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New strained ferrocenophane-based receptors for the selective electrochemical recognition of Mg^{2+} in the presence of Ca^{2+} cations

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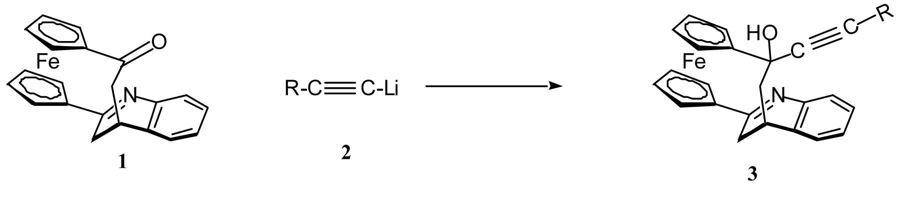
Abstract—Ferrocenophane derivatives **3** act as electrochemical sensors of Mg^{2+} ions: a new redox peak appears in the CVs anodically shifted compared to the $E_{1/2}$ of the free receptors by 268–382 mV. Receptors **3a**, **3c** and **3d** are selective for Mg^{2+}, whilst **3b** is also responsive to Ca^{2+} ion (302 mV shift). Receptor **3c** also gave a highly visual output response in the presence of Mg^{2+} consisting of a deep purple colour. © 2003 Elsevier Science Ltd. All rights reserved.

Design of redox-active receptors 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] In this context, receptors containing a neutral ferrocenyl moiety, most of which are substituted with macrocyclic ligands exhibit interesting electrochemical ion recognition effects, because the complexing ability of the receptors can be switched on and off by varying the applied electrochemical potential. In general, cation binding at an adjacent receptor site of a ferrocene-based host includes a positive shift in the redox potential of ferrocene/ferrocenium couple either by through-bond and/or through-space electrostatic interactions, interference or conformational change.[2]

In early work, macrocyclic receptors attached to a ferrocene were extensively studied and cation selectivity could be achieved by tailoring the cavity size. However, no selectivity towards magnesium or calcium ions have been reported for these systems.[3] Recently, non-macrocyclic functional groups such as imine,[4] oxazoline[5] and imidazoline,[6] which act as cation binding sites have provided new voltammetric sensors which display remarkably high selectivities to magnesium and calcium ions with no interference from a large excess of other metal ions.

The major challenge in the design of magnesium sensors lies for many applications in the discrimination of calcium.[7] Presently, the best discrimination of calcium



3a R = Ph (57%)
3b R = 2-pyridyl (55%)
3c R = 3-pyridyl (60%)
3d R = Fec (58%)

Scheme 1.

Keywords: ferrocenes; electrochemistry; complexation; magnesium and compounds; molecular recognition.

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is, however, achieved with a double-armed diazacrown ether ionophore.[8] Unfortunately, the spectacular discrimination of calcium is accompanied by sizeable increases in the interference from alkali metal ions. Very recently, it has been reported[9] a multiethynyl cyclophane incorporating two 2,2′-bipyridine units as a useful optical sensor for the detection of specific types of metal ions. However, no report dealing with the preparation of related ferrocenophane derivatives has been described to the best of our knowledge.

We now report the metal-binding properties of the previously unreported 2,5-difunctionalized-[5]ferrocenophane derivatives **3**. These ligands were prepared from the [5]ferrocenophane **1**, readily available in 39% overall yield from 1,1′-diacetylferrocene by sequential treatment with *o*-azidobenzaldehyde and tri-*n*-butylphospane,[10] and the corresponding alkynillithium **2**, in THF at −30°C. Purification by column chromatography afforded compounds **3** in 55–60% yield as orange compounds (Scheme 1).

First, the electrochemical behaviour of ferrocene ligands **3**, as well as in the presence of variable concentrations of HBF_4 was investigated. The cyclic voltammograms (CVs) of **3a**, **3b** and **3c** display a single anodic process with features of electrochemical reversibility.[11] Upon protonation, by addition of stoichiometric quantities of HBF_4 in CH_3CN to a solution of ligands in CH_2Cl_2, the redox potential of the ferrocene nucleus was shifted anodically, in each case. Protonation builds up a positive charge close to the ferrocene nucleus and this electrostatically repels the ferrocenium cation, thermodynamically hindering its formation. The CV of **3d** shows two closely spaced reversible one-electron oxidations for the two ferrocenyl groups ($\Delta E_{1/2} = 112$ mV) and, upon protonation under the above mentioned conditions, a clear evolution of the second wave, from $E_{1/2} = 0.726$ to 1.148 V ($\Delta E_{1/2} = 422$ mV), was observed, whereas there was no effect on the first one.

The high values of the redox potential shift on protonation ($\Delta E_{1/2} = 390$–422 mV) are in good agreement with the linear relationship $y = (-2.7 + 2.1x) \times 10^2$ between the inverse iron–nitrogen separation (x) and the shifts of the potentials (y) found upon protonation of several types of aza-substituted ferrocenes.[12] The magnitude of the electrochemical shift on protonation provides important thermodynamic information. The shift in redox potential on protonation is related to the ratio of protonation constant for the oxidized and reduced forms of the ligand. Thus, for ligand **3c** the potential shift on protonation was 394 mV and consequently the binding enhancement factor (BEF) is 2.19×10^{-7} and the reaction coupling efficiency[1e,f] (RCE) is 4.60×10^{6}. This means that it is 4,600,000 times more difficult to protonate the oxidized form of the ligand than the reduce one (Table 1).

Recognition properties of the redox-active receptors **3** were also evaluated by CV[13] (Table 1). Whereas no perturbation of the CVs of **3a**, **3c** and **3d** was observed upon addition of Ca^{2+} cation, significant modification of the CVs could be observed upon addition of Mg^{2+} cation. On addition of $Mg(ClO_4)_2$ a second redox peak appeared in the CV anodically shifted by 268–382 mV ascribed to the metal complexed species. Remarkably, the current intensity of the anodic peak of the second wave increases, while that of the first one decreases with a linear dependence on the equivalents of the added salt. Maximum perturbation of the CVs was obtained with 2 equiv. of added Mg^{2+} cation, and at this point the first wave disappears (Fig. 1). This 'two-wave' behaviour is diagnostic of a large value for the equilibrium constant for cation binding by the neutral receptor.[14] Receptor **3b** showed an identical affinity for Mg^{2+} and Ca^{2+} cations, although the latter cation required a slightly higher concentration (3 equiv.) than the Mg^{2+}, before the original ferrocene redox wave was lost. Remarkably, the presence of a range of other metal ions in solution ($LiClO_4$, $NaClO_4$ and $KClO_4$) had no effect on the CVs.

We have discounted the fact that the electrochemical reponse we observed for these receptors, upon addition of metal cations, is due to adventitious protonation or hydration of the receptors. Addition of water to the

Table 1. Cyclic voltammetric data

Receptor	$E_{1/2\ \mathrm{free}}$ (V)[a]	$E_{1/2\ \mathrm{complex}}$ (V)[a]	$\Delta E^{\circ}_{1/2}$ (mV)	K_{ox}/K_{red} (BEF)[b]	RCE
3a·H^+	0.175	0.565	390	2.6×10^{-7}	3.9×10^{6}
3a·Mg^{2+}	0.175	0.557	382	3.5×10^{-7}	2.9×10^{6}
3b·H^+	0.192	0.610	418	8.6×10^{-8}	1.2×10^{7}
3b·Mg^{2+}	0.192	0.477	285	1.5×10^{-5}	6.6×10^{4}
3b·Ca^{2+}	0.192	0.494	302	7.9×10^{-6}	1.3×10^{5}
3c·H^+	0.188	0.582	394	2.2×10^{-7}	4.6×10^{6}
3c·Mg^{2+}	0.188	0.456	268	3.0×10^{-5}	3.4×10^{4}
3d·H^+	0.074	0.108	34	7.4×10^{-8}	1.4×10^{7}
	0.186	0.608	422	7.4×10^{-8}	1.4×10^{7}
3d·Mg^{2+}	0.074	0.076	2	3.5×10^{-7}	2.9×10^{6}
	0.186	0.568	382	3.5×10^{-7}	2.9×10^{6}

[a] The apparent half-wave potential are given versus ferrocene as internal reference, in CH_2Cl_2.

[b] The equilibrium constants K_{ox} and K_{red} correspond to the complexation processes by the oxidized and reduced form of the receptor. The BEF has been calculated using the equation $\Delta E^{\circ} nF/RT = \ln(K_{ox}/K_{red})$.

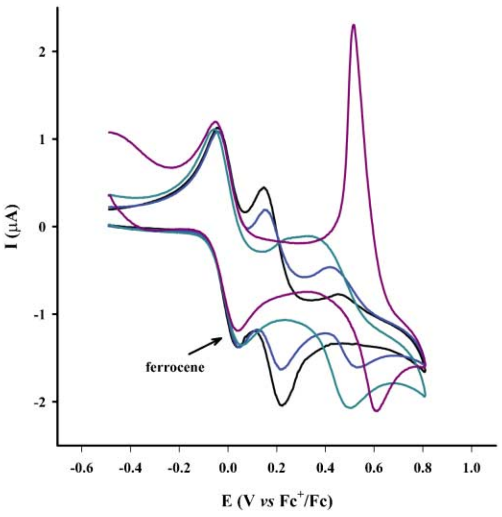


Figure 1. Cyclic voltammogram of receptor **3c** and the effect of magnesium(II) perchlorate addition. Free ligand (black); after addition of 0.5 equiv. of $Mg(ClO_4)_2$ (blue); after addition of 2 equiv. of $Mg(ClO_4)_2$ (green); after addition of 1 equiv. of HBF_4 (purple).

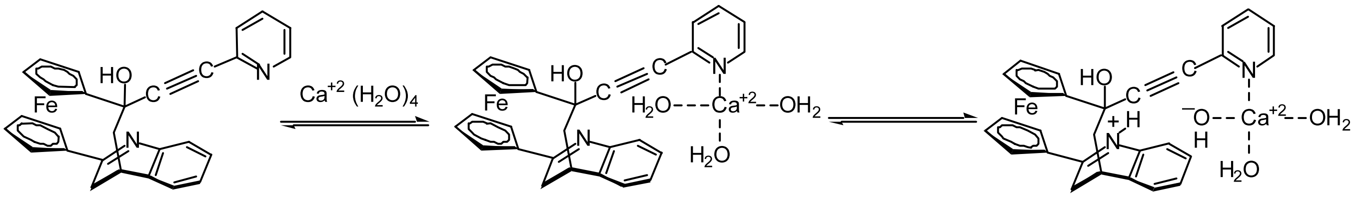
resultant electrochemical solutions did elicit a further redox response, with the evolution of a new redox wave, which correspond to those assigned to the free receptors. It can therefore be concluded that metal-ion coordination is observed in all cases. The receptors can be recovered unchanged in almost quantitative yield from solutions containing the metal salts by aqueous work-up.

We presume that the electrochemical response observed for receptors **3a** and **3d** arises from Mg^{2+} coordination to the nitrogen atom of the dihydroquinoline ring and are almost identical to those observed upon protonation ($\Delta E_{1/2\ \mathrm{protonation}} - \Delta E_{1/2\ \mathrm{complexed}} = 8–20$ mV). However, for receptors **3b** and **3c**, bearing a pyridine ring, the positive shift upon coordination with Mg^{2+} is notably lower than upon protonation ($\Delta E_{1/2\ \mathrm{protonated}} - \Delta E_{1/2\ \mathrm{complexed}} = 126–133$ mV), indicative of oxidation being facilitate by an additional coordination of the metal ion with the nitrogen atom of the pyridine ring. The different complexation behaviour of receptors **3b** and **3c** upon addition of Ca^{2+} cations [$Ca(ClO_4)_2 \cdot 4H_2O$] could be explained taking into account that in **3b** (2-pyridyl) the pyridine nitrogen atom could promote the displacement of the polarized molecules of water in such way that they could be placed close to the iminic nitrogen atom, whose basic character makes possible its intramolecular protonation giving rise to a complex which is stabilized by intramolecular hydrogen bonding between the C=NH$^+$ and the OH$^-$ linked to the cation as depicted in Scheme 2. In contrast, the absence of response when compound **3c** (3-pyridyl) was treated with Ca^{2+} cations under similar conditions could be due to the fact that the above mentioned intramolecular hydrogen bonding stabilization is not possible because of the greater distance between the iminic C=N and the pyridine nitrogen atom on which the metal is linked Nevertheless further quantum mechanical calculations on the receptors **3b** and **3c** at the DFT level are now carried out to confirm these suggestions.

Previous studies[15] on ferrocene ligands have shown that the characteristic band between 400 and 500 nm ascribed to the lowest energy spin-allowed d–d band of the ferrocene unit is perturbed by complexation.[16] Therefore, UV–vis spectroscopy was used for further complexation experiments with **3**. Typically, upon addition of Mg^{2+}, as a chelating metal ion, into CH_2Cl_2 solution of **3c**, the d–d band at $\lambda_{max} = 458$ nm ($\varepsilon = 1398$ M^{-1} cm^{-1}), entirely disappeared an was replaced by a new band at $\lambda_{max} = 520$ nm ($\varepsilon = 2674$ M^{-1} cm^{-1}), accompanied by an increase in absorbance (Fig. 2). Furthermore, its colour in CH_2Cl_2 solution changes from orange to purple. This colour changes of **3c** in CH_2Cl_2 solution can be used for 'naked-eye' detection of Mg^{2+} in the presence of Ca^{2+}. The association constant of the **3c**·Mg^{2+} complex ($K_a = 1.5 \times 10^3$ M^{-1}) could be evaluated by means of UV–vis spectrophotometric titration.[17] An isosbestic point was found, strongly indicating the presence of a unique complex in solution. A Job plot experiment between **3c** and $Mg(ClO_4)_2$ in CH_2Cl_2 at 25°C revealed a 1:1 stoichiometry.

We note that the different techniques used to monitor the metal binding do not always suggest the same stoichiometry, This is a known phenomenon in related systems[1c,18] arising from the different concentrations and timescales employed in the different techniques.

It is important to point out that the association constant determined by UV–vis spectrophotometry corresponds to the complexation of the Mg^{2+} cation by the neutral receptor, whereas the voltammetric shift reflects the interaction of the guest cation with the oxidized receptor.



3b

Scheme 2.

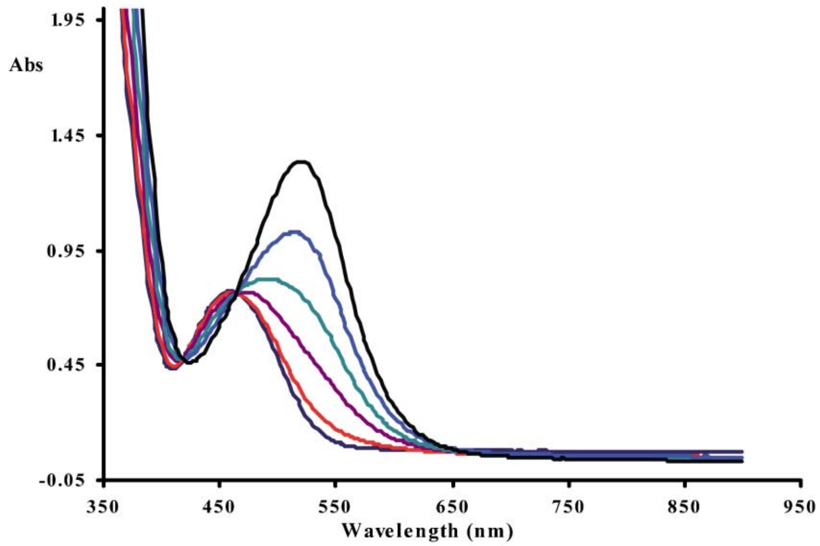


Figure 2. UV–vis spectrum of receptor **3c** and the effect of magnesium(II) perchlorate addition. Free ligand (deep blue); after addition of 0.2 equiv. of $Mg(ClO_4)_2$ (red); after addition of 0.4 equiv. of $Mg(ClO_4)_2$ (purple); after addition of 0.6 equiv. of $Mg(ClO_4)_2$ (green); after addition of 0.8 equiv. of $Mg(ClO_4)_2$ (blue); after addition of 1 equiv. of $Mg(ClO_4)_2$ (black).

In summary, we have demonstrated that ferrocenophane derivatives **3** are efficient redox sensors with remarkably selectively for Mg^{2+} in the presence of Ca^{2+} ions. This recognition process is easily monitored by CV which displays a large positive shift in the value of the ferrocene/ferrocinium redox couple. Additional evidence for cation binding is provided by UV–vis spectrophotometric data. To the best of our knowledge these systems are the first naked-eye detectable chemosensors that permit discrimination between Mg^{2+} and Ca^{2+} ions as the result of disparate changes in colour.

Acknowledgements

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17. Titration experiment was conducted adding increasing amounts of $Mg(ClO_4)_2$ to a solution at a constant concentration of the receptor. The value of the association constant is the average of three independent titrations with all nonlinear regresion giving high confidence outputs ($r^2 > 0.987$).

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