a considerably reduced anodic shift in the new redox peak and a lowering of the binding enhancement. The observed shift (160–190 mV) is consistent with the transmission of cation binding through a conjugated alkene link, with no contribution from a through-space effect.[3] System **5** required a considerably higher concentration of Mg^{2+} (15 equiv.) than the other ligands before the original ferrocene redox peak was lost.

Cation binding by systems **2a**, **2b** and **5** was also detected by changes in the UV–VIS spectra: on addition of Mg^{2+} or Ca^{2+} a new absorption peak appeared at lower energy. This was most striking for compound **5** which possesses an extended chromophore. Upon addition of $Mg(ClO_4)_2$ (1 equiv.) to a solution of compound **5** (10^{-3} M) in acetonitrile, the solution changed from pale yellow to purple, and the absorption peak of **5** at λ_{max} 449 nm entirely disappeared and was replaced by a new peak at λ_{max} 528 nm. For compounds **2a** and **2b** the colour change was less striking. For example, the absorption peak of **2b** at λ_{max} 446 nm in acetonitrile shifts to λ_{max} 472 nm on addition of $MgClO_4$ (1 equiv.): addition of more $Mg(ClO_4)_2$ gives no significant change in the spectra. A UV titration experiment suggested the formation of a complex of stoichiometry ligand : cation = 2 : 1. We presume that the electrochemical and spectrophotometric response observed for systems **2a**, **2b** and **5** arises from Mg^{2+} or Ca^{2+} coordination to the nitrogen atom of the substituent. The ligands can be recovered unchanged in *ca.* 60% yield from solutions containing the metal salts by aqueous workup.

We have discounted the fact that the electrochemical and spectrophotometric response is due to adventitious protonation or hydration of the ligands. The CV and UV–VIS spectra of ligands **2a** and **2b** in MeCN were unchanged by the addition of water to the solution. Protonation of the ligands (achieved by the addition of perchloric acid to the solution) was monitored by the appearance of a new redox wave at $E_{\frac{1}{2}}$ +680 mV (compound **2a**) and +980 mV (compound **2b**) which are decisively different potentials from those assigned to the metal complexes (Table 1). Moreover, ^{1}H NMR spectroscopic data supported these conclusions.¶

Oxazoline derivatives **2b** and **5** are chiral which may enable chiral recognition of magnesium-containing species, and may also offer a method for electrochemically modifying asymmetric reactions in which magnesium coordination plays a pivotal rôle.[13]

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Notes and References

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† Experiments used the ligand (10^{-3} M) and $NBu^n_4ClO_4$ (0.1 M) in HPLC grade MeCN, *vs.* Ag/AgCl with a platinum working electrode. Sequential additions of aliquots of 0.1 or 0.5 equiv. of 10^{-2} M solutions of the appropriate metal salt in MeCN were monitored by CV.

‡ In the presence of 1–4 equiv. of Zn^{2+} [$Zn(ClO_4)_2$ or $ZnCl_2$] an anodic drift (maximum 60 mV) in the redox potential for compounds **1**, **2** and **5** was observed. Addition of traces of Mg^{2+} ions to these mixtures resulted in the immediate appearance of the second redox peak listed in Table 1.

§ *Crystal data*: $C_{18}H_{21}FeNO$, M = 323.21, orthorhombic, space group $P2_12_12_1$ (no. 19), a = 5.8828(4), b = 10.948(1), c = 24.274(2) Å, U = 1563.4(3) Å^3, Z = 4, T = 150 K, μ = 9.6 cm^{-1}, $2\theta \leqslant 55.8°$, 8017 total data, 2840 unique, 2569 observed [$I \geqslant 2\sigma(I)$]; R_{int} = 0.052 before, 0.038 after numerical absorption correction (seven faces, T_{min} = 0.81, T_{max} = 0.93); $wR(F^2)$ = 0.061; $R(F$, obs. data) = 0.028; residual $\Delta\rho_{max}$ = 0.18, $\Delta\rho_{min}$ = -0.25 e Å^{-3}; absolute configuration was determined by Flack parameter, x = $-0.01(2)$. CCDC 182/757.

¶ The data for ligand **2b** are representative; the most diagnostic protons are those at the chiral centre (H_a), the methylene group adjacent to oxygen (H_b) and the unsubtituted Cp ring (H_c). For the free ligand in CD_3CN these protons appear at δ 3.97, 4.08 and 4.24, respectively. Addition of $KClO_4$ to this solution led to no change in the spectrum, whereas on addition of $Mg(ClO_4)_2$ (2 equiv.) the peaks shifted to δ 4.38, 4.81 and 4.46. ^{1}H NMR titration curves, monitoring the shifts of H_a, H_b and H_c upon addition of $Mg(ClO_4)_2$ support the UV–VIS and CV data in suggesting a stoichiometry of 2 : 1. The spectrum in the presence of Mg^{2+} was different from that of protonated **2b**.

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