

New Polyaza and Polyammonium Ferrocene Macrocyclic Ligands that complex and electrochemically recognise Transition Metal Cations and Phosphate Anions in Water

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A variety of new polyaza and polyammonium ferrocene macrocyclic ligands complex and electrochemically recognise Ni^{2+} , Cu^{2+} and Zn^{2+} transition metal cations and ATP, HPO_4^{2-} phosphate anions in water.

In pursuit of advancing chemical sensor technology, considerable interest is being shown in the syntheses of redox-active macrocyclic receptor molecules that contain a redox centre in close proximity to a cation or anion binding site.¹ These systems can be designed to recognise electrochemically the binding of a charged guest either *via* through space interactions and/or *via* various bond linkages between the receptor site and redox centre. Apart from one very recent example by Gokel and coworkers,² to our knowledge all the redox-responsive ligand systems reported to date give examples of guest-redox couple perturbations in organic solvents only, such as acetonitrile and dichloromethane. This communication demonstrates using new water-soluble polyaza and polyammonium ferrocene macrocyclic ligands, the electrochemical recognition of a variety of transition metal cations

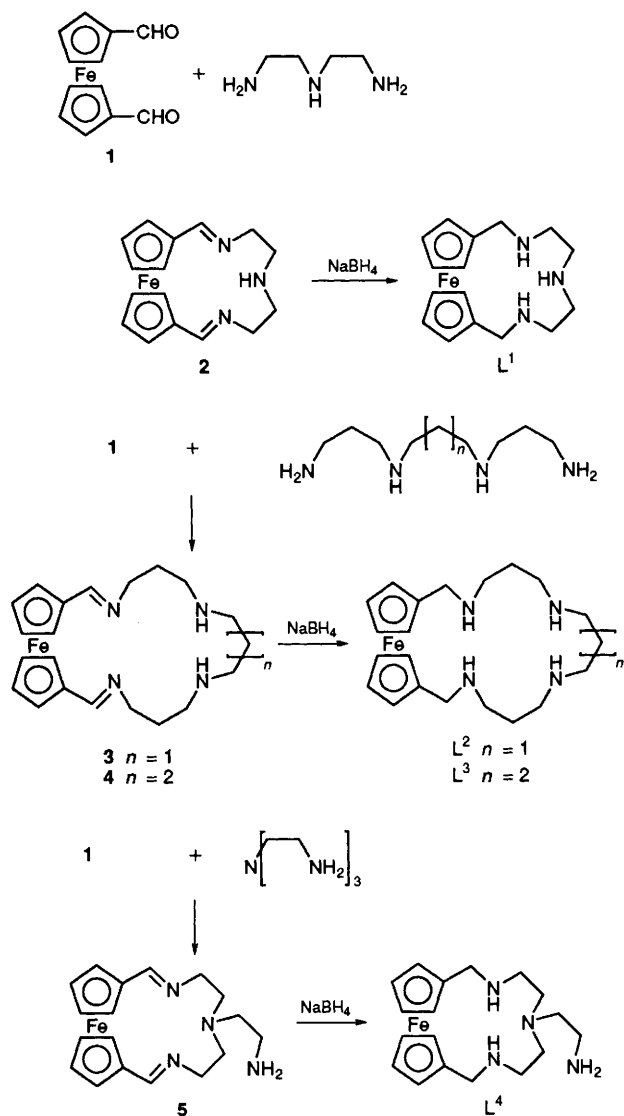
(Ni^{2+} , Cu^{2+} , Zn^{2+}) and phosphate anions (HPO_4^{2-} , ATP) in the aqueous environment.

The condensation of ferrocene-1,1'-dicarbaldehyde **1** and an appropriate diamine initially gave the Schiff base products **2-5** in excellent yields. These compounds were easily reduced using NaBH_4 to give the new polyaza ferrocene macrocyclic ligands $\text{L}^1\text{-L}^4$ in yields of up to 80% (Scheme 1).

Ligand L^5 was prepared *via* the reaction of 1,4-dimethyl-1,4,7-triazacyclononane **6** and (ferrocenylmethyl)trimethylammonium iodide **7** in the presence of potassium carbonate (Scheme 2). The structures of all these new ligands were characterised on the basis of spectroscopic and analytical evidence. Crystals of L^1 suitable for X-ray crystallographic investigation were obtained from acetonitrile.^{4†} The structure consists of discrete molecules of L^1 as shown in Fig. 1. The $\text{Fe}(\text{cp})_2$ unit is eclipsed with Fe-C distances in the range 2.025(12)-2.071(11) Å. The conformation of the aza methylene linkage indicates approximate C_s symmetry. The four C-C-N-C torsion angles (two on each side) closest to the cyclopentadienyl rings exhibit *trans* values close to 180°, while the other four in the link show *gauche* values *viz.* N(32)-C(33)-C(34)-N(35) 49.2, C(33)-C(34)-N(35)-C(36) 71.1, C(34)-N(35)-C(36)-C(37) -71.0 and N(35)-C(36)-C(37)-N(38) -54°.

Preliminary transition metal coordination investigations with $\text{Ni}(\text{ClO}_4)_2$, $\text{Cu}(\text{BF}_4)_2$ and $\text{Zn}(\text{ClO}_4)_2$ and $\text{L}^1\text{-L}^5$ led to the successful isolation of respective transition metal ligand complexes whose elemental analyses all suggested 1 : 1 ligand metal stoichiometry. With zinc, ¹³C and ¹H NMR titration experiments in CD_3CN solution produced titration curves confirming 1 : 1 Zn^{2+} ligand solution stoichiometry.

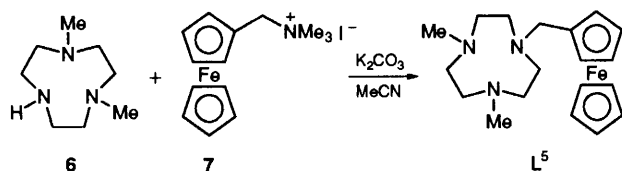
The electrochemical properties of $\text{L}^1\text{-L}^5$ were investigated using cyclic voltammetry in acetonitrile and water and the



Scheme 1

† Crystal Data for L^1 , $\text{C}_{16}\text{H}_{23}\text{FeN}_3$, $M = 313.0$, $F(000) = 332$, triclinic, $a = 6.392(7)$, $b = 9.208(9)$, $c = 12.389(13)$ Å, $\alpha = 102.1(1)$, $\beta = 86.2(1)$, $\gamma = 87.4(1)^\circ$, $U = 710.1 \text{ \AA}^3$, $D_c = 1.46 \text{ g cm}^{-3}$, $D_m = 1.46 \text{ g cm}^{-3}$, $Z = 2$, $\lambda = 0.7107 \text{ \AA}$, $\mu = 10.9 \text{ cm}^{-1}$, space group $P1$. A crystal of approximate size $0.3 \times 0.3 \times 0.3 \text{ mm}$ was set up to rotate about the a axis on a Stoe Stadi2 diffractometer and data were collected *via* variable width ω scan. Background counts were for 20 s and a scan rate of $0.0333^\circ/\text{s}$ was applied to a width of $(1.5 + \sin\mu/\tan\theta)$. 2321 independent reflections were measured of which 1604 with $I > 3\sigma(I)$ were used in subsequent refinement. The iron positions were located from the Patterson function and all non-hydrogen atoms were located subsequently *via* Fourier methods and refined anisotropically. The hydrogen atoms attached to carbon were added in fixed positions. The hydrogen atoms attached to nitrogen could be located in two alternative tetrahedral positions. We calculated a difference Fourier map and although the positions were not clear cut, in all three cases, there was more electron density in one position than the other. These atoms were also included in the calculation in fixed positions.

The structure was given a weighting scheme in the form $w = 1/[\sigma^2(F) + 0.003F^2]$. The final R value was 0.086 (R_w 0.088). Calculations were carried out using SHELX76² and some of our own programs on the Amdahl 5870 computer at the University of Reading. In the final cycles of refinement, no shift/error ratio was greater than 0.1σ . In the final difference Fourier maps, the maximum and minimum peaks were 0.75 and -0.62 \AA^{-3} . Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.



Scheme 2

Table 1 Electrochemical data for L¹–L⁵ in acetonitrile in the absence and presence of transition metal cations^a

Compound ^b	L ¹	L ²	L ³	L ⁴	L ⁵
$E_{pa}(\text{free})/mV$	520	600	410	600	480
$\Delta E_{pa}(\text{Cu}^{2+})/mV$	60	190	90	100	20
$\Delta E_{pa}(\text{Zn}^{2+})/mV$	135	<10	85	<10	
$\Delta E_{pa}(\text{Ni}^{2+})/mV$	100	<10	<10		

^a Data were obtained in acetonitrile solution containing 0.1 mol dm⁻³ [Buⁿ₄N]BF₄ as supporting electrolyte. Solutions were ca. 3 × 10⁻³ mol dm⁻³ in compound and potentials were determined with reference to a KCl saturated calomel electrode at 21 ± 1 °C at 50 mV s⁻¹ scan rate. ^b The CVs of L¹, L² and L⁴ consisted of a main current wave (reversible for L³ and L⁵ and EC mechanism for L¹, L² and L⁴) corresponding to the Fc⁺/Fc couple and minor current waves (irreversible or quasi-reversible) from the oxidation of the amino groups. ^c E_{pa} represents the anodic current peak potential of the Fc⁺/Fc couple. ^d Anodic shifts of the anodic current peak potential of the Fc⁺/Fc couple produced by the presence of metal cations (1 or 2 equiv. added as their perchlorate salts). For L¹, L² and L⁴, after addition of the cations, the current waves from the respective amino groups disappeared and that of the Fc⁺/Fc couple became reversible.

results are summarised in Tables 1 and 2. In acetonitrile each ligand exhibited a one-electron oxidation wave in the range + 0.4 to +0.6 V [vs. standard calomel electrode (SCE)]. In water, the reversibility and potential of the respective ferrocene redox couple of L¹–L⁵ was found to be dependent upon the pH of the aqueous solution.⁵ At pH values of 1–6 the ligands exhibit reversible one electron oxidation waves at potentials of +0.5 to +0.4 V (vs. SCE). As the pH of the electrochemical solution is increased the respective ferrocene oxidation wave becomes less anodic until at pH values of ≥ 10.5 the CV wave reaches a constant minimum anodic potential and displays EC mechanistic electrochemical behaviour (Table 2). Macrocyclic polyamines which possess amine nitrogens separated by three or four methylene groups typically exhibit p*K*_a values in the range of 7 and above⁶ whereas the smaller macrocycle 1,4,7-triazacyclononane displays p*K*_a values of <2, 6.82 and 10.42.⁷ Taking these literature p*K*_a values and the pH-dependent electrochemical observations into consideration, it is highly likely that ligands L² and L³ are fully protonated at pH values ≤ 6 and deprotonated at pH values ≥ 10.5, *i.e.* the respective p*K*_a values of L² and L³ lie in the range 6–10.5. Ligands L¹, L⁴ and L⁵ pH-dependent electrochemical behaviour also suggest that at pH values of ≥ 10.5 they are fully deprotonated. In the pH range 1–6 the respective $E_{1/2}$ values are independent of pH and attempts to investigate these ligands' electrochemical behaviour at pH values of <1 met with their decomposition.

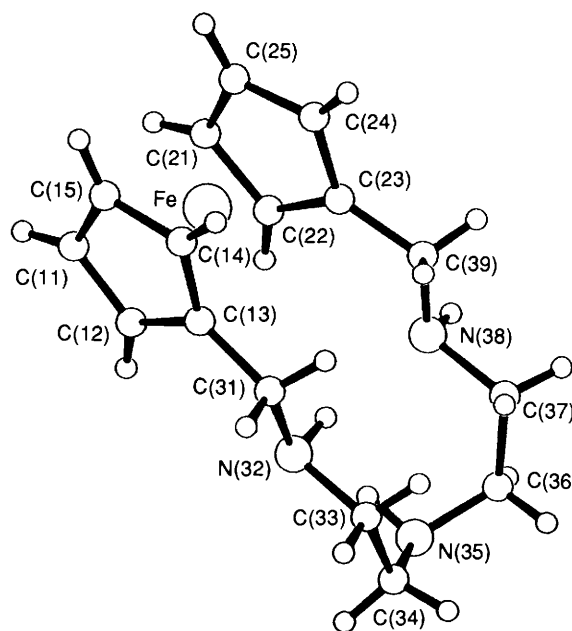
The addition of stoichiometric amounts of Ni²⁺, Cu²⁺ and Zn²⁺ to acetonitrile electrochemical solutions of L¹–L⁵ led to large anodic shifts of the respective ferrocene–ferrocenium redox couple of up to 190 mV in the case of L² and Cu²⁺ (Table 2). Analogous experiments in water at pH values 10.5–12 revealed L¹–L⁵ to recognise electrochemically these transition metal cations in the aqueous environment (Table 2).

Significant anodic perturbations were observed and interestingly, the CV waves of the solution ligand–transition metal complexes were found to be reversible implying that the

Table 2 Electrochemical data for L¹–L⁵ in water (10.5 < pH < 12) in the absence and presence of transition metal cations^a

Compound ^b	L ¹	L ²	L ³	L ⁴	L ⁵
$E_{pa}(\text{free})/mV$	215	230	250	210	235
$\Delta E_{pa}(\text{Cu}^{2+})/mV$	25	70	80	30	40
$\Delta E_{pa}(\text{Zn}^{2+})/mV$	105	<10	20	40	30
$\Delta E_{pa}(\text{Ni}^{2+})/mV$	60	<10	<10		<10

^a Data were obtained in aqueous solution containing 0.2 mol dm⁻³ KCl as supporting electrolyte. Solutions were ca. 3 × 10⁻³ mol dm⁻³ in compound and potentials were determined with reference to a KCl saturated calomel electrode at 21 ± 1 °C at 50 mV s⁻¹ scan rate. The solution pH was adjusted by 0.5 mol dm⁻³ KOH and 0.1 mol dm⁻³ HCl. ^b For L¹, L², L³ and L⁴, the CVs were reversible one electron oxidations at pH < 6. At pH = 11, an EC mechanism was observed for L¹, L² and L⁴. Minor oxidation waves of the amino groups appeared after that of the Fc⁺/Fc couple at slow scan rate. The CV of L⁵ was a one electron reversible oxidation wave, less dependent on the solution pH, and showed no oxidation of the amino groups in the pH range explored. ^c Anodic shifts of anodic current peak potential of the Fc⁺/Fc couple produced by presence of metal cations (1 or 2 equiv. added as their perchlorate salts).

Fig. 1 Structure of L¹

nitrogen donor atoms of the corresponding macrocyclic ring linkage may be responsible for the EC electrochemical mechanistic behaviour of the free ligands at high pH values.

Of particular relevance to chemical sensor technology were the novel results of electrochemical competition experiments.⁸ When an equimolar mixture of Ni²⁺, Cu²⁺ and Zn²⁺ was added to aqueous electrochemical solutions of L² and L³ the ferrocene–ferrocenium redox couple shifted anodically by an amount approximately the same as that induced by the Cu²⁺ cation alone. This result suggests L² and L³ are first generation prototype copper-selective amperometric sensors, capable of detecting the Cu²⁺ cation in the presence of Ni²⁺ and Zn²⁺ ions.

Macrocyclic polyamines, when protonated, have been shown to complex a variety of inorganic and organic anions *via* favourable electrostatic and hydrogen bonding interactions.^{6,9} Ligands L¹–L³ at appropriate pH values can be protonated to produce polyammonium redox-active macrocycles with the potential of complexing and electrochemically sensing anions. Preliminary anion coordination studies were carried out with

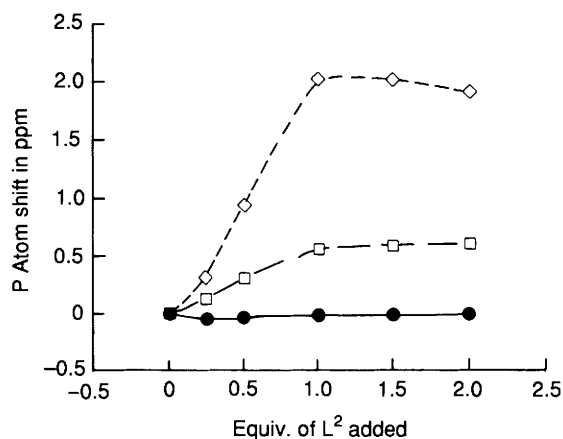


Fig. 2 ^{31}P NMR shifts ($\Delta\delta$) of the α -, β - and γ -phosphate signals of ATP as a function of molar equivalents of L^2 : ●, α ; □, β ; ◇, γ

the nucleotide adenosine triphosphate (ATP) and hydrogen-phosphate (HPO_4^{2-}) using initially ^{31}P NMR spectroscopy. At pH values of between 6 and 8 the respective pK_a values of ligands L^1 – L^3 are such that at least two of the nitrogen donor atoms are protonated. ^{31}P NMR titration experiments with L^1 – L^3 and ATP and HPO_4^{2-} revealed that these ligands at pH 6.5 form solution 1:1 complexes with these anionic guests. For example, Fig. 2 shows the $\text{P}(\beta)$ and in particular the terminal $\text{P}(\gamma)$ signal of ATP to be shifted by up to 2.0 ppm in the presence of protonated L^2 .

Cyclic voltammetric experiments reveal, to our knowledge for the first time, the electrochemical recognition of these phosphate anion guests in water. At pH 6.5 cathodic shifts of 60–80 mV of the respective ferrocene redox couple of L^1 – L^3 are observed in the presence of ATP and HPO_4^{2-} anions.

In conclusion these new polyazamacrocyclic ligands represent novel prototype amperometric sensors for the electrochemical recognition of transition metals and phosphate anions in water.

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