1,15-Diferrocenyl-2,5,8,11,14-pentaazapentadecane, an Open-Chain Redox-Active Ferrocene-Functionalized Polyazaalkane Ligand for Anions

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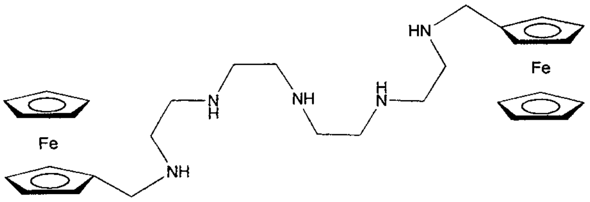
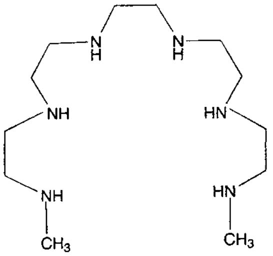
The interaction of the ferrocene-functionalized open-chain polyazaalkane 1,15-diferrocenyl-2,5,8,11,14-pentaazapentadecane (L^1) with the sulfate, phosphate, and ATP anions has been studied by potentiometric methods in THF/H_2O 70:30 (*v*/*v*) (containing 0.1M $(Bu_4N)ClO_4$ at 25°). Additionally, the electrochemical response of L^1 in the presence of H^+, HSO_4^-, $H_2PO_4^-$, Br^-, and Cl^- in a non-aqueous solvent such as MeCN has been studied. A remarkable cathodic shift of the ferrocene oxidation potential was induced for phosphate (198 mV) and sulfate (145 mV) showing an EC mechanistic response. Competitive electrochemical studies showed that L^1 is able to electrochemically and selectively recognize HSO_4^- *vs.* $H_2PO_4^-$ in a mixture of both anions in MeCN.

Introduction. – We have recently been involved in the design and synthesis of redox-functionalized molecules for electrochemical sensing of heavy-metal ions and anions of environmental and biological interest, such as phosphate, ATP, *etc.*, in aqueous environments [1–9]. These redox-functionalized molecules contain electroactive moieties (usually ferrocene), which are covalently attached to amino groups that can interact with anions in aqueous environments *via* positively charged ammonium groups or *via* H-bonding [10–12]. Two techniques have been mainly used for the study of these systems, standard electrochemical methods and potentiometric techniques. The first gives information about the shift of the oxidation potential of the ferrocenyl groups upon guest binding [13–16], whereas the second analyzes the different species formed in solution as a function of pH [17][18]. This allows deduction of which species are responsible for the oxidation potential shift of the ferrocenyl groups at a certain pH. These studies serve as an aid to rationalize the sensing behavior of the electro-active ligands in aqueous environments. We have recently reported the synthesis, characterization, and electrochemical behavior of the open-chain polyazaalkane molecule 1,5-diferrocenyl-2,5,8,11,14-pentaazapentadecane (L^1) in aqueous solution toward sulfate, phosphate, and ATP [7]. That study is herein complimented by the potentiometric determination of the stability constants of L^1 with the sulfate, phosphate, and ATP anions in the same medium in which the electrochemical experiments were carried out. Additionally, we have also studied the interaction of this ligand with protons and selected anions in a non-aqueous solvent (MeCN) and have compared electrochemical behavior of L^1 in this medium with the previously reported results for THF/H_2O 70:30 (*v*/*v*).



L^1



L^2

Results and Discussion. – *Potentiometric Studies.* The protonation behavior of L^1 has been studied by potentiometry in THF/H_2O 70:30 (*v*/*v*) (containing 0.1M $(Bu_4N)ClO_4$, 25°). The ligand L^1 contains five secondary amino groups and behaves as a pentaprotic base. *Table 1* shows the stepwise protonation constants (log *K*) of L^1 in THF/H_2O 70:30 (*v*/*v*) and in H_2O [7]. By comparison of the protonation constants, it can be noticed that there is a reduction of the basicity of L^1 in THF/H_2O. All stepwise protonation processes occur at lower pH values in THF/H_2O than in H_2O. For instance, the difference between the logarithms of the first and fifth protonation constants in H_2O is 6.94, whereas this difference is 6.11 in THF/H_2O. This decrease in the basicity in

Table 1. *Stepwise Protonation Constants (*log *K) of L^1 in THF/H_2O* (at 298.1 K in 0.1 mol · dm^{-3} Bu_4NClO_4) *and in H_2O* (at 298.1 K in 0.1 mol · dm^{-3} KNO_3)

Reaction	log *K* (THF/H_2O)	log *K* (H_2O)[a]
$L^1 + H \rightleftharpoons HL^1$ [b])	9.03(1)[c])	9.79(1)
$L^1 + 2\,H \rightleftharpoons H_2L^1$	16.60(1)	18.87(1)
$L^1 + 3\,H \rightleftharpoons H_3L^1$	22.57(1)	26.53(1)
$L^1 + 4\,H \rightleftharpoons H_4L^1$	26.08(1)	31.52(2)
$L^1 + 5\,H \rightleftharpoons H_5L^1$	29.00(1)	34.37(2)
$L^1 + H \rightleftharpoons HL^1$	9.03	9.79
$HL^1 + H \rightleftharpoons H_2L^1$	7.57	9.08
$H_2L^1 + H \rightleftharpoons H_3L^1$	5.97	7.66
$H_3L^1 + H \rightleftharpoons H_4L^1$	3.51	4.99
$H_4L^1 + H \rightleftharpoons H_5L^1$	2.92	2.85

[a]) Data from [7]. [b]) Charges have been omitted by clarity. [c]) Values in parentheses are standard deviations in the last significant digit.

H_2O/organic solvent mixtures, when compared with the basicity found in H_2O, has also been observed for other related polyammonium ligands [6].

Potentiometric studies of the anions sulfate, phosphate, and ATP with L^1 have also been carried out in THF/H_2O 70:30 (*v*/*v*) (containing 0.1M Bu_4NClO_4 at 25°). In *Table 2*, the stability constants found in this medium are listed. Sulfate forms with L^1, over a wide pH range, the complexes $[L^1HSO_4]^-$, $[L^1H_2SO_4]$, $[L^1H_3SO_4]^+$, $[L^1H_4SO_4]^{2+}$, and $[L^1H_5SO_4]^{3+}$. Generally, when both ligand and anion display protonation processes in the pH range studied, the determination of the nature of the complexes in solution is not straightforward when one takes into account only stability-constant values. However, that is not the case for sulfate. The logarithm of the last protonation constant for L^1 $(H_4L^1)^{4+} + H^+ \rightleftharpoons (H_5L^1)^{5+}$ is 2.92, whereas the first protonation constant of the sulfate anion SO_4^{2-} is 3.44. Both stability constants have a similar value, and, it can therefore, be argued that the species in the L-H^+-sulfate systems are related to the interaction of the dianion SO_4^{2-} with the $(H_jL^1)^{j+}$ cations. This is especially true for the $[L^1HSO_4]^-$, $[L^1H_2SO_4]$, $[L^1H_3SO_4]^+$, $[L^1H_4SO_4]^{2+}$ species, whereas the nature of the $[L^1H_5SO_4]^{3+}$ complex could involve the interaction of $(H_5L^1)^{5+}$ and SO_4^{2-}, or the interaction of $(H_4L^1)^{4+}$ and HSO_4^-.

Table 2. *Logarithms of the Stability Constants for the Interaction of L^1* with *Sulfate, Phosphate, and ATP in THF/H_2O 70:30* (*v*/*v*) (at 298.1 K in 0.1 mol · dm^{-3} Bu_4NClO_4)

Reaction	Sulfate	Phosphate	ATP
$L^1 + H + A \rightleftharpoons HL^1A$[a])	12.60(4)[b])		
$L^1 + 2\ H + A \rightleftharpoons H_2L^1A$	20.78(2)		
$L^1 + 3\ H + A \rightleftharpoons H_3L^1A$	27.29(2)	32.56(3)	30.23(3)
$L^1 + 4\ H + A \rightleftharpoons H_4L^1A$	31.05(2)	40.78(1)	37.39(2)
$L^1 + 5\ H + A \rightleftharpoons H_5L^1A$	33.49(4)	47.28(1)	41.50(3)
$L^1 + 6\ H + A \rightleftharpoons H_6L^1A$		51.58(2)	
$HL^1 + A \rightleftharpoons HL^1A$	3.57		
$H_2L^1 + A \rightleftharpoons H_2L^1A$	4.18		
$H_3L^1 + A \rightleftharpoons H_3L^1A$	4.72	9.99	7.66
$H_4L^1 + A \rightleftharpoons H_4L^1A$	4.97	14.7	11.31
$H_5L^1 + A \rightleftharpoons H_5L^1A$	4.49	18.28	12.5
$H_5L^1 + HA \rightleftharpoons H_6L^1A$		10.35	
$H_2L^1 + HA \rightleftharpoons H_3L^1A$		4.11	
$H_3L^1 + HA \rightleftharpoons H_4L^1A$		6.36	
$H_4L^1 + HA \rightleftharpoons H_5L^1A$		9.35	

[a]) Charges have been omitted for clarity; A = anion. [b]) Values in parentheses are the standard deviations in the last significant digit.

With phosphate and ATP, the nature of the complexes formed in solution is less clear. Both ATP and phosphate also form complexes with L^1 over a wide pH range (from pH *ca.* 10). The logarithm of the first protonation constant for ATP ($ATP^4 + H^+ \rightleftharpoons HATP^{3-}$) is 7.72. There is a large difference between this value and the last protonation process of the free L^1, and, therefore, it is difficult to determine which are the species involved in the formation of the $[L^1H_jATP]^{j-4}$ complexes. The logarithm of the first protonation constant for phosphate ($PO_4^{3-} + H^+ \rightleftharpoons HPO_4^{2-}$) is 12.23 in THF/water 70:30 (*v*/*v*). Even the last protonation process for phosphate has a quite high value (log $K = 4.55$ for $H_2PO_4^- + H^+ \rightleftharpoons H_3PO_4$). At least one complex must be related to HPO_4^{2-} species bearing in mind that the complex $[LH_6PO_4]^{3+}$, which probably involves interaction of HPO_4^{2-} and $(H_5L^1)^{5+}$ or $H_2PO_4^-$ and $(H_4L^1)^{4+}$ has been found to exist. The distribution diagram of the species for the system L-H^+-phosphate is shown in *Fig. 1.*

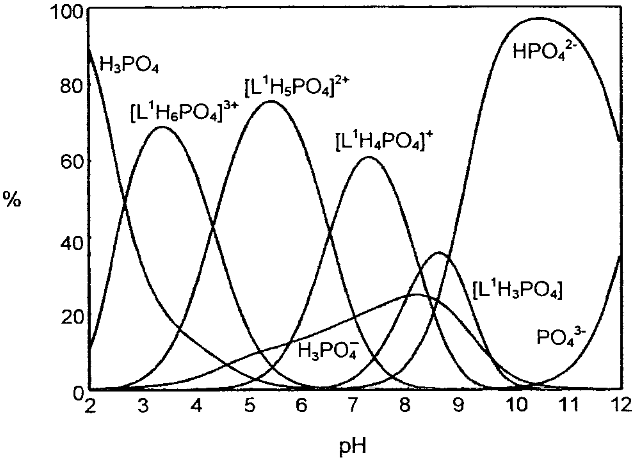


Fig. 1. *Distribution diagram of the species for the system L^1-H^+-phosphate*

The stability constants for L^1 with ATP, phosphate, and sulfate found in THF/H_2O 70:30 (*v*/*v*) appear to be higher than the stability constants reported for related molecules with the same anions in H_2O. For instance, L^1 forms more stable complexes with ATP in THF/H_2O than the analogous hexaprotic ligand L^2 with ATP in H_2O [20]. For the L^2-H^+-ATP system, the constants range from log $K = 2.89$ for $(H_3L^2)^{3+} + ATP^{4-} \rightleftharpoons [L^2H_3ATP]^-$ to log $K = 9.86$ for $(H_6L^2)^{6+} + ATP^{4-} \rightleftharpoons [L^2H_6ATP]^{2+}$; log $K = 7.47$ for $(H_5L^2)^{5+} + ATP^{4-} \rightleftharpoons [L^2H_5ATP]^+$. In our case, log $K = 7.66$ for $(H_3L^1)^{3+} + ATP^{4-} \rightleftharpoons [L^1H_3ATP]^-$ and log $K = 12.5$ for $(H_5L^1)^{5+} + ATP^{4-} \rightleftharpoons [L^1H_5ATP]^+$. This behavior probably reflects the different dielectric constant of H_2O and THF/H_2O mixture. Whereas permittivity in H_2O is 78, it must be *ca.* 54 in THF/water 70:30 (*v*/*v*), a reduction which would tend to enhance the electrostatic anion-cation interaction reflected in the values of the stability constants for the L^1 ligand with ATP found by potentiometric methods.

Anion-ligand stability constants can also be used to detect selectivity and determine the prevailing species in a mixture of a couple of anions in solution. This could be of some importance for the design and development of selective electrochemical sensing systems to discriminate between target anions. It has been suggested that a method to determine the relative selectivity of a ligand with a couple of anions is to plot diagrams of ternary systems L/H^+/anion 1/anion 2 by means of the calculation of the overall percentages of each anion bound to the ligand over a determined pH range. Towards this goal, we have plotted the distribution diagram of the ternary phosphate/ATP/L and sulfate/ATP/L^1 systems (*Fig. 2*).

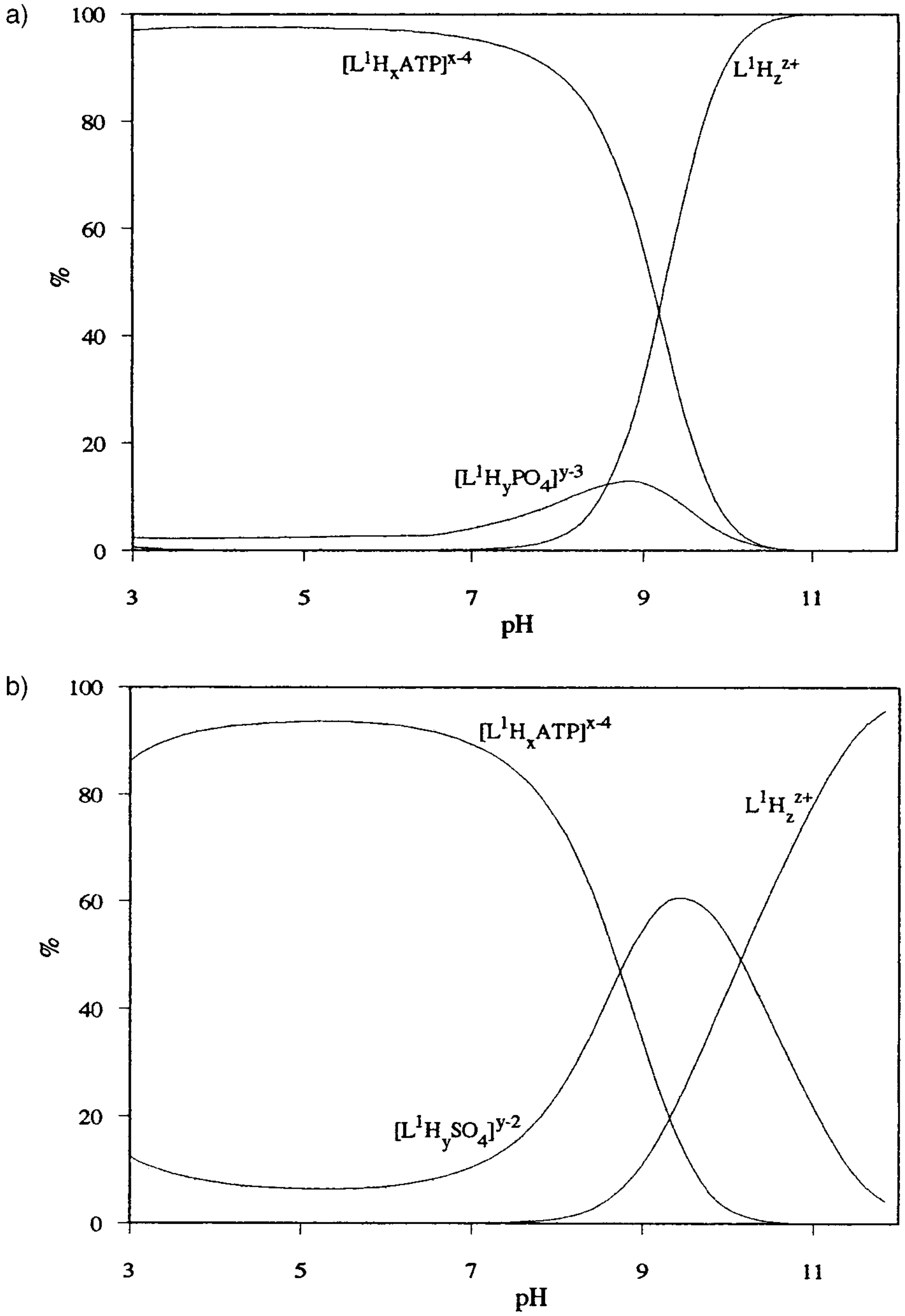


Fig. 2. *Distribution diagrams for the ternary system phosphate/ATP/L^1* (a) *and sulfate/ATP/L^1* (b). The sum of percentages of complexed species is plotted *vs.* pH.

The ternary phosphate/ATP/L^1 diagram appears to be in agreement with the electrochemical result we have recently reported in THF/H_2O 70:30 (*v*/*v*). We described that there was an electrochemical shift of up to 50 mV of the oxidation potential of the ferrocenyl groups in the presence of ATP at pH 5. It was also interesting to observe that neither phosphate nor nitrate perturbed the oxidation potential of the ligand in the pH range of 5–7 where the ATP response is significant. In fact, it was demonstrated that ATP could be quantitatively determined in the presence of phosphate or nitrate in THF/H_2O solutions at pH 4.9. The ternary diagrams reinforce the interpretation of selective ATP binding in the presence of phosphate. In the case where an equimolar amount of ATP and phosphate, in the presence of L^1, there is a selective complexation of ATP. The species $[L^1H_jATP]^{j-4}$ is present at higher than 95% over a wide pH range. Additionally, *Fig. 2,b*, displays the pH-dependent selective behavior of the ATP/sulfate couple, with ATP complexes predominant at acidic and neutral pH, and sulfate complexes predominant at basic pH.

Electrochemical Anion-Recognition Studies. – The electrochemical behavior of L^1 has been studied in dry MeCN to evaluate its electrochemical response to the bromide, chloride, HSO_4^-, and $H_2PO_4^-$ anions in this medium. Electrochemical recognition of anionic guest species has attracted great attention in recent years due to their potential application in fabrication of amperometric sensory devices or as sensing ligands for the electrochemical recognition of substrates.

The cyclic-voltammetry (CV) studies were carried out in MeCN, freshly distilled from CaH_2, with $(Bu_4N)ClO_4$ as supporting electrolyte. The CV data of L^1, and of L^1 in the presence of protons, are listed in the *Table 3*. The ligand L^1 displays a single wave, corresponding to a two-electron process, with a ratio between cathodic peak intensity and anodic peak intensity ip_c/ip_a of *ca.* 0.9–0.95, and with a difference between the oxidation and reduction wave potentials, E_{pa} and E_{pc}, of *ca.* 114 mV (ferrocene under the same experimental conditions gave $i_{pc}/i_{pa} = 1$ and $E_{pa} - E_{pc} = 80$ mV). The addition of protons (5 equiv.) caused an anodic shift of the oxidation potential ($\Delta E = 105$ mV) and a decrease of the wave intensity, probably due to the increase of the diffusion coefficient upon protonation.

Table 3. *Voltammetric Data for L^1 and for L^1 in the Presence of Protons in Dry MeCN in 0.1 mol·dm^{-3} Bu_4NClO_4*[a])

	E_{pa}/V	E_{pc}/V	$E_{1/2}$/V	E_{ac}/mV	i_{pa}/i_{pc}
L^1	0.50	0.39	0.44	114	0.95
$L^1 + H$	0.61	0.48	0.54	124	1.00

[a]) E_{pa} and E_{pc} are the oxidation and reduction wave potential on the CV; $E_{1/2} = (E_{pa} + E_{pc})/2$; $E_{ac} = (E_{pa} - E_{pc})$; i_{pa} and i_{pc} are the oxidation and reduction wave currents.

The electrochemical behavior with anions was recorded after progressive addition of stoichiometric equivalents of anionic guests as their Bu_4N^+ salts. The results are gathered in *Table 4*. The addition of Bu_4NBr or Bu_4NCl (up to 5 equiv.) to solutions of L^1 produced a small anodic shift of the oxidation potential ($\Delta E = 11$ and 45 mV, resp.), which may have been caused by some degree of protonation due to the hydroscopic nature of Bu_4N^+ salts. Successive additions of HSO_4^- (5 equiv.) to an MeCN solution of

Table 4. *Electrochemical Response for L^1 vs. Selected Anions in Dry MeCN in 0.1 mol · dm^{-3} Bu_4NClO_4*

	ΔE[a]) [mV] (±5 mV)
$L^1 + H_2PO_4^-$	–198
$L^1 + HSO_4^-$	–145
$L^1 + Cl^-$	45
$L^1 + Br^-$	11
$L^1 + (H_2PO_4^- + HSO_4^-)$	–139

[a]) ΔE is defined as E_{pa} (ligand + anion) – E_{pa} (free ligand)

L^1 led to a cathodic shift of 145 mV, as is shown in *Fig. 3*. The voltammetric wave becomes irreversible with a difference between E_{pa} and E_{pc} of 360 mV. The observed EC mechanism is an indication of the interaction between HSO_4^- and the ferricinium cation formed upon oxidation of ferrocene. Further addition of sulfate had no effect. In a similar manner, the addition of $H_2PO_4^-$ to MeCN solutions of L^1 produced a significant decrease of the ferrocenyl-oxidation current peak and a cathodic shift of the oxidation potential ($\Delta E = 198$ mV). As in the case of HSO_4^-, it is noteworthy that the shape of the oxidation wave changes from that of a reversible redox process to that of an irreversible EC mechanism. Additional studies were carried out, varying the conditions under which the cyclic voltammograms were recorded. Scan speed was varied from 10 to 500 mV/s, voltammetry was performed at two different temperatures (0° and 25°), and Au and Pt electrodes were used without any significant modification of the electrochemical behavior. Due to its insolubility, ATP could not be studied in MeCN. The electrochemical shifts in the oxidation potential of L^1 in MeCN measured in the presence of phosphate or sulfate were larger than the shift found for the same

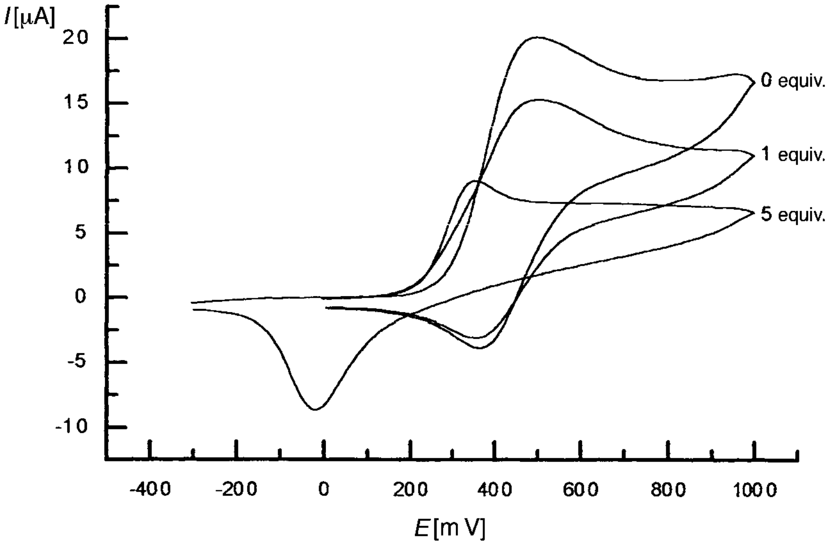


Fig. 3. *Electrochemical Data for L^1 with Stoichiometric Equivalents of Sulfate in MeCN at 298.1 K in 0.1 mol · dm^{-3} Bu_4NClO_4*

anions in H_2O. Whereas in MeCN values of ΔE larger than 150–200 mV are quite usual, in aqueous environments the electrochemical shifts reported are smaller. The protonated amine binds the anion through a combination of electrostatic forces and H-bonding interactions. When ferrocene is oxidized to ferricinium, additional electrostatic attraction between the positively charged ferricinium group and the anion is possible. In fact, this ferricinium-anion interaction is probably responsible for the electrochemical shift found during cyclic-voltammetry measurements. Taking into account that the electrostatic nature of the cation(ferricinium)-anion interaction would be influenced by the dielectric constant of the solvent (which is larger in H_2O than in MeCN, see below), a larger electrochemical shift would be expected in MeCN than in H_2O.

We have also carried out competition studies of the HSO_4^- and $H_2PO_4^-$ anions. When electrochemical studies of L^1 were carried out in the presence of both HSO_4^- and $H_2PO_4^-$ anions, the cathodic shift observed ($\Delta E = 139$ mV) was very similar to the shift observed for HSO_4^-, suggesting that L^1 is able to selectively recognize HSO_4^- *vs.* $H_2PO_4^-$ electrochemically.

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Experimental Part

The synthesis of L^1 has been described in [7]. Potentiometric titrations were carried out in THF/H_2O 70 : 30 (*v*/*v*) (containing 0.1M $(Bu_4N)ClO_4$ at 298.1 K) in a water-thermostatted reaction vessel at 298.1 ± 0.1 K under N_2. Exper. potentiometric details have been published previously [8]. The computer program SUPERQUAD [19] was used to calculate the protonation and stability constants. The titration curves for each system (*ca.* 250 exper. points corresponding to at least three titration curves, $pH = -\log[H]$ range investigated from 2.5 to 10, concentration of the ligands and metal ion *ca.* 1.5×10^{-3} mol dm^{-3}) were treated either as a single set or as separate entities without significant variations in the values of the stability constants. Finally, the data sets were merged and treated simultaneously to give the stability constants. Electrochemical data were collected in dry MeCN (containing 0.1M of Bu_4NClO_4 at 298.1 K) with a programmable function generator *Tacussel IMT-1*, connected to a *Tacussel PJT 120-1* potentiostat. The working electrode was graphite with a sat. calomel reference electrode separated from the test soln. by a slat bridge containing the solvent/supporting electrolyte. The auxiliary electrode was Pt wire. Voltammograms were obtained at 100 mV s^{-1}.

REFERENCES

[1] M. J. L. Tendero, A. Benito, R. Martínez-Máñez, J. Soto, J. Payà, A. J. Edwards, P. R. Raithby, *J. Chem. Soc., Dalton Trans.* **1996**, 343.

[2] M. J. L. Tendero, A. Benito, R. Martínez-Máñez, J. Soto, E. García-España, J. A. Ramírez, M. I. Burguete, S. V. Luis, *J. Chem. Soc., Dalton Trans.* **1996**, 2923.

[3] M. J. L. Tendero, A. Benito, R. Martínez-Máñez, J. Soto, *J. Chem. Soc., Dalton Trans.* **1996**, 4121.

[4] M. E. Padilla-Tosta, R. Martínez-Máñez, T. Pardo, J. Soto, M. J. L. Tendero, *Chem. Commun.* **1997**, 887.

[5] J. M. Lloris, R. Martínez-Máñez, T. Pardo, J. Soto, M. E. Padilla-Tosta, *Chem. Commun.* **1998**, 837.

[6] J. M. Lloris, R. Martínez-Máñez, T. Pardo, J. Soto, M. E. Padilla-Tosta, *J. Chem. Soc., Dalton Trans.* **1998**, 2635.

[7] J. M. Lloris, R. Martínez-Máñez, M. E. Padilla-Tosta, T. Pardo, J. Soto, M. J. L. Tendero, *J. Chem. Soc., Dalton Trans.* **1998**, 3657.

[8] J. M. Lloris, A. Benito, R. Martínez-Máñez, M. E. Padilla-Tosta, T. Pardo, J. Soto, M. J. L. Tendero, *Helv. Chim. Acta* **1998**, *81*, 2024.

[9] P. D. Beer, J. Cadman, J. M. Lloris, R. Martínez-Máñez, M. E. Padilla-Tosta, T. Pardo, D. K. Smith, J. Soto, *J. Chem. Soc., Dalton Trans.* **1999**, 127.

[10] P. D. Beer, Z. Chen, M. G. B. Drew, J. Kingston, M. Ogden, P. Spencer, *J. Chem. Soc., Chem. Commun*. **1993**, 1046.
[11] P. D. Beer, Z. Chen, M. G. B. Drew, A. O. M. Johnson, D. K. Smith, P. Spencer, *Inorg. Chim. Acta* **1996**, *246*, 143.
[12] P. D. Beer, M. G. B. Drew, D. K. Smith, *J. Organomet. Chem.* **1997**, *543*, 259.
[13] H. Plenio, H. El-Desoky, J. Heinze, *Chem. Ber.* **1993**, *126*, 2403.
[14] H. Plenio, J. Yang, R. Diodone, J. Heinze, *Inorg. Chem*. **1994**, *33*, 4098.
[15] H. Plenio, D. Burth, *Organometallics*, **1996**, *15*, 4054.
[16] P. D. Beer, *Acc. Chem. Res.* **1998**, *31*, 71.
[17] A. Bencini, A. Bianchi, C. Giorgi, P. Paoletti, B. Valtancoli, V. Fusi, E. García-España, J. M. Llinares, J. A. Ramírez, *Inorg. Chem*. **1996**, *35*, 1114.
[18] J. Aragó, A. Bencini, A. Bianchi, E. García-España, M. Micheloni, P. Paoletti, J. A. Ramírez, P. Paoli, *Inorg. Chem*. **1991**, *30*, 1843.
[19] P. Gans, A. Sabatini, A. Vacca, *J. Chem. Soc., Dalton Trans.* **1985**, 1195.
[20] A. Andrés, J. Aragó, A. Bencini, A. Bianchi, A. Domenech, V. Fusi, E. García-España, P. Paoletti, J. A. Ramírez, *Inorg. Chem*. **1993**, *32*, 3418.

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