

Binding, electrochemical and metal extraction properties of the new redox-active polyazacycloalkane 1,4,7,10,13,16-hexa-(ferrocenylmethyl)-1,4,7,10,13,16-hexaazacyclooctadecane

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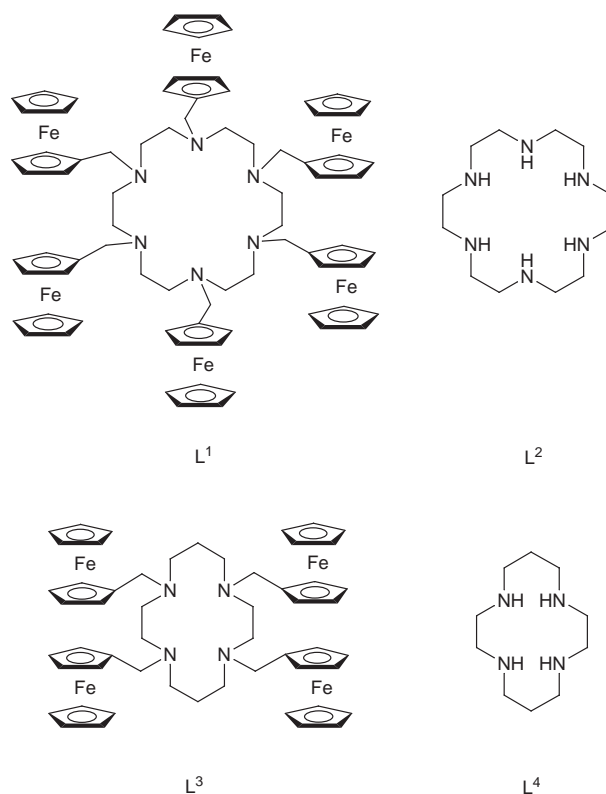
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The redox-functionalised polyazacycloalkane receptor 1,4,7,10,13,16-hexa(ferrocenylmethyl)-1,4,7,10,13,16-hexaazacyclooctadecane (L^1) has been designed and synthesized and its binding, electrochemical and metal extraction properties studied. The results have been compared to those obtained for the parent redox-active polyazacycloalkane 1,4,8,11-tetra(ferrocenylmethyl)-1,4,8,11-tetraazacyclotetradecane, L^3 . The cadmium complex of L^1 and the free receptor L^3 have been crystallographically characterised. The structure of $[CdL^1][PF_6]_2 \cdot 4CH_3CN \cdot 4H_2O$ consists of cationic $[CdL^1]^{2+}$ units in which the cadmium ion exhibits a distorted octahedral environment. Solution studies by potentiometric methods have also been carried out in the presence of H^+ and Cu^{2+} in 1,4-dioxane–water (70:30 v/v, 25 °C, 0.1 mol dm^{-3} KNO_3) for L^1 and thf–water (70:30 v/v, 25 °C, 0.1 mol dm^{-3} $[NBu^4][ClO_4]$) for L^3 . Electrochemical experiments as a function of the pH in the presence of Ni^{2+} , Cu^{2+} , Zn^{2+} , Cd^{2+} or Pb^{2+} have been carried out for L^1 and L^3 . The solvent extraction properties of L^1 have also been studied.

Among recently developed functionalised molecules are redox-responsive receptors which have proved to be suitable molecules for the electrochemical recognition of both cationic and anionic substrates.¹ These new functionalised receptors comprise a well known framework able to bind substrates and reversible redox-active units. Different electroactive moieties have been covalently anchored² near binding sites but probably the most widely used has been ferrocene. However most of the work has been devoted to the recognition of alkali- and alkaline-earth metal ions³ and relatively less effort has been carried out in the recognition of transition-metal ions and anions.⁴ Functionalisation of ferrocenyl groups with polyazacycloalkanes leads to new receptor molecules which (i) can bind transition-metal ions,⁵ (ii) can be water soluble⁶ and (iii) are good candidates for anion binding due to the formation of highly charged species and/or hydrogen bonding networks.⁷ Apart from their electroactive character, these ferrocene-functionalised polyazaalkanes have other interesting properties which have probably not been fully studied. The lipophilic character of the ferrocenyl units and the presence of metal binding sites makes these molecules good candidates to be used in preconcentration of trace elements by solvent extraction for analytical purposes or as models for the elimination of toxic metals from water. Additionally the electroactive character of the ferrocenyl groups could make these molecules able to drive ions against a chemical concentration gradient by changing the co-ordination ability by oxidation or reduction of the electroactive groups.⁸

We have designed and synthesized the redox-functionalised polyazacycloalkane receptor 1,4,7,10,13,16-hexa(ferrocenylmethyl)-1,4,7,10,13,16-hexaazacyclooctadecane (L^1) and have studied its binding, electrochemical and metal extraction properties and the results have been compared to those obtained for the redox-active polyazacycloalkane 1,4,8,11-tetra(ferrocenylmethyl)-1,4,8,11-tetraazacyclotetradecane, L^3 .

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Experimental

Solvents and reagents

Tetrahydrofuran and 1,4-dioxane were freshly distilled. 1,4,7,10,13,16-Hexaazacyclooctadecane (L^2), L^3 and (ferrocenylmethyl)trimethylammonium iodide were synthesized follow-

ing refs. 9, 10 and 11, respectively. Metal cations Cu^{2+} , Ni^{2+} , Zn^{2+} , Cd^{2+} and Pb^{2+} were used as their nitrate salts.

Syntheses

L¹. 1,4,7,10,13,16-Hexaazacyclooctadecane (0.5 g, 1.94 mmol) and (ferrocenylmethyl)trimethylammonium iodide (7.45 g, 19.4 mmol) were heated to reflux in acetonitrile (250 cm³) for 4 d in the presence of sodium carbonate (7 g). The warm reaction mixture was filtered and the yellow solution evaporated to dryness. The resulting solid was dissolved in dichloromethane and chromatographed using dichloromethane–methanol (100:1) as eluent. Further recrystallisation in dichloromethane–hexane gave **L¹** as a yellow solid (600 mg, 20%) (Found: C, 61.79; H, 6.07; N, 5.70. $\text{C}_{78}\text{H}_{90}\text{Fe}_6\text{N}_6\cdot\text{CH}_2\text{Cl}_2$ requires C, 61.96; H, 6.01; N, 5.50%). NMR (CDCl_3): ¹H δ 4.09, 4.06 (two br resonances, 54 H, C_5H_5 and C_5H_4), 3.35 (br, 12 H, CH_2) and 2.40 (br, 24 H, CH_2); ¹³C-¹H} δ 83.24 (C_{ipso} , C_5H_4), 70.23, 68.44 (C_5H_5), 67.89 (C_5H_4), 54.09 (CH_2) and 51.22 (CH_2). Mass spectrum (FAB): m/z 1446 (M^+).

[CdL¹][PF₆]₂. Compound **L¹** (70 mg, 0.05 mmol) and $\text{Cd}(\text{NO}_3)_2\cdot 4\text{H}_2\text{O}$ (15 mg, 0.05 mmol) were heated to reflux in ethanol (75 cm³) for 20 h. After cooling to room temperature the reaction mixture was filtered. An excess of $[\text{NH}_4][\text{PF}_6]$ and water were added to the yellow solution to give a yellow precipitate which was filtered off, washed with water and dried *in vacuo* to give $[\text{CdL}^1][\text{PF}_6]_2$ (35 mg, 40%) (Found: C, 49.78; H, 4.76; N, 4.50. $\text{C}_{78}\text{H}_{90}\text{CdF}_{12}\text{Fe}_6\text{N}_6\text{P}_2$ requires C, 50.0; H, 4.87; N, 4.54%). NMR (CDCl_3): ¹H δ 4.54 (t, 12 H, C_5H_4), 4.39 (t, 12 H, C_5H_4), 4.29 (s, 30 H, C_5H_5), 4.18 (s, 12 H, CH_2), 3.09 (br, 6 H, CH_2), 3.05 (br, 6 H, CH_2), 2.71 (br, 6 H, CH_2) and 2.68 (br, 6 H, CH_2).

Physical measurements

The NMR spectra were measured on a Varian Gemini spectrometer operating at 300 K. Chemical shifts for ¹H and ¹³C-¹H} are referenced to SiMe_4 and CDCl_3 , respectively. Electrochemical data were obtained with a Tacussel IMT-1 programmable function generator, connected to a PJT 120-1 potentiostat. The working electrode was platinum with a saturated calomel reference electrode separated from the test solution by a salt bridge containing the solvent/supporting electrolyte. The auxiliary electrode was platinum wire. Potentiometric titrations were carried out in 1,4-dioxane–water (70:30 v/v, 0.1 mol dm⁻³ KNO_3) for **L¹** and thf–water (70:30, v/v, 0.1 mol dm⁻³ $[\text{NBu}_4][\text{ClO}_4]$) for **L³** using a reaction vessel water-thermostatted at 25.0 ± 0.1 °C under nitrogen. Experimental potentiometric details have been published previously.⁵ The concentrations of the metal ions were determined using standard methods. The computer program SUPERQUAD¹² was used to calculate the protonation and stability constants. The titration curves for each system (*ca.* 250 experimental points corresponding to at least three titration curves, $\text{pH} = -\log[\text{H}^+]$ range investigated 2.5–10, concentration of the ligand and metal ion *ca.* 1.2×10^{-3} mol dm⁻³) were treated either as a single set or as separated entities without significant variations in the values of the stability constants. Finally the sets of data were merged and treated simultaneously to give the stability constants.

Metal extraction

Metal extraction experiments were carried out using water and dichloromethane. The corresponding metal ion (nitrate salts) was dissolved in water (100 cm³, metal concentration *ca.* 3×10^{-4} mol dm⁻³), whereas the **L¹** receptor was dissolved in the organic phase (100 cm³, ligand concentration *ca.* 3×10^{-4} mol dm⁻³). Both phases were placed in a flask and the mixture stirred. Samples of the aqueous phase were taken as a function of time and the metal concentration determined using standard atomic absorption methods.

Electrolysis of the dichloromethane solutions containing the **L¹** complex of Pb^{2+} were carried out using a Tacussel PJT 120-1 potentiostat. The working electrode was graphite, whereas a saturated calomel electrode and platinum were used as reference and auxiliary electrodes, respectively.

Crystallography

[CdL¹][PF₆]₂·4CH₃CN·4H₂O. *Crystal data.* $\text{C}_{78}\text{H}_{90}\text{CdF}_{12}\text{Fe}_6\text{N}_6\text{P}_2\cdot 4\text{CH}_3\text{CN}\cdot 4\text{H}_2\text{O}$, $M = 208.48$, monoclinic, space group $P2_1/n$, $a = 16.974(3)$, $b = 15.987(3)$, $c = 18.375(3)$ Å, $\beta = 108.635(12)^\circ$, $Z = 2$, $U = 4725(1)$ Å³, $D_c = 1.632$ g cm⁻³, $\lambda(\text{Mo-K}\alpha) = 0.71069$ Å, $T = 293(2)$ K, $\mu(\text{Mo-K}\alpha) = 12.83$ cm⁻¹.

Well shaped crystals were obtained by slow diffusion of water into acetonitrile solutions of the complex. They were unstable owing to loss of solvent. A capillary containing a crystal with approximate dimensions $0.2 \times 0.2 \times 0.1$ mm and the mother-liquor was mounted on a Siemens P4 four-circle diffractometer. A total of 5092 reflections were measured of which 4852 were unique ($R_{\text{int}} = 0.052$) ($3.6 \leq 2\theta \leq 45.0^\circ$) using the $2\theta - \omega$ method. Lorentz-polarisation corrections were applied but no allowance was made for absorption. The structure was solved by direct methods (SHELXTL)¹³ and refined by full-matrix least-squares analysis on F^2 . Disorder appears to affect some atoms in unattached cyclopentadienyl rings and some atoms modelled highly anisotropically. However no well defined peaks were found near these atoms and no attempts were made to model the disorder. The refinement converged at $R1$ 0.061 [$F > 4\sigma(F)$] and $R2$ 0.188 (all data). Largest peak and hole in the final difference map $+0.50, -0.36$ e Å⁻³.

L³. *Crystal data.* $\text{C}_{54}\text{H}_{64}\text{Fe}_4\text{N}_4$, $M = 992.49$, monoclinic, space group $P2_1/c$, $a = 17.593(4)$, $b = 10.915(2)$, $c = 12.764(3)$ Å, $\beta = 105.54(3)^\circ$, $Z = 2$, $U = 2361.4(8)$ Å³, $D_c = 1.396$ g cm⁻³, $\lambda(\text{Mo-K}\alpha) = 0.71069$ Å, $T = 293(2)$ K, $\mu(\text{Mo-K}\alpha) = 12.45$ cm⁻¹.

A well shaped orange crystal of **L³** with approximate dimensions $0.21 \times 0.19 \times 0.14$ mm was mounted on a Siemens P4 four-circle diffractometer equipped with Mo-K α radiation. A total of 4644 reflections were measured of which 2203 were unique ($R_{\text{int}} = 0.169$) ($4.4 \leq 2\theta \leq 40.0^\circ$) using the $2\theta - \omega$ method. Corrections were applied and the structure solved as above. Disorder appears to affect some atoms in unattached cyclopentadienyl rings but no attempts were made to model it. The refinement converged at $R1$ 0.066 [$F > 4\sigma(F)$] for 856 reflections] and $R2$ 0.1127 (all data). Largest peak and hole in the final difference map $+0.27, -0.27$ e Å⁻³.

CCDC reference number 186/1022.

Results and Discussion

We have designed and synthesized the molecule 1,4,7,10,13,16-hexa(ferrocenylmethyl)-1,4,7,10,13,16-hexaazacyclooctadecane (**L¹**) by reaction of 1,4,7,10,13,16-hexaazacyclooctadecane (**L²**) with (ferrocenylmethyl)trimethylammonium iodide in acetonitrile in the presence of sodium carbonate. The compound was isolated after column chromatography as a crystalline yellow solid in a 20% yield. The ¹H NMR spectrum shows only four signals indicating that the molecule is highly symmetric in solution on the NMR timescale. Two signals at δ 4.09 and 4.06 are attributed to the protons of the cyclopentadienyl rings whereas broad signals at δ 3.35 and 2.40 are assigned to the CH_2 protons from the ferrocenylmethyl groups and from the hexaazacyclooctadecane ring. The ¹³C-¹H} NMR and FAB mass spectra ($m/z = 1446, M^+$) are also consistent with the proposed formulation.

Compound **L¹** is a potential N-donor hexadentate ligand containing redox-active peripherally attached groups. It seemed to us interesting to check (i) its chelating ability towards metal ions and analyse, by comparison with the analogous

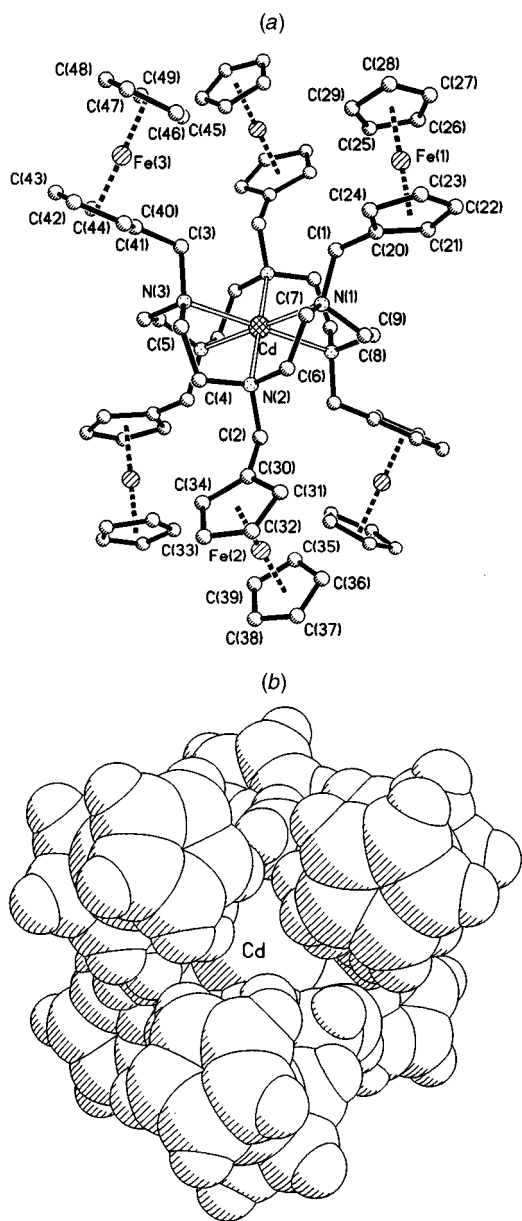


Fig. 1 (a) Molecular structure of the cation $[\text{CdL}^1]^{2+}$ showing the atomic numbering scheme. (b) An alternative representation showing the outer lipophilic sphere

non-functionalised receptor L^2 , the influence of the bulky ferrocenyl groups near the co-ordination site, (ii) the influence of the co-ordination of substrates (H^+ and metal ions) in the redox properties of the electroactive groups and (iii) the solvent extraction properties of L^1 further to study potential back-extraction processes by oxidation of the redox-active moieties. Additional studies on the related redox-active polyazacycloalkane 1,4,8,11-tetra(ferrocenylmethyl)-1,4,8,11-tetraazacyclotetradecane have also been carried out.

The cadmium complex of L^1 has been obtained by reaction with cadmium nitrate in dichloromethane-ethanol mixtures and further addition of $[\text{NH}_4][\text{PF}_6]$ and water. The ^1H NMR spectrum of $[\text{CdL}^1][\text{PF}_6]_2$ shows magnetically equivalent ferrocenylmethyl groups and only four signals [two pseudo-triplets δ 4.54, 4.39 and two singlets δ 4.29 (C_5H_5) and 4.18 (CH_2)]. However protons in the polyazacycloalkane framework are not equivalent and four broad signals were observed. In order fully to characterise the co-ordination mode of L^1 we have solved the crystal structure of the cadmium complex by using X-ray single crystal procedures.

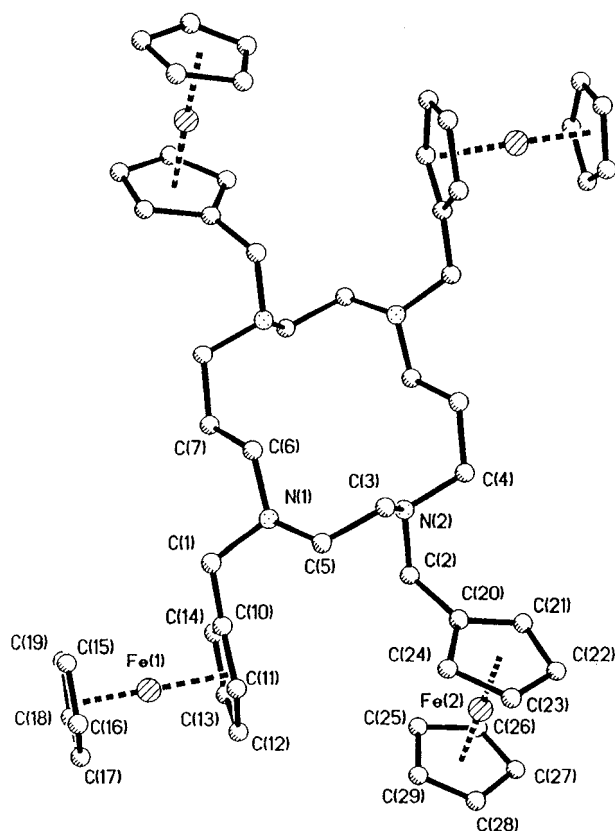


Fig. 2 Molecular structure of compound L^3 showing the atomic numbering scheme

Crystal structure of $[\text{CdL}^1][\text{PF}_6]_2 \cdot 4\text{CH}_3\text{CN} \cdot 4\text{H}_2\text{O}$

The crystallographic characterisation of L^1 as its cadmium complex has been carried out. Table 1 lists selected bond distances and angles. Suitable crystals of $[\text{CdL}^1][\text{PF}_6]_2$ were obtained from slow diffusion of water into an acetonitrile solution of the complex. The $[\text{CdL}^1]^{2+}$ unit is depicted in Fig. 1. The structure of the $[\text{CdL}^1]^{2+}$ cation consists of an inner binding domain of six nitrogen atoms co-ordinating the central metal ion giving it a distorted octahedral geometry. The six nitrogen atoms are also covalently attached to six ferrocenylmethyl groups making up an outer redox-active sphere. The hexaazacyclotetradecane moiety adopts the *fac* configuration (D_{3d} symmetry). The Cd–N distances range from 2.338(8) to 2.535(10) Å. Some angles around the central atom are far from the ideal octahedral geometry such as N(3)–Cd–N(2) 73.7(3) or N(1)–Cd–N(2) 74.4(3)°, probably due to geometrical constraints imposed by the ferrocenyl moieties. However no important distortions are present in the ferrocenylmethyl groups. The ferrocenyl units show the typical sandwich conformation with the cyclopentadienyl rings parallel within the experimental error; Fe–Cp (centroid) distances range from 1.617 to 1.655, averaging 1.639 Å, whereas Fe–C (Cp) lengths are between 1.93(2) and 2.05(2) [average 2.01(2) Å]. The three crystallographically non-equivalent Cd–Fe distances are Cd \cdots Fe(1) 6.326, Cd \cdots Fe(2) 6.593 and Cd \cdots Fe(3) 6.479 Å.

Crystal structure of L^3

A view of the L^3 molecule is depicted in Fig. 2. Selected bond distances and angles are in Table 2. The structure consists of the polyazacycloalkane 1,4,8,11-tetraazacyclotetradecane (cyclam) containing ferrocenylmethyl groups covalently attached to the four nitrogen atoms. The ferrocenyl moieties show the typical sandwich configuration with parallel and planar cyclopentadienyl rings within the experimental error. The iron–cyclopentadienyl (centroid) distances range from 1.634 to 1.655 Å,

Table 1 Selected bond lengths (Å) and angles (°) for [CdL¹][PF₆]₂·4CH₃CN·4H₂O

Cd–N(1)	2.338(8)	Cd–N(2)	2.535(10)
Cd–N(3)	2.488(9)	N(3)–C(5)	1.490(14)
N(3)–C(9 ^b)	1.500(13)	N(3)–C(3)	1.503(14)
N(1)–C(7)	1.465(14)	N(1)–C(8)	1.511(13)
N(1)–C(1)	1.520(13)	N(2)–C(4)	1.456(13)
N(2)–C(6)	1.491(13)	N(2)–C(2)	1.491(13)
N(1 ⁱ)–Cd–N(1)	180.0	N(1 ⁱ)–Cd–N(3)	77.4(3)
N(1)–Cd–N(3)	102.6(3)	N(1)–Cd–N(2)	74.4(3)
N(1)–Cd–N(2 ⁱ)	105.6(3)	N(3)–Cd–N(2 ⁱ)	106.3(3)
N(3)–Cd–N(2)	73.7(3)	C(7)–N(1)–C(8)	110.9(9)
C(7)–N(1)–C(1)	110.1(9)	C(8)–N(1)–C(1)	109.0(9)
C(7)–N(1)–Cd	108.2(7)	C(8)–N(1)–Cd	104.9(6)
C(1)–N(1)–Cd	113.6(6)	C(4)–N(2)–C(6)	111.0(9)
C(4)–N(2)–C(2)	108.6(9)	C(6)–N(2)–C(2)	109.6(8)
C(4)–N(2)–Cd	105.6(7)	C(6)–N(2)–Cd	107.0(7)
C(2)–N(2)–Cd	115.0(7)	C(5)–N(3)–C(3)	111.1(9)
C(5)–N(3)–Cd	107.9(6)	C(3)–N(3)–Cd	112.2(7)
C(5)–N(3)–C(9 ^b)	110.5(9)	C(9 ^b)–N(3)–C(3)	109.7(9)
C(9 ^b)–N(3)–Cd	105.3(6)		

Symmetry transformation used to generate equivalent atoms: $i - x + 1, -y + 1, -z + 1$.

Table 2 Selected bond lengths (Å) and angles (°) for compound L³

Fe(1)–C(15)	1.98(2)	Fe(1)–C(19)	1.99(2)
Fe(1)–C(16)	1.97(2)	Fe(1)–C(18)	1.990(14)
Fe(1)–C(17)	1.975(14)	Fe(1)–C(14)	2.00(2)
Fe(1)–C(13)	2.06(2)	Fe(1)–C(11)	2.050(14)
Fe(1)–C(10)	2.08(2)	Fe(1)–C(12)	2.05(2)
N(1)–C(6)	1.470(12)	N(1)–C(5)	1.491(14)
N(1)–C(1)	1.473(14)	Fe(2)–C(26)	1.99(2)
Fe(2)–C(25)	2.00(3)	Fe(2)–C(28)	1.99(2)
Fe(2)–C(23)	2.02(2)	Fe(2)–C(29)	2.00(2)
Fe(2)–C(24)	2.019(13)	Fe(2)–C(27)	2.03(2)
Fe(2)–C(21)	2.035(14)	Fe(2)–C(20)	2.048(12)
Fe(2)–C(22)	2.06(2)	N(2)–C(3)	1.46(2)
N(2)–C(2)	1.481(13)	N(2)–C(4)	1.488(13)
C(6)–N(1)–C(1)	112.0(9)	C(6)–N(1)–C(5)	110.9(10)
C(10)–C(1)–N(1)	112.6(10)	C(5)–N(1)–N(1)	109.6(10)
C(3)–N(2)–C(2)	114.2(10)	C(3)–N(2)–C(4)	109.9(12)
C(2)–N(2)–C(4)	111.0(10)	N(2)–C(2)–C(20)	116.0(10)
N(2)–C(3)–C(5)	112.8(12)	N(1)–C(5)–C(3)	113.6(11)

averaging 1.643 Å. The corresponding Fe–C distances range from 1.97(2) to 2.05(2) Å [averaging 2.02(2) Å]. Cyclic tetraamines such as cyclam and their derivatives can occur in several conformations. For instance in [14]aneN₄ or R₄[14]aneN₄ macrocycles with alternating five- and six-membered chelating rings a total of five combinations can be produced. Compound L³ shows a conformation with two ferrocenylmethyl groups above the N₄ plane and the remaining two below the N₄ plane (configuration IV as described in ref. 14). Important changes are produced in the configuration of the L³ receptor when it interacts with metal ions as we have recently reported.¹⁵

Protonation behaviour

Data for L¹ and L³ have been determined in 1,4-dioxane–water (70:30 v/v) and thf–water (70:30 v/v), respectively because of their insolubility in other solvents such as water or dmsO–water mixtures in a wide pH range. Comparing the protonation constants of L² in water¹⁶ and L¹ in 1,4-dioxane–water (70:30 v/v) it can be noted that there is a reduction of the basicity of the first three protonations and an enhancement of the basicity for the last three (see Table 3). A similar effect can be observed when we compare the protonation constants of L⁴ in water with those obtained for L³ which behaves as a stronger acid than L⁴ for the first two protonation steps but as a strong base when the

Table 3 Stepwise protonation constants (log *K*) of L¹ and L² determined at 25 °C in 0.1 mol dm⁻³ KNO₃ in 1,4-dioxane–water (70:30 v/v)

Reaction	L ¹	L ^{2a}	L ^{2b}
L + H ⇌ HL ^c	9.64(3)	9.56(3)	10.15
HL + H ⇌ H ₂ L	8.33(2)	8.97(3)	9.48
H ₂ L + H ⇌ H ₃ L	6.71(3)	5.46(2)	8.89
H ₃ L + H ⇌ H ₄ L	6.01(2)	1.76(3)	4.27
H ₄ L + H ⇌ H ₅ L	4.52(2)	—	2.21
H ₅ L + H ⇌ H ₆ L	3.87(2)	—	1.0

^a This work, 1,4-dioxane–water (70:30 v/v), 25 °C, 0.1 mol dm⁻³ KNO₃.

^b Data from ref. 16, in water. ^c Charges have been omitted for clarity.

^d Values in parentheses are standard deviations of the last significant figure.

Table 4 Stepwise protonation constants (log *K*) of L³ and L⁴ determined in thf–water (70:30 v/v) at 25 °C in 0.1 mol dm⁻³ [NBu₄][ClO₄]

Reaction	L ³	L ^{4a}	L ^{4b}
L + H ⇌ HL ^c	8.90(1) ^d	10.54(1)	11.59
HL + H ⇌ H ₂ L	7.56(1)	9.49(1)	10.62
H ₂ L + H ⇌ H ₃ L	6.24(1)	2.01(2)	1.61
H ₃ L + H ⇌ H ₄ L	3.50(1)	2.21(4)	2.42

^a This work, thf–water (70:30 v/v), 25 °C, 0.1 mol dm⁻³ [NBu₄][ClO₄].

^b Data from ref. 16 in water at 25 °C, 0.5 mol dm⁻³ KNO₃. ^c Charges have been omitted for clarity. ^d Values in parentheses are standard deviations of the last significant figure.

last two protonations are compared (see Table 4). For instance, the difference between the logarithms of the first and the sixth protonation constants of L² in water is 9.15, whereas this difference for L¹ is only 5.77 in 1,4-dioxane–water. Two accumulated factors could have an effect on the observed behaviour: (i) the use of different solvents (water and mixtures of water–thf or water–1,4-dioxane) and (ii) the functionalisation with ferrocenyl groups which transform secondary amines into tertiary ones. To study the influence of the solvent the protonation constants of L⁴ have also been determined in thf–water (70:30 v/v), see Table 4. It can be noted that a reduction of the basicity behaviour for the first two protonations is also found when compared with the protonation constants obtained for L⁴ in water, whereas the last two protonation constants remain similar. Comparison between L¹ and L² in 1,4-dioxane–water (70:30 v/v) cannot be carried out owing to the fact that only four protonation constants can be determined for L² (see Table 3). In contrast all six protonation constants were determined for L² in water. This different behaviour may be explained by taking into account that an important reduction of the relative permittivity, and therefore an enhancement of the electrostatic repulsion between ammonium groups, occurs in 1,4-dioxane–water (70:30 v/v) when compared with water or thf–water (70:30 v/v).

Metal co-ordination

Solution studies directed to the determination of the stability constants for the formation of complexes of L¹ and L³ with Cu²⁺ have been carried out in 1,4-dioxane–water (70:30 v/v, 0.1 mol dm⁻³ KNO₃) for L¹ and in thf–water (70:30 v/v, 0.1 mol dm⁻³ [NBu₄][ClO₄]) for L³ (see Table 5). To evaluate the effect that the bulky ferrocenyl groups and the solvent have on L¹, potentiometric titrations of L² with copper in 1,4-dioxane–water (70:30 v/v) have also been carried out. The use of 1,4-dioxane–water mixtures significantly reduces the stability constants with copper (see Table 5). For instance the formation constant of [CuL²]²⁺ in 1,4-dioxane–water is about 10⁸ times smaller than that in water (log *K* = 24.40).¹⁶ Additionally, the logarithms of the first and second protonation constants of [CuL²]²⁺ in 1,4-dioxane–water {[CuL²]²⁺ + H⁺ ⇌ [Cu(HL²)]³⁺ and [Cu(HL²)]³⁺ + H⁺ ⇌ [Cu(H₂L²)]⁴⁺} are

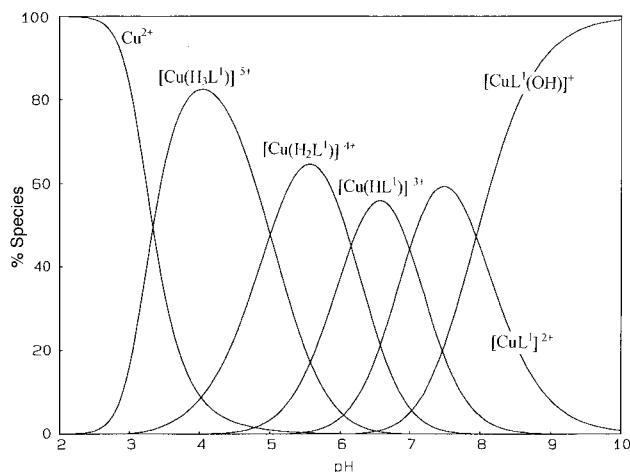


Fig. 3 Distribution diagram for the $L^1-H^+-Cu^{2+}$ system

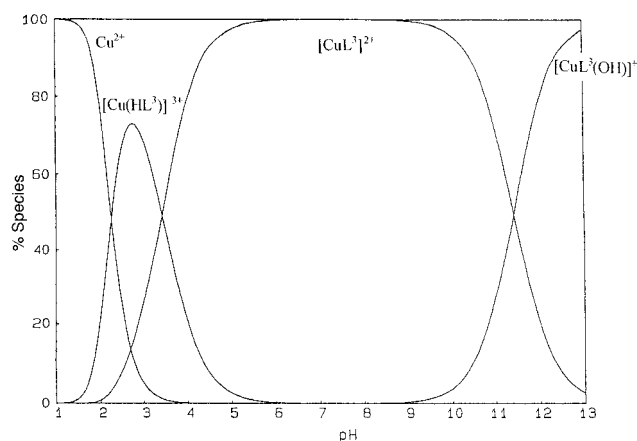


Fig. 4 Distribution diagram for the $L^3-H^+-Cu^{2+}$ system

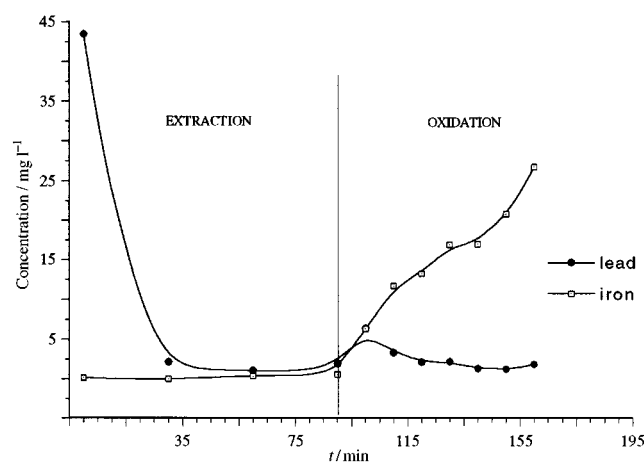


Fig. 5 Concentration of Pb^{2+} and Fe^{2+} in the aqueous phase using L^1 as extractant and of Pb^{2+} and Fe^{2+} in the aqueous phase after oxidation of the ferrocenyl groups

smaller than those of the second and third protonation constants of the free receptor suggesting that L^2 is acting as hexadentate in the $[CuL^2]^{2+}$ complex. In contrast the logarithms of the first and the second protonation constants of $[CuL^1]^{2+}$ in 1,4-dioxane-water are higher than those of the third and fourth protonation constants of L^1 suggesting that not all the nitrogen atoms are involved in the co-ordination to the copper(II) ion. This is also suggested by the smaller stability constant found for $[CuL^1]^{2+}$ in relation to that of $[CuL^2]^{2+}$ in 1,4-dioxane-water. This result appears to stand in contradiction with the crystal structure of L^1 with Cd^{2+} (see above) which shows L^1

Table 5 Stability constants ($\log K$) for the formation of copper(II) complexes of L^1 and L^2 in 1,4-dioxane-water (70:30 v/v) at 25 °C in 0.1 mol dm^{-3} KNO_3 and of L^3 in thf-water (70:30 v/v) at 25 °C in 0.1 mol dm^{-3} $[NBu^+][ClO_4^-]$

Reaction	L^1	L^2	L^3
$Cu + L + 3H \rightleftharpoons Cu(H_3L)^a$	31.60(3) ^b	—	—
$Cu + L + 2H \rightleftharpoons Cu(H_2L)$	26.6(3)	24.42(3)	—
$Cu + L + H \rightleftharpoons Cu(HL)$	20.45(2)	21.67(2)	22.48(2)
$Cu + L \rightleftharpoons CuL$	13.46(2)	16.75(2)	19.06(2)
$Cu + L + H_2O \rightleftharpoons CuL(OH) + H$	5.52(3)	9.63(2)	7.64(3)
$H + CuL \rightleftharpoons Cu(HL)$	6.99	4.92	3.42
$H + Cu(HL) \rightleftharpoons Cu(H_2L)$	6.15	2.75	—
$H + Cu(H_2L) \rightleftharpoons Cu(H_3L)$	5.00	—	—
$CuL + H_2O \rightleftharpoons CuL(OH) + H$	-7.94	-7.12	-11.4

^a Charges have been omitted for clarity. ^b Values in parentheses are standard deviations of the last significant figure.

Table 6 Extraction efficiency (E) and distribution coefficient (D) for extraction of Ni^{2+} , Cu^{2+} , Zn^{2+} , Cd^{2+} and Pb^{2+} metal ions from water using L^1 as extractant in dichloromethane

M^{2+}	$E(\%)$	D
Ni^{2+}	44	0.8
Cu^{2+}	99	99.0
Zn^{2+}	15	0.8
Cd^{2+}	64	1.8
Pb^{2+}	85	5.3

acting as hexadentate. However it has to be noted that both a different solvent and a different temperature have been used for the potentiometric studies and the synthesis of $[CdL^1][PF_6]_2$.

Compound L^3 only forms mononuclear complexes with Cu^{2+} . Fig. 4 shows the distribution diagram for the $L^3-H^+-Cu^{2+}$ system. The logarithm of the constant of the first protonation step $\{[CuL^3]^{2+} + H^+ \rightleftharpoons [Cu(HL^3)]^{3+}\}$ is smaller than that of the third $\{[H_2L^3]^{2+} + H^+ \rightleftharpoons [H_3L^3]^{3+}\}$ of the free receptor in thf-water (70:30 v/v) suggesting a M-N cleavage upon protonation and indicating that the number of nitrogens co-ordinated in $[CuL^3]^{2+}$ is four. In fact the crystal structure of $[CuL^3][ClO_4]_2$ shows the L^3 receptor acting as tetradentate.¹⁵ However the presence of four ferrocenyl groups imposes some constraints that makes the formation constant of $[CuL^3]^{2+}$ 10^8 times smaller than that of $[CuL^4]^{2+}$ ($\log K = 27.2$)¹⁷ although it is quite similar to that of $[Cu(Me_4cyclam)]^{2+}$ ($\log K = 18.3$, $Me_4cyclam = 1,4,8,11$ -tetramethyl-1,4,8,11-tetraazacyclotetradecane).

Solvent extraction

Compound L^1 is the analogous receptor to the well known L^2 molecule but with an important change in the solubility properties because of the presence of the lipophilic ferrocenyl units. Many ligands with lipophilic substituents have been reported to be able to solubilise transition-metal ions in organic solvents but to our knowledge no work has been devoted to this property using ferrocene-functionalised receptors.

To study the lipophilic properties of the ferrocenyl groups we have carried out solvent extraction experiments of the cations Ni^{2+} , Cu^{2+} , Zn^{2+} , Cd^{2+} and Pb^{2+} typically present in water, in dichloromethane using L^1 as extractant. Experiments have been carried out with and without $[NBu^+][PF_6^-]$ in the organic phase. The results obtained are in Table 6. They show a selective preference for Cu^{2+} and extraction efficiencies follow the order $Cu^{2+} > Pb^{2+} > Cd^{2+} > Ni^{2+} > Zn^{2+}$; Cu^{2+} is quantitatively extracted with an extraction efficiency up to 99% followed by Pb^{2+} which shows an efficiency of 85%. Additionally we have observed that the presence of PF_6^- anions in the organic phase enhances the distribution coefficient. For instance extraction

Table 7 Values of ΔE_i /mV for receptors L^1 and L^3 in their interaction with metal ions at five different pH values

pH	L^1 ^a					L^3 ^b				
	Ni ²⁺	Cu ²⁺	Zn ²⁺	Cd ²⁺	Pb ²⁺	Ni ²⁺	Cu ²⁺	Zn ²⁺	Cd ²⁺	Pb ²⁺
3.0	<5	<5 ^c	10	10	<5	10	38	18	<5	<5
4.5	<5	<5	12	14	<5	10	41	18	9	7
6.0	<5	10	11	8	<5	<5	58	33	18	<5
7.5	<5	12	16	16	<5	<5	87	52	31	<5
9.0	<5	8	14	14	<5	<5	90	52	31	<5

^a 1,4-Dioxane–water (70:30 v/v), 25 °C, 0.1 mol dm⁻³ KNO₃. ^b thf–water (70:30 v/v), 25 °C, 0.1 mol dm⁻³ [NBu₄][ClO₄].

efficiencies without PF₆⁻ in the organic phase for Cu²⁺ and Pb²⁺ were 85 and 47%, respectively. Extraction appears to be due to the presence of the lipophilic ferrocenyl sphere which encapsulates a hydrophilic inner binding domain [see Fig. 1(b)] as suggested by the fact that the lower extraction efficiencies were observed when the similar ferrocene-containing tetraazacycloalkane L^3 (containing four ferrocenyl groups and four N-donor sites) is used as extractant under similar conditions (for example E values for L^3 with Cu²⁺ and Pb²⁺ were 34 and 22%, respectively). However the smaller number of N-donor sites and the smaller size of the macrocyclic cavity can also be factors which could explain the different extraction efficiency of L^3 when compared with L^1 .

Metals extracted in the organic phase can usually be back-extracted using acidic water solutions. However the presence in L^1 of redox units suggests that a new method to remove the metal from the organic solution to water can be used. As the oxidation of the ferrocenyl groups decreases the affinity of the ligands for metal ions, due to electrostatic reasons, a switching mechanism could occur and the uptake or release of the central metal ion could be controlled by oxidising or reducing the ferrocenyl groups. Towards this goal we have performed oxidations on dichloromethane solutions containing the L^1 complex of Pb²⁺ in contact with an aqueous phase. Fig. 5 shows that after 0.5 h the extraction of lead into the organic phase is complete. Subsequent oxidation of the ferrocenyl groups shows, after 1 equivalent of electrons, an increase of the Pb²⁺ concentration in water but further oxidation to six electrons makes [Pb²⁺] decrease again. This behaviour could be explained by assuming that a chemical reaction is coupled to the electrochemical one as suggested by the fact that the iron concentration increases in the aqueous phase as the oxidation in the organic phase progresses, indicating that some kind of decomposition of L^1 takes place preventing back extraction of Pb²⁺ to water. This is in line with the chemical instability observed for the oxidised form of L^1 obtained by electrolysis of dichloromethane solutions of L^1 . Further studies are being carried out using other redox-active systems.

Electrochemical behaviour

The main interest in the L^1 and L^3 receptors is the incorporation of redox centres near binding sites. This gives the ability to recognise substrates electrochemically. Part of the electrochemical behaviour of L^3 has been published elsewhere.¹⁸ The electrochemical study has been performed in 1,4-dioxane–water (70:30 v/v) for L^1 (25 °C, 0.1 mol dm⁻³ KNO₃), and thf–water (70:30 v/v) for L^3 (25 °C, 0.1 mol dm⁻³ [NBu₄][ClO₄]). The redox potential of L^1 and L^3 is, as expected, pH-dependent. When the pH was decreased a steady displacement of E_i to more anodic potentials was observed. The difference found between the oxidation potential at basic (12) and acidic pH (0) obtained by extrapolation of the curves E_i versus pH was 67 and 68 mV for L^1 and L^3 respectively. We have also electrochemically studied the variation of E_i versus pH for the L–H⁺–M²⁺ systems (L = L^1 or L^3 ; M = Ni²⁺, Cu²⁺, Zn²⁺, Cd²⁺ or Pb²⁺; M²⁺:L molar ratio = 1:1). In order to rationalise all these data

Table 8 Determination of the concentration of Cu²⁺ in the presence of Pb²⁺ with receptor L^3 (pH 7.0) from current measurements at the fixed potential of 455 mV vs. SCE

10 ⁴ [Cu ²⁺]/mol dm ⁻³	0.79(6) ^c [0.73]
0.69(6) ^a [0.74] ^b	1.3(2) [1.4]
1.3(2) [1.3]	1.6(2) [1.7]

^a Determined by electrochemical methods. Values in parentheses are the standard deviations of the last significant digit. ^b Determined by standard methods. ^c Determined in the presence of [Pb²⁺] = 2.6 × 10⁻⁴ mol dm⁻³.

the difference found between E_i for the receptor–metal system and that for the free receptor [$\Delta E_i = E_i(\text{receptor–metal}) - E_i(\text{receptor})$] has been monitored at five different pH values from 3 to 9. To screen the electrochemical receptor response for each metal ion, ΔE_i has been measured by rotating-disc electrode experiments (scan speed 10 mV s⁻¹, rotation speed 7000 revolutions min⁻¹); the values found at different pH values for receptors L^1 and L^3 are shown in Table 7. Compound L^1 shows a poor shift of E_i ($\Delta E_i < 20$ mV), whereas L^3 is selective for Cu²⁺, Zn²⁺ or Cd²⁺ in a wide pH range over Ni²⁺ and Pb²⁺.

One of the most promising applications of redox-active systems would be the development of modified electrodes and their use as amperometric sensors. The shift of E_i in redox systems has been suggested as a method for considering that there is a recognition process, but another approach could be the monitoring of the current at a fixed potential. We have checked this possibility using receptor L^3 and Cu²⁺ and measured the current at the fixed potential of 455 mV vs. SCE (pH 7.0) when increasing amounts of Cu²⁺ were added to a solution of L^3 . The current decreases when Cu²⁺ is added until a 1:1 molar ratio is reached. A linear relationship is observed between the intensity and the Cu²⁺ concentration from [Cu²⁺]/[L^3] = 0 to 0.9. Table 8 shows the quantitative determination of Cu²⁺ from the decrease in current at a fixed potential in thf–water (70:30 v/v). The concentration is compared to that obtained from standard methods. The selectivity in Table 7 can be confirmed by the fact that Cu²⁺ can also accurately be determined in the presence of Pb²⁺.

As was observed by one of the referees, there is no clear relation between the electrochemical receptor response for metal ions and the extraction power of L^1 and L^3 . The receptor response of L^3 is better than that of L^1 but L^1 is a better extractant. This has to be related with the better lipophilicity of L^1 when compared with that of L^3 . In fact both processes, metal extraction and electrochemical response, are quite different. The parameter ΔE_i does not give necessarily a good evaluation of the receptor affinity for cations. We have found, at least in aqueous solution, that a selective electrochemical response along with large ΔE_i values can be related with (i) the presence of predominant receptor–metal complexes in a wide pH range (see below), (ii) the existence of pH ranges of selective complexation.¹⁵

The oxidation potential of L^1 and L^3 decreases when the pH increases. Qualitatively we can understand this behaviour by

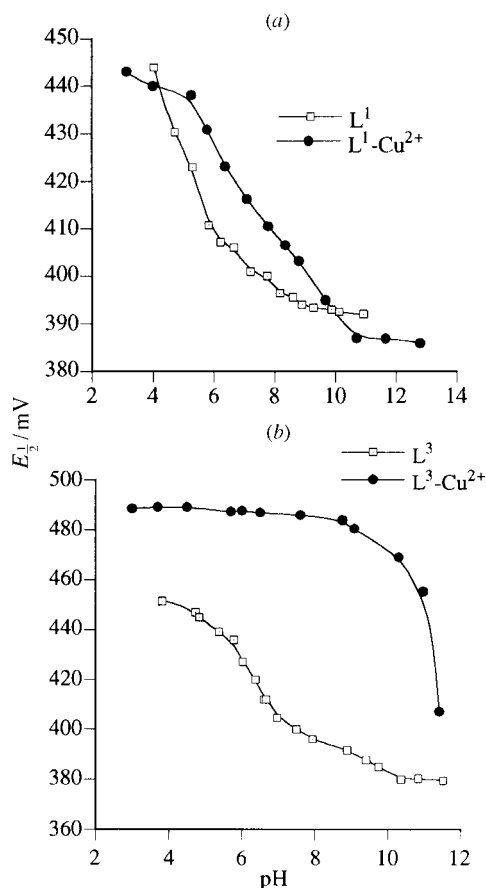


Fig. 6 Plots of $E_{1/2}$ vs. pH for (a) L^1-H^+ and $L^1-H^+-Cu^{2+}$, (b) L^3-H^+ and $L^3-H^+-Cu^{2+}$

taking into account that a steady change from highly charged species (more difficult to oxidise due to electrostatic repulsion between the positively charged electrode and the positively charged species) to neutral species is found (from H_nL^{n+} to L). A similar steady change from +5 charged species $[Cu(H_3L)]^{5+}$ to +1 species $[CuL^1(OH)]^+$ was observed in the $L^1-H^+-Cu^{2+}$ system (see the distribution diagram in Fig. 3). In contrast, L^3 forms the complex $[CuL^3]^{2+}$ with Cu^{2+} which is predominant (see distribution diagram in Fig. 4). That behaviour is reflected in the electrochemistry of the L^3-Cu^{2+} system in which $E_{1/2}$ does not change when the pH changes over a wide range (see Fig. 6 where a comparison between the $E_{1/2}$ vs. pH curves for the $L^1-H^+-Cu^{2+}$ and $L^3-H^+-Cu^{2+}$ systems is shown). Taking into account that a steady shift of $E_{1/2}$ is observed for polyamines when the pH changes, the formation of predominant species with metal ions over a wide pH range leads to large $\Delta E_{1/2}$ values. In fact the highest shift found in the presence of transition-metal ions was for the L^3 receptor with Cu^{2+} ($\Delta E_{1/2} = 90$ mV).

In order to evaluate the role played by the water, the electrochemical recognition ability of receptors against transition-metal ions has also been studied in aprotic solvents such as acetonitrile. Protonation of amine groups is not possible in this solvent and we have found that the oxidation potential shift, $\Delta E_{1/2}$, was approximately always the same for all metal ions. Differences of selectivity in aqueous solution have therefore to be attributed to the rich chemistry (with a large number of species in solution as described above in the potentiometric experiments) of these systems in the presence of water.

Conclusion

The new redox-active polyazacycloalkane L^1 and the related ferrocene-functionalised L^3 receptor have been characterised. Metal extraction into dichloromethane from water using L^1 as extractant has been carried out. The idea of back extraction to

water by oxidation of the ferrocenyl groups has been tested, but the chemical instability of the oxidised form of L^1 prevents back-extraction processes. However the idea of redox-switchable extraction is an appealing one and further work is now in progress. Additionally L^1 and L^3 have the ability to recognise metal ions electrochemically. The combination of electrochemical and potentiometric techniques appears to indicate that the existence in solution of predominant receptor-metal complexes over a wide pH range (as was found for the $[CuL^3]^{2+}$ complex) can lead to a large electrochemical response.

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