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Voltammetric metal cation sensors based on ferrocene derivatives with oxazoline and imine substituents

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Abstract

Ferrocene derivatives **1a**, **1b** and **2** containing oxazoline substituents act as efficient voltammetric 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, positively shifted by 310–360 mV for **1a** and **1b**, and by 160–190 mV for **2**, compared to $E^{1/2}$ of the free ligand. For the bisferrocenyldiimine derivative **3** the shift is 150–160 mV. Compounds **1a**, **1b** and **3** are also responsive to Cu^{2+} ions (shifts of 250, 320 and 160 mV, respectively) and compound **3** is responsive to Zn^{2+} ions (150 mV shift) with no interference from a large excess of several other metal salts. UV–vis spectrophotometric studies and ^{1}H-NMR titration experiments confirm that the oxazoline or imine groups are the sites of metal complexation.

Keywords: Ferrocene; Oxazoline; Electrochemistry; Sensors; Molecular recognition

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1. Introduction

Early work on the selective chelation of metal cations [1] laid the foundation for the study of redox-active ligands in molecular recognition processes whereby a change in electrochemical behaviour in solution can be used to monitor complexation of a neutral or ionic guest species [2–7]. In this context ferrocene derivatives, most of which are substituted with macrocyclic ligands, are prototype molecules which have proved to be especially versatile as ion sensors [8,9]. Cation binding at an adjacent receptor site induces a positive shift in the redox potential of the ferrocene–ferrocenium couple by through-space electrostatic communication, and the complexing ability of the ligand can be switched on and off by varying the applied electrochemical potential. Selected derivatives show strong affinities for Group 1 metals [10–12] (typically Li^+, Na^+ or K^+) and selectivity for Li^+ has been observed for ferrocene bis(tertiary amides) which are insensitive to Na^+ or K^+ [13,14]. In a recent communication we noted that certain ferrocenyloxazoline derivatives displayed remarkably high selectivity towards magnesium and calcium ions in solution [15].

We now report the details of this work, and extend our studies to include ferrocene derivatives **1a**, **1b**, **2** and **3**, bearing oxazoline or imine functionality as a metal binding site. We note that in a study of voltammetric sensing of Group 1 and 2 metal cations by bis(ferrocenyl)dibenzo-18-crown-6 ligands in which the ferrocene units are appended to the crown by imine linkages, Beer and Wild provided evidence that Mg^{2+} was interacting with the imine bonds rather than the crown unit. Moreover, they observed that 1,2-dimethoxy-4-(iminoferrocenyl)benzene was responsive to Mg^{2+} indicating that a crown ether site was not a prerequisite for the detection of this cation [16]. The new derivative **2** was designed to probe the effect of inserting a conjugated spacer between the imine moiety and the ferrocene core. The rationale behind our study of **3** was that the two ferrocenyl groups will lead to a two-electron oxidation wave in the cyclic voltammogram (CV) to form the dication of **3**, and this species might show an enhanced voltammetric response in the presence of a coordinated guest cation as a result of increased intramolecular electrostatic repulsion. Chirality was incorporated into derivatives **1b**, **2** and **3** for

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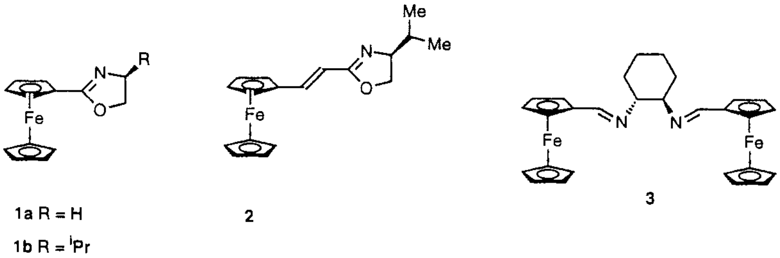
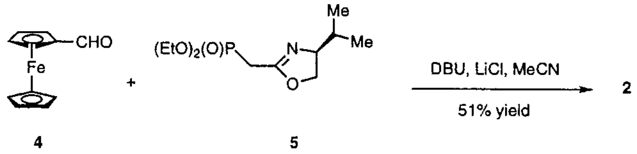


1a R = H
1b R = ^{i}Pr
2
3

Chart 1.



Scheme 1.

applications of these ligands as catalysts in metal-mediated asymmetric transformations which we are exploring in a separate work [17]. The C_2 symmetry of **3** has been identified as a beneficial feature in this respect [18] (Chart 1).

2. Results and discussion

2.1. Synthesis

Compounds **1a** [19], **1b** [19] and **3** [18] were synthesised as described previously. Compound **2** was prepared in 51% yield by a Horner–Wadsworth–Emmons reaction of ferrocenecarboxaldehyde **4** and reagent **5** [20]. The *trans* configuration of the alkene unit of **2** in solution was confirmed by ^{1}H-NMR data (Scheme 1).

2.2. Metal coordination studies

The electrochemical properties of **1a**, **1b**, **2** and **3** were investigated using CV in acetonitrile. Each compound exhibited a reversible redox wave typical of a ferrocene derivative. For the bis(ferrocene) system **3** this was a two-electron wave, with non-interacting ferrocene units. The criteria applied for reversibility was a ratio of 1.0 ± 0.1 for the intensities of the cathodic and anodic currents I_c/I_a, and no shift of the half-wave potentials with varying scan rates. Titration studies with the addition of metal perchlorate salts, as shown in Table 1, resulted in the appearance of a second redox wave ($E^{1/2}_{\mathrm{complex}}$) in the CV at the expense of the first wave ($E^{1/2}_{\mathrm{free}}$) which was positively shifted compared to the free ligand. The positive shift (ΔE) for compound **2** is significantly lower (160–190 mV) compared to com-

Table 1
Cyclic voltammetric data

Ligand–M	$E^{1/2}$ free (mV)	$E^{1/2}$ complex (mV)	ΔE (mV)	Min. equiv. M^{2+} [a]	Max. equiv. M^{2+} [b]	K_1/K_2 [c]
1a–Mg	670	1000	330	0.1	3	3.8×10^5
1a–Ca	670	980	310	0.1	1	1.7×10^5
1a–Cu	670	920	250	1	2 [d]	1.7×10^4
1a–Zn	670	– [e]				
1b–Mg	680	1040	360	1	5	1.2×10^6
1b–Ca	680	1040	360	0.1	3	1.2×10^6
1b–Cu	680	1000	320	1	2[d]	2.5×10^5
1b–Zn	680	– [e]				
2–Mg	650	840	190	1	15	1.6×10^3
2–Ca	650	810	160	0.1	3	5.1×10^2
3–Mg	560	710	150	0.3	1	1.2×10^5
3–Ca	560	720	160	0.4	1	2.6×10^5
3–Cu	560	720	160	0.4	1	2.6×10^5
3–Zn	560	710	150	0.2	1	1.2×10^5

[a] Minimum equivalents of metal $\mathrm{ClO_4^-}$ salt required to produce a detectable second redox peak.

[b] Equivalents of metal salt required for the complete disappearance of the original ligand redox peak (E free).

[c] Binding enhancement for the complexation of the metal cation calculated using the equation employed in Ref. [5]. The equilibrium constants K_1 and K_2 correspond to the complexation processes by the neutral and oxidised forms of the ligand.

[d] The complex rapidly decomposed in the presence of air or moisture.

[e] A second redox peak was not observed; instead, an anodic drift (maximum 60 mV) occurred upon addition of Zn^{2+} [$\mathrm{Zn(ClO_4)_2}$ or $\mathrm{ZnCl_2}$] (one to four equivalents) to **1a** and **1b**.

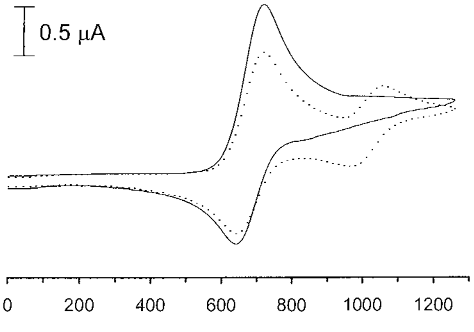


Fig. 1. Cyclic voltammograms of **1b** in MeCN (—) and after the addition of $Mg(ClO_4)_2$ (one equivalent) (- - - -).

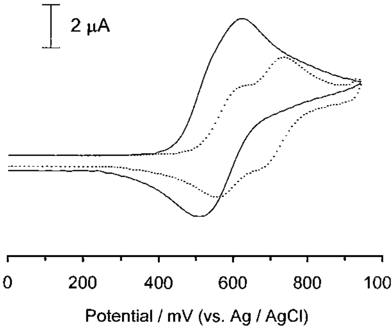


Fig. 2. Cyclic voltammograms of **3** in MeCN (—) and after the addition of $Mg(ClO_4)_2$ (0.6 equivalents) (- - - -).

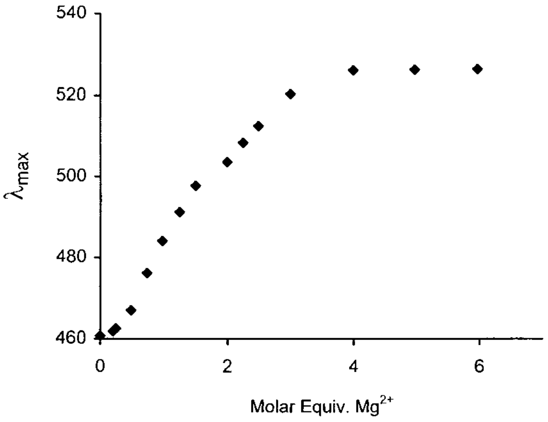


Fig. 3. Shift in UV–vis absorption spectra of **2** in MeCN with sequential addition of $Mg(ClO_4)_2$ in MeCN.

pounds **1a** and **1b** (250–360 mV) presumably because the increased separation of the redox centre and the binding site in compound **2**, precludes through-space electrostatic communication. The relatively small positive shift upon metal binding to compound **3** (150–160 mV) is harder to explain, as on purely electrostatic grounds [bis(ferrocenium) dication–metal cation repulsion] an enhanced ΔE value would be expected. The observed data may reflect steric constraints about the bis(imine) binding site imposed by the *trans* substitution of the cyclohexane ring. It is notable that for certain ligand–metal combinations, e.g. **1a**·Mg^{2+}, **1a**·Ca^{2+}, **1b**·Ca^{2+} and **2**·Ca^{2+}, only 0.1 equivalents of metal was needed to give a clearly observable separate redox wave from the complexed species. 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%. The addition of Cu^{2+} ions gave a clean response with **1a**, **1b** and **3**. In the presence of one to four equivalents of zinc ions [$Zn(ClO_4)_2$ or $ZnCl_2$] a positive drift (maximum 60 mV) in the redox potential for compounds **1a** and **1b** was observed, whereas a clean 'two-wave' response was seen with ligand **3**. A positive drift is diagnostic of weak binding of the metal and the neutral ligand [5] and prevented the calculation of a binding enhancement for **1a** and **1b**. Data for Cu^{2+} and Zn^{2+} are included in Table 1. Addition of traces of Mg^{2+} ions to the mixtures of **1a**·Zn^{2+} and **1b**·Zn^{2+} resulted in the immediate appearance of the second redox peak ascribed to the species **1a**·Mg^{2+} and **1b**·Mg^{2+}.

These ligands (especially **1b**) display a large binding enhancement [5,21] in the presence of Mg^{2+}, Ca^{2+} and Cu^{2+} ions and these data are quantitatively similar to those reported by Beer for the interaction of cations (Na^+, Li^+) with a macrocycle, 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 [4]. The binding enhancement for **2** is significantly reduced compared to **1a** and **1b**. The presence of the isopropyl group in **1b** slightly increased the strength of binding of Mg^{2+}, Ca^{2+} and Cu^{2+} compared to **1a**, presumably for electronic rather than steric reasons (which would be expected to hinder metal binding) whilst the amount of Mg^{2+} required to achieve a response was increased by a factor of 10 over that observed for **1a**. Representative CV data are shown in Figs. 1 and 2 for ligands **1b** and **3**, before and after the addition of Mg^{2+}, showing the clear 'two-wave' response with the new wave at more positive potentials corresponding to the metal complexed species.

Cation binding by systems **1a**, **1b** and **2** was also cleanly 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 **2** which possesses the extended chromophore. A spectrophotometric study revealed that upon addition of $Mg(ClO_4)_2$ to a solution of compound **2** in acetonitrile the lowest energy absorption peak of uncomplexed **2** ($\lambda_{max} = 460$ nm) entirely disappeared and was replaced by a new peak from the complexed species at $\lambda_{max} = 528$ nm, with a concomitant colour change from yellow to purple which was clearly visible to the naked eye. The response saturated upon addition of four to five equivalents of Mg^{2+} (Fig. 3). For compounds **1a** and **1b** the colour change was less striking. For example, the absorption peak of **1b** at $\lambda_{max} = 446$ nm in acetonitrile red shifts to $\lambda_{max} = 472$ nm on addition of $MgClO_4$ (saturating with one equivalent of Mg^{2+}) and a modest darkening of the solution is observed visually. The ligands can be recovered unchanged in ca. 60% yield from solutions containing the metal salts by a standard aqueous workup. A less clear UV–vis response was seen upon addition of metal salts to ligand **3**: the lowest energy absorption at $\lambda_{max} = 445$ nm in acetonitrile drifted to $\lambda_{max} = 475$ nm.

We have discounted the fact that the electrochemical and spectrophotometric response we observe for these ligands upon addition of metal cations is due to adventitious protonation or hydration of the ligands. The CV and UV–vis spectra of ligands **1a**, **1b**, **2** and **3** in acetonitrile were unchanged by the addition of water to the solution. Ligands **1a** and **1b** were readily protonated by the addition of perchloric acid to the solution which resulted in the appearance of a new redox wave at $E^{1/2}$ 680 and 980 mV, respectively, which do not correspond to those assigned to the metal complexes (Table 1).

^{1}H-NMR titration studies for **1a**, **1b** and **2** provide further evidence that metal binding occurs at the oxazoline site. The data for ligand **1b** are representative; the most diagnostic protons are those at the chiral centre (H_a), the adjacent methylene group (H_b) and on the unsubstituted Cp ring (H_c) (Fig. 4). For the free ligand dissolved in CD_3CN these protons appear at δ 3.97, 4.08 and 4.24, respectively. Upon addition of $Mg(ClO_4)_2$ the peaks shifted downfield to δ 4.38, 4.81 and 4.46, respectively, with the response saturating with ca. one equivalent of Mg^{2+} (Fig. 4). The fact that hydrogens H_b experience a significantly larger shift than hydrogen H_a leads us to suggest that the oxygen atom as well as the imine group of the oxazoline participates in metal complexation. Very similar shifts were observed for the corresponding oxazoline protons of **2**: the alkene protons of **2** also shifted downfield, whereas the protons of the Cp rings were essentially unchanged due to the increased separation from the binding site. Upon addition of aliquots of $Mg(ClO_4)_2$ to compound **3** the singlet from the imine hydrogens (δ 8.09) predictably shifted downfield (0.1 equivalents Mg^{2+} δ 8.11; 0.5 equivalents δ 8.29) but the spectra showed the concomitant appearance of a new singlet (0.1 equivalents Mg^{2+} δ 9.89; 0.5 equivalents δ 9.82) which was indicative of aldehyde formation by decomposition of ligand **3**. The spectra of ligands **1a**, **1b** and **2** in the presence of Mg^{2+} were different from those of the corresponding protonated ligands. For example, for protonated **1b**, obtained by addition of anhydrous CF_3SO_3H to a solution of the free ligand in CD_3CN, the signals from H_a, H_b and H_c were broadened and observed at δ 4.23, 4.78 and 4.31, respectively.

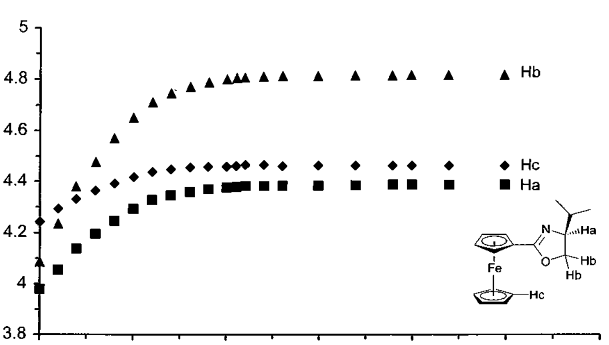


Fig. 4. ^{1}H-NMR titration curves of H_a, H_b and H_c of **1b** with added equivalents of $Mg(ClO_4)_2$ in CD_3CN.

We note that the different techniques used to monitor the metal binding do not always suggest the same stoichiometry for some ligand/metal combinations. For example, for $\mathbf{1b}{\cdot}Mg^{2+}$ the CV data show that five equivalents of Mg^{2+} are required to saturate the voltammetric response (Table 1 and Fig. 1) whereas the ^{1}H-NMR shifts are saturated with one equivalent (Fig. 4). This is a known phenomenon in related systems [5,13,14] arising from the different concentrations and timescales employed in the different techniques.

In summary, we have demonstrated that ferrocene derivatives substituted with an oxazoline or imine group are efficient redox sensors with remarkable selectivity for Mg^{2+}, Ca^{2+} and Cu^{2+} over a range of other metal cations in acetonitrile solution. This recognition process is easily monitored by CV which displays a large positive shift in the value of the ferrocene–ferrocenium redox couple. Additional evidence for cation binding is provided by UV–vis spectrophotometric and ^{1}H-NMR spectroscopic data. The fact that oxazoline derivatives **1b** and **2** and bisimine **3** are chiral may enable chiral recognition of Mg^{2+}, Ca^{2+} and Cu^{2+} containing species, and may also offer a method for electrochemically modifying asymmetric reactions [17,22] in which these metals are involved. We are currently exploring these aspects along with the development of related materials in thin film chemosensor devices [23,24].

3. Experimental

Cyclic voltammetry experiments were performed on a BAS CV50 electrochemical analyser using the ligand (10^{-3} M) and $^nBu_4NClO_4$ (0.1 M) in HPLC grade MeCN, versus Ag | AgCl with a platinum working electrode at 20 °C. Sequential additions of aliquots of 0.1 or 0.5 equivalents of 10^{-2} M solutions of the appropriate metal perchlorate salt in MeCN were monitored by CV. UV–vis data were obtained on a Pharmacia Biotech Ultrospec 4000 instrument using the ligand (10^{-3} M) and addition of aliquots of metal perchlorate salts (10^{-2} M) in dry MeCN.

Compounds **1a** [19], **1b** [19] and **3** [18] were prepared following the literature procedures.

*3.1. 4(S)-4-(1-Methylethyl)-2-[(E)-1-ferrocenyl]-2-oxazoline (**2**)*

To a solution of phosphonate ester **5** [20] (1.66 g, 6.3 mmol) in anhydrous MeCN (50 ml) were added sequentially, lithium chloride (0.21 g, 5 mmol), diazabicycloundecane (DBU) (0.7 g, 4.67 mmol) and ferrocene carboxaldehyde **4** (1.0 g, 4.67 mmol). The resultant solution was stirred under Ar for 16 h, whereupon it was diluted with water (150 ml) and extracted with CH_2Cl_2 (3 × 150 ml). The combined organic extracts were washed with brine (50 ml), dried ($MgSO_4$) and the solvent removed in vacuo to afford a brown residue. Purification by column chromatography on silica gel with CH_2Cl_2 as the eluent afforded compound **2** (0.75 g, 51%) as a red solid, m.p. 104–105 °C. Elemental analysis; Anal. Found: C, 66.77; H, 6.63; N, 4.40. Calc. for $C_{18}H_{21}FeNO$: C, 66.89; H, 6.54; N, 4.33%. MS; m/z (CI): 324 ([$M^+ + 1$], 100%). UV–vis; λ_{max} (nm) (ε, $M^{-1}\,cm^{-1}$) (CH_2Cl_2): 252 (8754), 297 (9821), 460 (475). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.20 (d, 1H, $J = 15.7$ Hz), 6.20 (d, 1H, $J = 15.7$ Hz), 4.40 (t, 2H, $J = 1.2$ Hz), 4.33 (t, 2H, $J = 1.2$ Hz), 4.14 (s, 5H), 3.97 (m, 3H), 1.80 (sextet, 1H, $J = 3.5$, 1.6 Hz), 1.00 (d, 3H, $J = 3.5$ Hz), 0.89 (d, 3H, $J = 3.5$ Hz). $[\alpha]_D^{20}$ $-63°$ (c 0.25, CH_2Cl_2).

Acknowledgements

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