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Ferrocene-Based Small Molecules for Multichannel Molecular Recognition of Cations and Anions

Pedro Molina,*[a] Alberto Tárraga,[a] and Antonio Caballero[a]

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This manuscript provides a summary of the relatively large body of research on the preparation and sensing properties of ferrocenes containing nitrogen functionalities, which have been mainly developed by our research group. After a general overview of the topic, selected recent advances in this field are described. In particular, new acyclic and cyclic structural motifs, in which the ferrocene unit is linked by unsaturated aza bridges (azadiene, azine, urea, guanidine, azaheterocycles) to a chromogenic or fluorescent signalling unit. Attention is drawn to the electrochemical and optical properties of these aza-substituted ferrocene derivatives as well as their use in multichannel molecular recognition processes towards metal cations and anions.

Introduction

The design of molecular receptors having the ability to selectively bind and sense cations, anions or even neutral molecules by a macroscopic physical response is an area of intense activity. In this context, ferrocene has largely proved to be a simple and remarkably robust building block for the preparation of derivatives, most of which are substituted with macrocyclic ligands, which have been considered as prototype chemosensor molecules displaying interesting electrochemical sensing properties.[1] In ferrocene-containing macrocyclic ligands, 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 complexation ability of the ligand can be switched on and off by varying the applied electrochemical potential. The magnitude of the shift in the redox potential produced by guest binding is a factor of primary importance. In particular, it has been suggested that an added degree of recognition is conferred by the appearance of a new set of redox waves (*two-wave behaviour*) associated with the oxidation of the ferrocenyl subunits in the host–guest complex, as compared with a single gradual shift in the potential of the original ferrocene redox couple.[2]

The redox-active ferrocene moiety has also been exploited in the electrochemical sensing of anions, both in organic and aqueous media.[3] Electrochemical ferrocene-based receptors for anions are expected to show cathodic shifts in their redox process when complexed to an anion, as they are easier to oxidize or harder to reduce than a free redox-active receptor. In this context, ferrocene units appended with secondary amides have been used for anion recognition.[4] Being neutral, these receptors have no inherent electrostatic attraction for anions, which makes the stability constants smaller than those of the analogous cobaltocenium systems. Electrostatic interaction can, however, be switched on by oxidation of the ferrocene group to the ferrocenium ion, and consequently these molecules exhibit interesting electrochemical anion-recognition effects. Ferrocenyl dendrimers exhibiting anionic electrochemical recognition properties by taking advantage of the dendritic effect have also been described.[5]

The magnitude of the electrochemical shift ($\Delta E_{1/2}$) upon complexation provides important thermodynamic information. The shift in redox potential upon complexation is related to the ratio of the complexation constants, as described by the equation $\Delta E_{1/2} = (RT/nF)\ln(K_{red}/K_{ox})$, where K_{red} is the guest binding constant for the neutral unoxidized redox-responsive ligand and K_{ox} is the guest binding constant for its oxidized form. The quantity K_{red}/K_{ox} has been defined by Beer et al.[1b,6] as reaction coupling efficiency (RCE), whereas the quantity K_{ox}/K_{red} has been defined as binding enhancement factor (BEF), and represents a quantitative measure of the perturbation of the redox centre induced by complexation to the receptor unit.

Binding at a proximate site can also affect the UV/Vis properties of the ferrocene unit. In general, metal complexation or protonation induces bathochromic shifts in the lower-energy, spin-allowed ferrocene absorption band, which is between 400 and 500 nm.[7] The field of research dealing with dual fluorescent and redox ferrocene-based chemosensors is still in its infancy, probably because ferrocene derivatives are known to be efficient fluorescence

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[a] Departamento de Química Orgánica, Universidad de Murcia,
Facultad de Química,
Campus de Espinardo, 30100 Murcia, Spain
Fax: +34-968364149
E-mail: pmolina@um.es

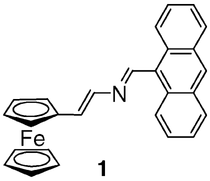
quenchers.[8] These kinds of probes contain one or several ferrocene units, a complexing moiety and one or several fluorescent moieties. In the absence of a guest, the ferrocene residue acts as a quencher for the fluorescent unit, through the involvement of a photoinduced electron-transfer process. In the presence of a guest, the fluorescence revival observed is the result of the inhibition of this mechanism.[9]

The current microreview provides an overview of the studies on aza-substituted ferrocene receptors, placing significant emphasis on the work done by our research group, without relegating the very important work done by other groups. From the standpoint of our own group, selective multichannel recognition of metal cations, especially heavy- and transition-metal cations, has been achieved with acyclic or cyclic (ferrocenophanes) structural motifs in which the ferrocene unit is linked by an unsaturated aza bridge, a 2-aza-1,3-diene or azine, to a chromogenic or fluorescent unit. The presence of N–H groups in the bridge (urea, guanidine or even imidazole ring) allows the sensing of anionic species, as it has been mentioned in numerous reviews during the last years.[10]

Ferrocenyl Azadienes

Ferrocenyl-substituted 2-aza-1,3-butadienes have been prepared from the readily available diethyl aminomethylphosphonate, which, by condensation with the appropriate aromatic or organometallic aldehyde, provides the corresponding *N*-substituted diethyl aminomethylphosphonate. Generation of the metalloenamine by treatment with *n*BuLi at –78 °C and subsequent reaction with 1 equiv. of the second aldehyde gave the 1,4-disubstituted 2-aza-1,3-butadienes.[11]

By following this protocol, receptor **1** was prepared from 9-anthraldehyde and formylferrocene. Dyad **1** displays a weak emission spectrum; however, upon addition of acid to a solution of **1** in acetonitrile/H_2O (7:3), a remarkable enhancement of the emission intensity (10-fold) is observed. More importantly, addition of Li^+ cations produces a remarkable fluorescence enhancement at pH = 5. Interestingly, the response is much higher for Li^+ than for other alkaline cations such as Na^+ or K^+. The difference is even more clear when Li^+ is compared with divalent cations including Ca^{2+}, Cu^{2+} or Zn^{2+}. From titration results, it becomes evident that the best opportunities for selective Li^+ sensing by means of receptor **1** have to be developed in a narrow pH window, centred at pH = 5.



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From a ^1H NMR spectral study, it was possible to obtain additional information about the coordination of the Li^+ cation by receptor **1** at pH = 5. The spectrum of the free

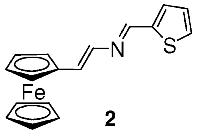
Prof. Pedro Molina was born in Totana (Murcia). He graduated with honours in chemistry from the University of Murcia in 1968 and he obtained his Ph.D. in 1973. During the period 1976–1978 he joined the group of Prof. A. R. Katriztky at the University of East Anglia (Norwich, UK). Since 1980, he is full professor at the Department of Organic Chemistry in the University of Murcia. He is recipient of the Spanish Royal Society of Chemistry Award in Organic Chemistry. His research has been mainly devoted to the area of heterocyclic chemistry. However, in the last few years he has turned his interests into the synthesis of new derivatives of ferrocene to be studied as molecular receptors.

Prof. Alberto Tárraga Tomás was born in Almansa (Albacete) and obtained his degree in chemistry at the University of Murcia (Spain), where he also received his Ph.D. in 1979. After accomplishing his postdoctoral studies in Prof. A. Katriztky's group at the University of East Anglia, Norwich (UK), in 1980 and at the University of Florida (USA) in 1981, he joined the group of Prof. P. Molina at the University of Murcia. In 1984 he held a position as Assistant Professor at the University of Murcia, and since 2004 he is Full Professor at the Department of Organic Chemistry in the same university. The major focus of his research interest relates to heterocyclic chemistry, synthesis of products with biological interest and novel molecular receptors.

Dr. Antonio Caballero was born in Murcia (Spain) in 1976. He graduated in Chemistry from the University of Murcia in 2001 and he obtained his Ph.D. in 2007 under the supervision of Profs. Pedro Molina and Alberto Tárraga. His research interest is focused on the study of intramolecular electron transfer phenomena and in the development of new fluorescent, electrochemical and chromogenic chemosensors.

receptor in CD_3CN/D_2O shows the typical pattern of signals corresponding to the monosubstituted ferrocene and anthracene units as well as those corresponding to the protons of the bridge. While the monosubstituted ferrocene protons do not change upon addition of acid to the solution until pH = 5, significant changes are evidenced in the chemical shifts of both the imine and olefin protons. From the magnitude of the downfield shifts observed, it can be surmised that the protonation exerts a more powerful deshielding effect on the bridge than on the anthracene or ferrocene units. Interestingly, addition of $LiClO_4$ to the previously protonated receptor **1**·H^+ (pH = 5) gives rise to a new species that only shows a significant change in the pattern of the ferrocene unit with respect to that of the protonated ligand **1**·H^+. In contrast, signals attributable both to the bridge and to the anthryl unit do not change their chemical shift upon addition of Li^+. It is important to underline that, when these experiments were carried out in the absence of added water, the addition of Li^+ to the receptor did not promote any change in the ^1H NMR spectrum of the protonated ligand. The optical and spectroscopic data clearly show that the fluorescence enhancement observed in the presence of Li^+ must be associated with a synergic participation of protons, water, the bridge and the ferrocene unit.[12]

Ferrocene-thiophene dyads with a 2-azadiene spacer have also been shown to be efficient chemosensor molecules for metal cations. No changes are observed in the UV/Vis spectra of compounds **2** and **3** in dichloromethane upon addition of 1 equiv. Li^+, Na^+, K^+, Mg^{2+} and Ca^{2+} (as their perchlorate salts). However, addition of increasing amounts of Ni^{2+}, Cd^{2+} and Hg^{2+} ions to compound **2** and Ni^{2+} and Cd^{2+} ions to compound **3** induce a redshift of the low-energy (LE) bands by $\Delta\lambda$ = 121–189 mm, which results in a colour change of the solution from orange to purple.



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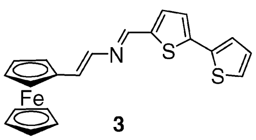

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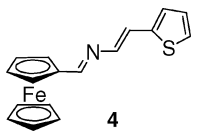
For compounds **4** and **5**, the presence not only of Ni^{2+}, Cd^{2+} and Hg^{2+} ions but also of Mg^{2+} ions induces a redshift of the LE bands by $\Delta\lambda$ = 56–95 mm. The redshift of the LE bands is twofold higher for compounds **2** and **3** than for compounds **4** and **5**. So far as the metal ion is concerned, in compounds **2** and **3** the redshift induced by both $Ni^{2+}$and Cd^{2+} is higher than that induced by Hg^{2+}, whereas in compounds **4** and **5**, Ni^{2+}, Cd^{2+} and Hg^{2+}induce a redshift higher than that caused by Mg^{2+} ions. Interestingly, while compounds **4** and **5** function as highly selective chemosensor molecules for Mg^{2+} ions, they do not show any response to Ca^{2+} or alkali-metal ions. On the other hand, ligand **2** shows a selective sensing response, preferring the soft Cd^{2+} ions over Hg^{2+} cations.[13]



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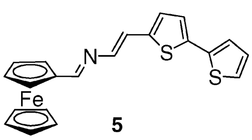

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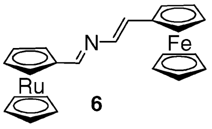
Heterodimetallic ferrocene-ruthenocene dyads **6** and **7** behave not only as suitable models to study the intramolecular charge-transfer across the aza-conjugated linker, but they also display interesting cation-sensing properties. Whereas no perturbation of the absorption spectra of the dimetallocene dyads **6** and **7** are observed upon addition of Li^+, Na^+, K^+ and Ca^{2+}, even in a large excess, a significant redshift of the high-energy (HE) ($\Delta\lambda$ = 36–38 nm) and low-energy (LE) ($\Delta\lambda$ = 83–85 nm) absorption bands are observed upon addition of Mg^{2+} cations. The titrations fitted a 2:1 (ligand/metal ion) binding model, and competitive binding assays between Ni^{2+}, Zn^{2+}, Cd^{2+} and Hg^{2+} ions and the receptors clearly show that **6** and **7** are not selective towards these metal cations tested. One of the most interesting aspects is the discrimination between Mg^{2+} and Ca^{2+} cations.[14]



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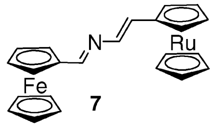

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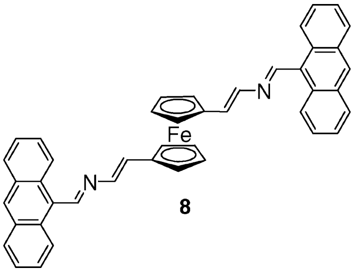
The new probe **8**, based on a 1,1′-disubstituted ferrocene, senses Zn^{2+} selectively among heavy- and transition-metal (HTM) ions through three different channels: redox, colorimetric and fluorescent. Whereas negligible changes in the Osteryoung Square Wave Voltammetry (OSWV) are observed upon addition of Ca^{2+}, Mg^{2+}, Cu^{2+}, Ni^{2+}, Co^{2+}, Pb^{2+}, Hg^{2+} and Cd^{2+} cations, a significant modification is observed upon addition of Zn^{2+} ions: the oxidation peak is shifted anodically by 140 mV. Therefore, the ability to recognize Zn^{2+} electrochemically in the presence of Cd^{2+} is one attractive feature of this ferrocene derivative. The UV/Vis spectrum of **8** is also substantially affected by Zn^{2+} recognition. The LE band is redshifted ($\Delta\lambda$ = 70 nm), which is responsible for the change of colour from orange to deep purple. Assessments of the cation affinities also come from observing the extent to which the fluorescence intensity of receptor **8** is affected in the presence of cations. The emission spectrum displays typical bands attributed to the anthracene monomeric emission, with a low quantum yield. The addition of 1 equiv. Zn^{2+} to a solution of receptor **8** in acetonitrile increases the integrated fluorescence intensity 16-fold and the quantum yield 15-fold. The reported detection limit for Zn^{2+} is 6.9×10^{-6} M. Thus, receptor **8** represents the first example of a Zn^{2+} chemosensor molecule, which combines the simplicity of electrochemical detection and the sensitivity of fluorescence detection with the convenience and aesthetic appeal of a colorimetric assay.[15]

Oligomeric metallocene-based species assembled on conjugated frameworks displaying multielectron redox chemistry have attracted much attention with respect to their electrochemical, electronic and magnetic properties. An interesting feature of these multi-redox systems is that the extent of communication between the redox centres can be controlled and modulated in several ways, including proton-



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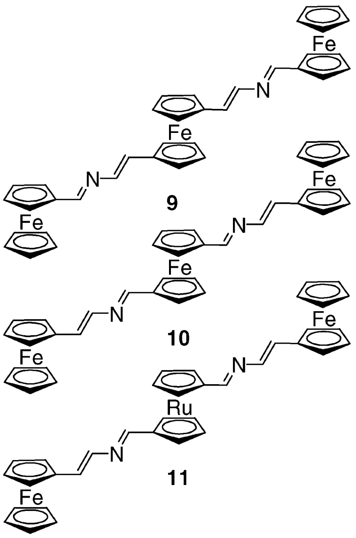
ation or alkylation of the ligands as well as upon complexation in the presence of guest metal cations.[16] In this context, triads **9**–**11** containing ferrocene and ruthenocene units as redox centres, linked through azadiene bridges which additionally comprise putative cation-binding sites, have been described. These receptors behave as dual redox and optical chemosensor molecules for Zn^{2+}, Hg^{2+} and Pb^{2+}. Their oxidation redox peaks are anodically shifted (up to 130 mV), and the LE bands of their absorption spectra are redshifted (up to 115 nm) upon complexation with these metal cations. These changes in the absorption spectra are accompanied by dramatic colour changes that allow the "naked-eye" detection of these metal cations. Compound **9** also exhibits a selective Hg^{2+} redox-induced complexation/decomplexation process.[17]



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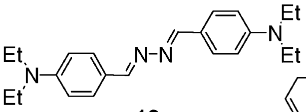
Ferrocenyl Azines

1,4-Bis(4-diethylaminophenyl) azine (**12**),[18] 1,4-bis(1-pyrenyl)azine (**13**)[19] and 1-(1-pyrenyl)-4-(4-methoxyphenyl)-azine (**14**)[20] have recently been used as recognition sites for Hg^{2+} and Cu^{2+}. For ligand **13**, the detection limits reported are 3.4×10^{-6} M and 3.2×10^{-6} M for Hg^{2+} and Cu^{2+}, respectively. For ligand **14**, the value for Cu^{2+} is 4.6×10^{-6} M.



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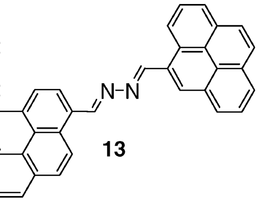

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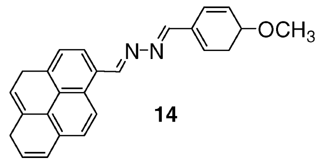

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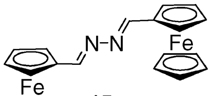
In view of these ideas, the metal-recognition properties of probe **15** have been evaluated by electrochemical and optical analysis. The differential pulse voltammograms (DPVs) in acetonitrile/H_2O (7:3) show only one oxidation peak around 0.65 V vs. decamethylferrocene. While no perturbation of the DPV of **15** is observed upon addition of Mg^{2+}, Ca^{2+}, Zn^{2+}, Ni^{2+} and Cd^{2+} ions, the oxidation peak is anodically shifted ($\Delta E_{1/2}$ = 60 mV) upon complexation with Hg^{2+} cations. The addition of increasing amounts of Hg^{2+} to a solution of **15** in acetonitrile/H_2O (7:3) causes the appearance of a redshifted ($\Delta\lambda$ = 45 nm) new LE band, which is responsible for the change of colour from yellow to deep purple, which can be used for a "naked-eye" detection of Hg^{2+} ions in aqueous environments.[21]



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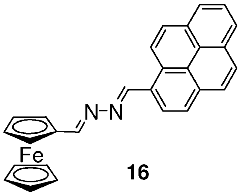
Cellulose-based probes have been prepared to confirm the potential application of ligand **15** for detecting Hg^{2+} ions on a solid support. The quantitative detection measurements of the cellulose probe were made by using UV/Vis spectroscopy. The increasing concentration of Hg^{2+} in the tested solution caused an apparent shift of the band initially appearing at 485 nm (due to the cellulose indicator paper coated only with the free receptor **15**) up to 565 nm (due to the completely complexed receptor **15**·Hg^{2+}). The large bathochromic shift of 80 nm observed for this band is responsible of the spectacular colour change suffered by the cellulose indicator paper. This impressive colour change, as well as the high reproducibility and the long persistence (days) of the colouration of the cellulose probes, permit a "naked-eye" detection of Hg^{2+} ions similar to the well-known pH paper indicator. Additionally, this protocol takes advantage of surpassing the drawback of the low aqueous solubility of most of the reported Hg^{2+} chemosensors, allowing them to be used for detecting Hg^{2+} ions in water solutions (detection limit: 5.2×10^{-5} M).[22]

Preparation of ferrocene-based fluorescence switches requires that the fluorescence spectrum of the fluorophore unit should not overlap largely with the absorption spectrum of the corresponding oxidized ferrocenium unit. Otherwise, intramolecular energy transfer would occur under oxidation, and in this case the expected fluorescence enhancement would not be observed. In this context, the ferrocene-pyrene dyad **16** acts as a robust and reversible fluorescence-redox switchable bistable molecular system, whose fluorescence emission intensity depends on the oxidation state of the ferrocene unit. The neutral dyad **16** shows a weak fluorescence. Quenching by the ferrocene subunit may occur either by electron transfer or by energy transfer from the ferrocenyl group, which acts as an electron donor, to the excited state of the pyrenyl group, acting as an electron-acceptor unit. After oxidation (chemical or electrochemical) of neutral dyad **16**, the electron-donating ability of the ferrocene subunit is reduced, and as a result electron transfer is arrested, which leads to a fluorescence enhancement. Now, the spectral overlap between the absorption spectrum of the ferrocenium unit and the emission spectrum of the pyrene unit is small. Consequently, the resonance energy transfer from the excited state of pyrene to the ferrocenium unit cannot take place efficiently.



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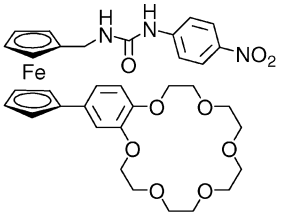
As the ferrocene/ferrocenium pair transformation in **16** can be reversibly carried out over several cycles, and as the fluorescence intensity is fully recovered after each step, a simple, robust and fast redox-fluorescence molecular switch can be established on the basis of dyad **16** by taking advantage of the properties of the ferrocene as electron donor and the pyrene as a fluorescent read-out unit.[23]

Ferrocenyl Ureas

Urea is an attractive building block for anion receptors, because it contributes two relatively strong hydrogen-bonding sites.[24] The N–H groups can bind with a single acceptor atom to yield a six-membered chelate ring or with two adjacent oxygen atoms in an oxyanion to yield an eight-membered chelate ring. For strong and selective binding, this group should be preorganized to complement the target anion and minimize intramolecular hydrogen bonding. A variety of urea-based hosts containing one or more urea subunits have been designed and tested for anion recognition and sensing over the past years, and new insights into the nature of urea–anion interactions, providing structural criteria for the deliberate design of anion-selective receptors containing two or more urea binding groups, have also been recently reported.[25] There are, however, few examples of urea/ferrocene redox-active anionophores.[26] In this context, the behaviour of the ditopic ferrocene receptor **17**, containing a urea and a benzo crown ether unit,[27] as a chromogenic molecular sensor has been reported: the absorption maxima associated with the nitrobenzene moiety (λ = 304 and 332 nm in acetonitrile solution) clearly separate (λ = 288 and 356 nm) after addition of 10 equiv. F^- with the appearance of a new absorbance centred at 472 nm and the simultaneous change in colour of the solution from colourless to yellow. Addition of K^+ (10 equiv.) reverses the chromogenic process, and the solution turns colourless. At the same time, the absorption maximum at 472 nm disappears. Reversing the order of the guest addition: first K^+ and second F^-, gives similar results. In both cases, the presence of the cation appears to inhibit the chromogenic response of the system to F^- anions.



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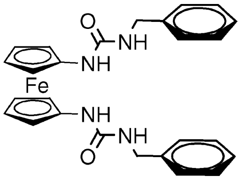
Another important group of ferrocene-functionalized ureas are the receptors **18**, **19**, **20**,[28] **21** and **22**,[29] in which the ferrocene moiety is simultaneously attached to two urea groups.

The behaviour of the urea/ferrocene ligand **18** as a versatile redox-active receptor has been demonstrated by electrochemical measurements. Compound **18** exhibited a reversible one-electron redox wave at $E_{1/2}$ = –0.320 V vs. Fc^+/Fc, and, while it was unresponsive to Cl^-, Br^-, AcO^-, NO_3^- and HSO_4^- anions in dmso solution, addition of F^- and $H_2PO_4^-$ salts revealed its capability for acting as an electrochemical sensor for those anions. In fact, upon addition of F^-, a new wave at a more negative potential ($E_{1/2}$ = –0.480 V), ascribed to the complexed species, was observed. For the case of $H_2PO_4^-$ it is notable that the response observed during the stepwise addition of the anion also promotes the appearance of a new negatively shifted wave ($\Delta E_{1/2}$ = –142 mV). ^{1}H NMR spectroscopic titration experiments have also been used to monitor the anion-recognition process: upon addition of aliquots of F^- and $H_2PO_4^-$ anions, the urea protons were clearly shifted downfield, demonstrating that these protons are involved in the ligand–anion binding event. The binding profiles associated with the observed chemical shifts of the NH urea protons suggest a 1:2 and a 1:1 (ligand/anion) binding fashion for F^- and $H_2PO_4^-$, respectively.



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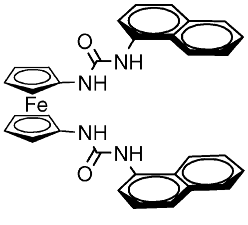
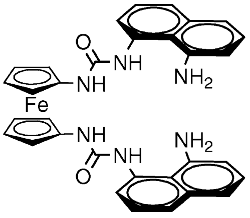
Anion-binding properties of receptors **19** and **20**, bearing two photoactive naphthalene groups connected to the ferrocene unit by two urea moieties, have been evaluated by both electrochemical and fluorescence analysis. The fluorescence response of the acyclic receptor **19** in the presence of F^-, Cl^-, Br^-, AcO^-, NO_3^-, HSO_4^- and $H_2PO_4^-$ anions was very close to that found for the free receptor, indicating that the presence of those anions has little effect on the fluorescence behaviour despite the formation of stable complexes. Nevertheless, its electrochemical anion-sensing behaviour was determined by cyclic voltammetry experiments in dmso. The results obtained by the stepwise addition of F^- anion revealed the appearance of a second reversible wave ($E_{1/2}$ = –0.540 V vs. Fc^+/Fc), corresponding to the ferrocene redox couple of the complexed receptor, together with that corresponding to the free receptor ($E_{1/2}$ = –0.330 V vs. Fc^+/Fc). The current of the new redox couple increased until 2.2 equiv. of the guest fluoride anion was added. At this point, the reversible wave corresponding to uncomplexed receptor **19** disappeared. This two-wave behaviour is diagnostic of a large value for the equilibrium constant for F^- binding by the neutral receptor **19** with a BEF of 3312, which means that the complexation in the reduced form of ligand **19** with F^- anions is 3312 times more difficult than that in the oxidized one. Likewise, upon addition of increasing amounts of $H_2PO_4^-$ to the electrochemical solution of **19**, a similar effect was observed with $\Delta E_{1/2}$ = –90 mV (BEF = 25). It is noteworthy that the presence of other anions (Cl^-, Br^-, AcO^-, HSO_4^- and NO_3^-) in solution had no effect on the cyclic voltammogram (CV) even in high concentrations.



19

Titration experiments by ^1H NMR spectroscopy in [D$_6$]-dmso to follow the change in chemical shift of the urea protons were used to determine the binding constants of **19** with both F^- and $H_2PO_4^-$ anions. During the titration experiment, all of the NH urea signals are shifted downfield, indicating that all these protons participate in an authentic hydrogen-bonded complex. Titration isotherms obtained from these changes in the chemical shifts of the host NH signals fitted nicely to a 1:2 and 1:1 (receptor/anion) binding model for F^- and $H_2PO_4^-$ anions, respectively.

The novel receptor **20** presents the characteristic structural features of incorporating a redox centre proximate to a neutral hydrogen bond urea donor together with a fluorophore unit bearing a neutral amino group, which can act as both hydrogen-bond donor and acceptor. These structural motifs are of special importance in nature where a variety of hydrogen-bonding groups, both donors and acceptors, are used to discriminate between anionic guests.[30] The recognition of anions in solution by **20** was investigated by means of both electrochemical and fluorescence techniques. The CV of this receptor, in dmso, exhibits a reversible ferrocene/ferrocenium redox couple at $E_{1/2}$ = –0.342 V and, at more positive potential, an irreversible oxidation wave (E_p = 0.034 V) corresponding to the amine oxidation process. The electrochemical response of **20** upon addition of Cl^-, Br^-, AcO^-, NO_3^- and HSO_4^- anions produces CVs identical to that of the free receptor, indicating that the presence of those anions has little effect on the electrochemical response of **20**. In contrast, the addition of variable concentrations of F^- and $H_2PO_4^-$ caused a notable electrochemical response. Remarkably, the amine oxidation peak exhibited a two-wave behaviour, with the appearance of a second wave at more negative potentials, together with that corresponding to the free receptor (ΔE_p = –374 mV for F^- and ΔE_p = –332 mV for $H_2PO_4^-$, vs. Fc^+/Fc), which completely disappears upon addition of 2 equiv. of the corresponding anion. This electrochemical response to anionic guests provides tentative evidence for the involvement of this group in the coordination of these anions. Simultaneously, the ferrocene/ferrocenium redox couple showed a shifting behaviour, and a new oxidation peak emerged at a potential cathodically shifted from that of the free receptor ($\Delta E_{1/2}$ = –60 mV for F^- and $\Delta E_{1/2}$ = –108 mV for $H_2PO_4^-$ vs. Fc^+/Fc), indicating that coordination of an anionic guest to the urea group close to the ferrocene group facilitates its oxidation.

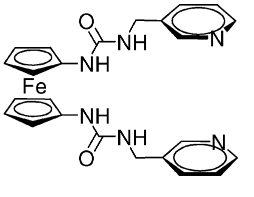


20

Thus, for non-acidic guests, such as F^-, the binding mode is based on the receptor's donation of hydrogen bonds from the urea (and probably to a lesser extent from the amino) group to the guest. For the moderately strongly acidic $H_2PO_4^-$ guests, the binding mode consists of a previous protonation of the primary amino group followed by hydrogen bonding and electrostatic interaction with the guest anion: proton transfer is followed by hydrogen-bond formation and subsequent anion coordination.

The presence of a naphthalene unit within the structure of receptor **20** has allowed the study of its recognition capability by fluorimetric analysis: the fluorescence spectrum of **20** excited at λ = 330 nm in dmf shows a weak emission-band profile typical of the naphthalene moiety. Nevertheless, upon addition of the set of the above-mentioned anions (F^-, Cl^-, Br^-, AcO^-, NO_3^-, HSO_4^- and $H_2PO_4^-$), no significant changes in the spectra were observed. This observation can be justified by the presence of the electron-donating NH_2 group, which prevents the enhancement of fluorescence by the receptor upon coordination with the corresponding anions.

Another example of a ferrocenyl-urea derivative reported is the heteroditopic receptor **21**, whose electrochemical behaviour in the presence of metal cation guests has been investigated in dmso solution. The CV of receptor **21** showed a reversible one-electron redox couple due to the ferrocene/ferrocenium oxidation process ($E_{1/2}$ = –0.310 V vs. Fc^+/Fc). While the stepwise addition of several metal ions (Li^+, Na^+, K^+, Ca^{2+}, Mg^{2+}, Ni^{2+}, Zn^{2+} and Cd^{2+}) caused no perturbation in the CV of the free receptor, the addition of Cu^{2+} (as its triflate salt) gave rise to a CV containing a reversible redox wave, which appears at the same potential as that observed in the free receptor ($E_{1/2}$ = –0.310 V vs. Fc^+/Fc), together with a quasireversible oxidation wave at a more positive potential (E_p = +0.007 V vs. Fc^+/Fc) due to the Cu^{2+}/Cu^+ redox couple. It has to be noted that identical results were described when Cu^+ instead of Cu^{2+} was added to the electrochemical solution. Interestingly, during these experiments, based on the addition of substoichiometric quantities of a solution of anhydrous $Cu(OTf)_2$ in acetonitrile (c = 2.5×10^{-2} M) to a solution of **21** in dmso (c = 2×10^{-4} M), an immediate and significant colour change from yellowish to pale green was also observed.



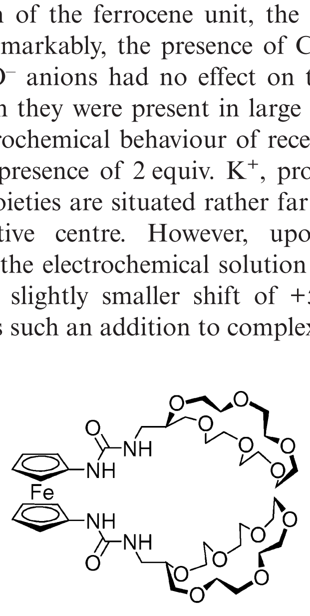
21

The electronic spectrum of receptor **21** in dmso showed two absorption bands: one at 294 nm, in the tail of a UV band rising to higher energy, and a broad band at 444 nm (ε = 300 $M^{-1}cm^{-1}$), which are likely ferrocene-centred transitions. The addition of $Cu(OTf)_2$ to a dmso solution of **21** induces the appearance and development of two bands of similar intensities at 609 nm (ε = 230 $M^{-1}cm^{-1}$) and 802 nm (ε = 240 $M^{-1}cm^{-1}$). The absorption band observed at 609 nm is very common in Cu^{II} complexes of receptors containing donor sp^2 nitrogen atoms and can be ascribed to a metal-to-ligand-charge-transfer (MLCT) transition[31] but not to a ferrocenium charge transfer transition. This assignment is also supported by the fact that the free-copper-oxidized free receptor $\mathbf{21}^+$, electrochemically generated in a dmso solution did not show bands at $\lambda > 500$ nm. When the pale green solution of the [$\mathbf{21}\cdot Cu^{2+}$] complex was allowed to stand at room temperature, a slow evolution of its colour from green to yellow was observed. Simultaneously, the disappearance of the absorption bands at 609 and 802 nm was detected, the resulting spectrum being identical to that displayed by $\mathbf{21}^+$ when it was electrochemically generated. These experimental results seem to indicate that, upon addition of Cu^{2+} ion to receptor **21**, an initial fast formation of the pale green [$\mathbf{21}\cdot Cu^{2+}$] complex takes place. Later, a slower intramolecular electron–electron transfer process, between the Fe^{2+}~Cu^{2+} and Fe^{3+}~Cu^+ valence tautomers,[31,32] occurs, as evidenced by the occurrence of a LE band in the NIR region at 802 nm, leading to the formation of a [$\mathbf{21}^+\cdot Cu^+$] complex which undergoes rapid decomposition to give the oxidized free ligand $\mathbf{21}^+$ together with Cu^+ [Equation (1)].

$$\left[\mathbf{21}\cdot Cu^{2+}\right] \xrightleftharpoons{\text{IET}} \left[\mathbf{21}^{+}\cdot Cu^{+}\right] \rightleftharpoons \mathbf{21}^{+} + Cu^{+} \tag{1}$$

The electrochemical response of **21** to the presence of F^-, Cl^-, Br^-, AcO^-, NO_3^-, HSO_4^- and $H_2PO_4^-$ guest anions has also been reported, demonstrating that only host–guest interactions were observed when F^- and $H_2PO_4^-$ were added to the electrochemical solution. However, it is worth mentioning that, while the reversible wave appearing in the free receptor is gradually replaced by a new reversible wave at more negative potentials upon addition of increasing amounts of F^- ($\Delta E_{1/2}$ = –216 mV), the addition of $H_2PO_4^-$ anion promotes a shifting behaviour ($\Delta E_{1/2}$ = –144 mV). Titration isotherms obtained by ^{1}H NMR spectroscopic titrations were used to evaluate stability constants with the EQNMR computer program by assuming 1:2 and 1:1 binding stoichiometries for the cases of F^- and $H_2PO_4^-$, respectively.

A similar study on the recognition properties of receptor **22**, containing anion-binding urea moieties together with cation-binding crown ether groups, has also been reported. The CV of this heteroditopic receptor, compound **22**, in dichloromethane showed a reversible one-electron oxidation process at $E_{1/2}$ = –0.31 V vs. Fc^+/Fc. On the stepwise addition of 1.5 equiv. F^-, a modest cathodic shift of $\Delta E_{1/2}$ = –52 mV in this redox couple was observed. However, upon addition of $H_2PO_4^-$ anion, the cathodic shift observed was $\Delta E_{1/2}$ = –0.19 V, reflecting a strong binding of the guest upon oxidation of the ferrocene unit, the calculated BEF being 1628. Remarkably, the presence of Cl^-, Br^-, HSO_4^-, NO_3^- and AcO^- anions had no effect on the voltammogram, even when they were present in large excess. Interestingly, the electrochemical behaviour of receptor **22** did not change in the presence of 2 equiv. K^+, probably since the crown ether moieties are situated rather far from the ferrocene redox-active centre. However, upon addition of 2 equiv. K^+ to the electrochemical solution of the complex [$\mathbf{22}\cdot H_2PO_4^-$], a slightly smaller shift of +50 mV was observed, whereas such an addition to complex [$\mathbf{22}\cdot F^-$] had no effect.

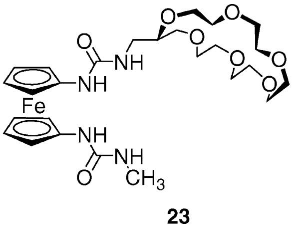


22

Anion binding by receptor **22** was also cleanly detected by changes in the ^{1}H NMR spectra. Upon addition of 1 equiv. F^-, all the NH protons of receptor **22** showed significant downfield shifts, indicating that such protons are involved in the formation of the complex. Addition of 1 equiv. $H_2PO_4^-$ as a guest anion resulted in a lower downfield shift of the NH resonances, which is also consistent with the formation of a hydrogen-bonded complex. Titration isotherms generated from the change in chemical shift of the host NH signals upon addition of both anions were fitted to a 1:1 binding model. With Cl^-, Br^-, HSO_4^-, NO_3^- and AcO^- anions, there were no chemical shift changes for the NH peaks, even when up to 10 equiv. of these anions were added.

On the other hand, the presence in this molecule of a macrocyclic subunit bearing binding sites for metal cations allowed the study of the capability of this receptor to simultaneously bind anions and cations. Likewise, when 2 equiv. K^+ were added to a solution of **22**, the urea NH protons were shifted upfield due to cation complexation, preventing hydrogen bonding from the crown ether. A ^1H NMR spectroscopic dilution study in $CDCl_3$ revealed that the urea crown ether hydrogen bonding in **22** was intramolecular rather than intermolecular. The resulting titration isotherm fitted nicely a 1:2 binding model. Interestingly, addition of 1 equiv. K^+ to a solution of complex [**22**·$H_2PO_4^-$] resulted in a higher upfield shift of the urea NH protons; the titration isotherm fitted a 1:1 binding model.

In order to grasp the nature of these latter binding interactions, the behaviour of **22** towards the $H_2PO_4^-$ anion was initially evaluated by means of theoretical calculations on the model compound **23** at the moderate B3LYP/3-21G* level of theory.[33] The global minimum for complex **23**·KH_2PO_4 shows the K^+ ion to be almost at the centre of the [18]crown-6 moiety in the usual way,and the closest urea group directs its NH functionalities inwards to form two hydrogen bonds with a PO and a POH group. The latter acts as a bridge between the two side arms around ferrocene by connecting the carbonyl group of the second urea, which is chelated by the other POH. The coordination sphere around the K^+ cation is completed by the bridging POH group and the remaining PO group that is not complexed with urea. Finally, the crown ether scaffold is bound to the anion by at least four additional CH···OP contacts overall, yielding a highly stable 1:1 complex.



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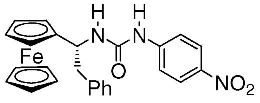
The spectral and electrochemical results of the titration of receptor **22** with K^+ cations in the presence of $H_2PO_4^-$ anions could be rationalized by assuming that K^+ forms a sandwich complex between the two crown ethers by bringing the two urea binding functionalities close together in a constrained conformation and thus preventing the required optimal array of convergent urea binding sites for strong $H_2PO_4^-$ complexation. Therefore, the resulting **22**·KH_2PO_4 complex would have a lower complexation electronic energy, and, in addition to the sandwich-like complexation of K^+ between the two [18]crown-6 subunits, it would mainly consist of an eight-contact-point binding of the $H_2PO_4^-$ anion, three of the contact points involving the two urea units: the terminal O phosphate atoms form an eight-membered chelate ring with the H atoms of one urea group, while one of the POH groups forms a hydrogen bond with the carbonyl O atom of the other urea unit.

Chiral urea **24**, containing the redox-active ferrocene group, binds chiral carboxylates in organic solvents through hydrogen-bonding interactions, as evidenced by spectroscopic and cyclic voltammetry measurements, the latter allowing these guests to be electrochemically sensed in solution. The enantioselectivity in the complexation of the protected amino acid N-benzenesulfonylproline by a ferrocenylbenzyl host is high enough to allow opposite enantiomers to be distinguished by electrochemical means.[34]

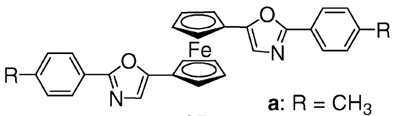


24

Ferrocenyl Heterocycles

In azaheteroaromatic ring systems capped by ferrocenyl groups, the nitrogen atom in the heteroaromatic ring provides an interesting and useful function, which is the ability of the ring to act as a metal-ion ligand. The reversibility of the ferrocene/ferrocenium redox couple and the ability of the heteroaromatic ring to act as a ligand towards metal ions may operate cooperatively within the molecule. This synergistic relation may create a molecular switch, which would allow the complexing ability of the heteroaromatic subcomponent to be turned off when a positive charge is generated within the ferrocene moiety. Upon reduction, the complexing ability would be restored, and consequently, the combination of ferrocenes and heteroaromatic rings could be of interest for the construction of redox-switching receptors, by electrochemical and/or optical methodologies, with the capability of selectively sensing metal-ion guests.

One of the most interesting attributes of 1,1′-bis(oxazolo)ferrocenes **25**[35] is the presence of two proton-binding oxazole sites in the proximity of the ferrocene redox-active moiety. The CVs of receptors **25** display a single anodic process with features of chemical and electrochemical reversibility ($E_{1/2}$ = 0.53–0.56 V vs. SCE). Upon protonation by addition of stoichiometric quantities of HBF_4 in acetonitrile, the redox potential of the ferrocene nucleus is shifted anodically in each case ($\Delta E_{1/2}$ = 144–248 mV): oxazole protonation builds up positive charge close to the ferrocene nucleus, and this electrostatically repels the ferrocenium cation, thermodynamically hindering its formation.

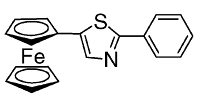


25

a: R = CH_3
b: R = OCH_3
c: R = H

The effect of several metal cations on receptor redox chemistry showed that only addition of Zn^{2+} cations in acetonitrile elicited different potential shifts ($\Delta E_{1/2}$ = 104–164 mV) from those assigned to the protonated species. Taking into account that in aza-substituted ferrocene derivatives, the redox shifts corresponding to protonation are larger than that for coordination, it can therefore be concluded that metal-ion coordination is observed for receptors **25**. The *syn* spatial arrangement may be induced by the cation in a optimal manner by the ball-bearing motion of the two cyclopentadienyl rings of the ferrocene unit to give rise to a more effectively organized donor set, and consequently the strength of the coordination is enhanced.[16f]

Likewise, the thio analogues, the ferrocenyl thiazole derivatives, exhibit interesting cation-sensing properties with high selectivity for divalent metal ions, giving responses through one or two channels. Ferrocenyl thiazoles linked across the 5-position of the heteroaromatic ring are selective chemosensors for Hg^{2+} and Pb^{2+} ions; 5-ferrocenylthiazole **26** operates through two channels: optical and redox, whereas 1,1′-bis(thiazolyl)ferrocene **27** only operates as an optical chemosensor. Ferrocenylthiazole **28**, having the ferrocenyl unit linked to the 2-position of the heterocyclic ring, is a selective redox chemosensor for Hg^{2+} ions, and it responds, as the bis(thiazolyl)ferrocene **29** does, to a narrow range of cations comprising Zn^{2+}, Cd^{2+}, Hg^{2+}, Ni^{2+} and Pb^{2+}.



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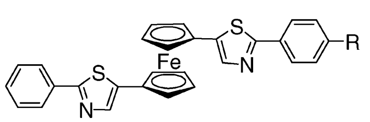

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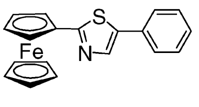

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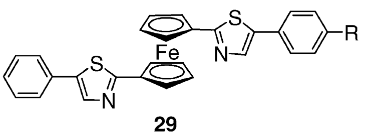

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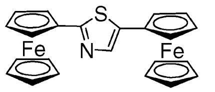
Bis(ferrocenyl)thiazole **30** is a dual optical and redox chemosensor for Zn^{2+}, Cd^{2+}, Hg^{2+}, Ni^{2+} and Pb^{2+}, whereas bis(ferrocenyl) compound **31**, bearing a bis(thiazole) bridge, is only a chromogenic chemosensor for Zn^{2+}, Cd^{2+}, Ni^{2+} (colour changes from orange to blue) and Hg^{2+} (colour changes from orange to green).[36]



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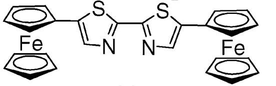
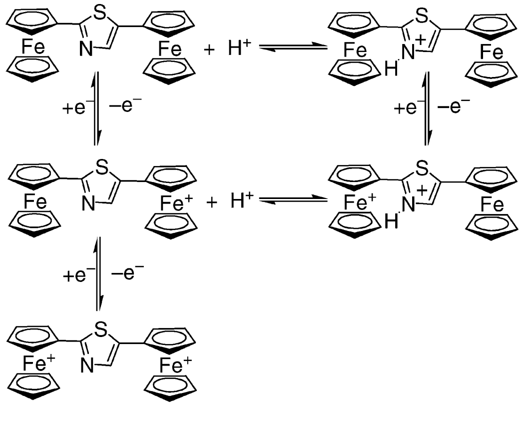


31

A further exciting property of these ferrocenyl thiazole ligands is that they are not only able to monitor binding but they are also able to behave as actuators through the progressive electrochemical release of the metal cation; that is, the binding constant decreases upon electrochemical oxidation.

The CV of bis(ferrocenyl) derivative **30** shows two closely spaced reversible one-electron oxidations for the ferrocenyl groups. Upon protonation, the CV showed a clear evolution of the first wave from 0.49 V to 0.63 V, whereas there was no effect on the second wave. Remarkably, the current intensity of the cathodic peak of the second wave increases, while that of the first one decreases. The second wave reaches the maximum current intensity value at 1 equiv. of added acid, and at this point the first wave disappears. The occurrence of this wave at the same potential for the unprotonated **30** suggests that, after oxidation of the ferrocene unit linked at the 5-position, the adduct is deprotonated and subsequent oxidation takes place on the partially oxidized $\mathbf{30}^{\cdot+}$. In other words, adduct $\mathbf{30}\cdot H^+$ undergoes a reversible, electrochemically induced deprotonation/reprotonation processes on a time scale faster than that of the electrochemical experiment (Scheme 1).[37]

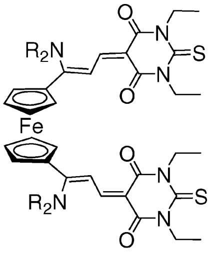


Scheme 1.

Similarly, a spectroelectrochemical study of complex $\mathbf{26}\cdot Hg^{2+}$ revealed the high degree of reversibility of the complexation/decomplexation process. The complexed $\mathbf{26}\cdot Hg^{2+}$ species, which exhibits an intense purple colour, was oxidized at +0.9 V until the oxidation was complete and the colour of the solution was changed from purple to yellow. Afterwards, the solution was completely reduced with a potential of –0.1 V, and the initial spectrum was fully recovered as well as the purple colour. Thus, the free oxidized ligand $\mathbf{26}^{\cdot+}$ is reduced to **26**, which has a higher cation Hg^{2+} binding affinity, leading to the initial complex $\mathbf{26}\cdot Hg^{2+}$. Oxidation of the complex and its subsequent reduction can be carried out over several cycles, and after each step the optical spectrum was found to be recovered. These results revealed the ability of the ferrocenyl thiazole derivatives to control the trapping and the expulsion of these metal ions by application of an external electrochemical stimulus, which can be used for the construction of more elaborate supramolecular switching systems.

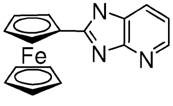
Ferrocene derivatives containing an oxazoline substituent are efficient redox chemosensors with remarkable selectivity for Mg^{2+}, Ca^{2+} and Cu^{2+} over a range of other metal cations in acetonitrile solution. A new redox peak appears in the cyclic voltammogram, which positively shifted by 360–160 mV relative to the $E_{1/2}$ of the free ligand. Additional evidence for the function of oxazoline as a cation-binding site is provided by UV/Vis spectrophotometric and ^{1}H NMR spectroscopic data.[38]

Several new ferrocene derivatives **32**,[39] bearing two donor-acceptor systems in which the ferrocene unit acts both as a donor group and as rotating spacer, have been reported. These molecules, bearing acceptor groups such as thiobarbiturylidene and donor groups such as dialkylamino or aza crown ethers, are capable of selectively sensing cations and anions by cooperative binding of the two α,α′ groups bonded to the ferrocene nucleus, thus permitting the selective "naked-eye" colorimetric detection of Cu^{2+} cations and benzoate, acetate or cyanide anions.



32

Among the various artificial receptors reported in the literature, those employing benzimidazole derivatives have attracted considerable attention.[40] More recently, it has been found that the introduction of an additional nitrogen atom into the benzimidazole ring, with similar basicity to that of the imidazole nitrogen atom, imparts an interesting behaviour. The pyridine-like nitrogen atom cooperates with the basic nitrogen atom of the imidazole ring and consequently enhances the binding affinity towards metal cations. In this context, 2-ferrocenylimidazo[4,5-*b*]pyridine **33** constitutes an example of a chemosensor where the fluorescent reporter (imidazopyridine ring) is integrated in and the redox unit (ferrocene) is linked to the guest cation binding site.

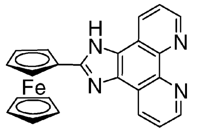


33

The metal cation complexing properties of **33**, investigated by electrochemical and spectroscopic measurements, showed that the univalent metal ions do not cause significant changes in either the redox potential or the absorption and fluorescence emission spectra. However, this chemosensor molecule based on a deazapurine ring selectively senses aqueous Pb^{2+} in acetonitrile over other divalent metal ions examined; a redox ($\Delta E_{1/2}$ = 150 mV) redshift of the LE absorption band ($\Delta\lambda$ = 44 nm) with a concomitant change in colour from colourless to orange and a large chelation-enhanced fluorescence (620-fold) are observed with an unprecedented detection limit of 2.7 μg L^{-1} (1.32×10^{-8} M). The turn-on response is reversible, because the signal transduction disappears upon the addition of an excess of cyclen or ethylenediamine.[41] The selectivity of **33** for Pb^{2+} over Ca^{2+}, Cd^{2+} and Hg^{2+} is particularly important, because Pb^{2+} targets Ca^{2+} binding sites in vivo, and Cd^{2+} and Hg^{2+} are metal cations that frequently interfere with Pb^{2+} analysis.

The chemosensor molecule **34**, which is based on a ferrocene-imidazophenanthroline dyad, effectively recognizes aqueous hydrogenpyrophosphate and the organic anions ADP and ATP through three different channels. A cathodic shift of the ferrocene/ferrocenium oxidation wave ($\Delta E_{1/2}$ ranging from –130 mV, for hydrogenpyrophosphate and fluoride, to –40 mV for ADP) was observed. In the UV/Vis spectra, addition of such anions gave rise to a progressive redshift of the absorption bands and/or appearance of a new LE band at 314–319 nm. These changes in the absorption spectra are accompanied by colour changes from pale yellow to orange or pink, which demonstrate the potential for "naked-eye" detection. The emission spectrum (λ_{exc} = 390 nm) undergoes an important chelation-enhanced fluorescence effect (CHEF = 50) in the presence of 2.5 equiv. hydrogenpyrophosphate anion and with a large excess of fluoride anion (CHEF = 114). Interestingly, the emission spectrum obtained at a different excitation energy (λ_{exc} = 340 nm) in the presence of AcOH acid is redshifted and not only perturbed by the hydrogenpyrophosphate anion (CHEF = 71, detection limit = 5.18×10^{-6} M) but also by the organic anions ATP (CHEF = 25, detection limit = 1.8×10^{-5} M), ADP (CHEF = 1, detection limit = 1.5×10^{-5} M) and the dihydrogenphosphate (CHEF = 25, detection limit = 2.1×10^{-5} M). As a consequence, selective fluorescence detection of hydrogenpyrophosphate anions in the presence of the related competitors dihydrogenphosphate anions, ADP and ATP could be achieved by careful selection of the excitation energy. About the deprotonation/coordination dualism, the combined electrochemical, absorption, emission and NMR spectroscopic data strongly support that the fluoride anion induces only deprotonation, the anions dihydrogenphosphate, ATP and ADP form hydrogen-bonded complexes, and the formation of hydrogen-bonded complexes between the hydrogenpyrophosphate anion and receptor **34** and deprotonation proceed simultaneously.

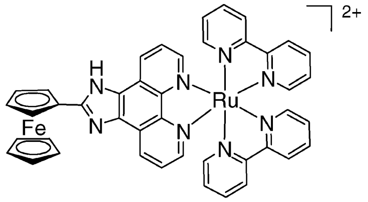
Ruthenium derivatives containing quenchers such as ferrocene follow an appealing approach to anion sensing. It is well-known that the redox character of ferrocene can induce quenching of the emission from the $Ru(bipy)_3^{2+}$ core. The design idea in those receptors is that coordination of



34

anionic species may alter the interaction between the Ru(bipy)$_3^{2+}$ excited core and the ferrocene, therefore inducing emission enhancement.[10b]

Remarkably, the stable heterodimetallic ruthenium(II) complex **35** selectively senses chloride anions over the other anions examined through two channels: cathodic redox shift ($\Delta E_{1/2}$ = –80 mV) of the Fe^{II}/Fe^{III} redox couple, keeping the oxidation wave of the ruthenium(II) centre unchanged, and a significant red emission enhancement (CHEF = 30). All available data (electrochemical, absorption, emission and ^{1}H NMR spectroscopy) strongly support the formation of a [**35**·Cl$^-$] hydrogen-bonded complex (detection limit = 2.0×10^{-5} M), in which the heteroaromatic and ferrocenyl protons participate in complex formation. The anion-sensing behaviour of complex **35** provides a nice example of a switchable fluorescent chemosensor molecule mediated by metal-ion coordination.[42]



35

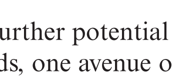
Ferrocenophanes

The most prevalent organometallic analogues of cyclophanes are the ferrocenophanes with a bivalve-like structure, in which the two cyclopentadienyl rings of ferrocene are joined by an atomic of molecular bridge. In these sorts of compounds, many of the desirable characteristics of the parent ferrocene are retained, and these bridged compounds are expected to show unique chemical properties owing to the functionality of the side arms.

Many different classes of ferrocenophanes have been described, most of which possess exclusively carbon-based bridges with three modes of ring attachment:[43] mononuclear [*m*]ferrocenophanes (type I), mononuclear multiply bridged [*m*][*n*] ferrocenophanes (type II) and multinuclear [*m,n*]ferrocenophanes (type III).

I

II

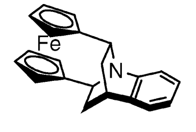


III

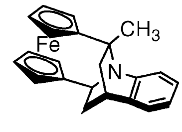
To establish new properties and further potential applications of these fascinating compounds, one avenue of special interest would be to create ferrocenophane architectures which additionally incorporate sites in the bridge for the purpose of binding cations and/or anions. The combined structural features comprising rigid preorganization and spatially well-defined shape would yield a new class of organometallic materials that would be expected to display sensing properties. In this context, a variety of ferrocenophane hosts, containing appropriate aza-substituted bridges, have been designed for recognition and sensing of metal cations, anions and neutral molecules.

[*m*]-Ferrocenophanes

2-Aza[3]ferrocenophanes **36** and **37**, which comprise a benzoquinuclidine framework incorporating a 1,1′-disubstituted ferrocene unit, have been prepared from the preformed ferrocene derivative **38**, which was obtained by selective reduction of the C=N double bond in **39**.[44] This [5]-ferrocenophane **39** was, in turn, synthesized from the readily available 1,1′diacetylferrocene, by sequential treatment with *o*-azidobenzaldehyde and *n*-Bu$_3$P.[45]



36



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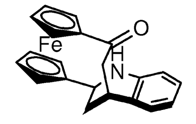
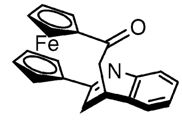


38



39

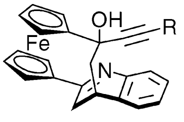
These compounds possess specific structural features such as: (1) a rigid framework with a blocked rotation of cyclopentadienyl rings; (2) a highly basic benzoquinuclidine ring and (3) a short Fe···N distance. The summed effects of these characteristics suggested that **36** and **37** might experience electron cloud perturbation upon coordination and may function as sensors for metal ions.

A detailed picture of the coordination properties of ferrocenophanes **36** and **37** is obtained through their electrochemical behaviour in the presence of variable concentrations of HBF$_4$. The CVs of these species display a single anodic process with features of electrochemical reversibility, with no subsidiary amine oxidation observed. However, upon protonation by addition of 1 equiv. HBF$_4$, the redox potential of the ferrocene nucleus was shifted anodically in each case. For compound **36**, the potential shift upon protonation was 390 mV, and, consequently, the binding enhancement factor (BEF) is 2.5×10^{-7} and the reaction coupling efficiency (RCE) is 3.9×10^{6}. This means that it is 3 900 000 times more difficult to protonate the oxidized form than the reduce one. Similar values were found for compound **37**.[46]

Investigation into the metal ion coordination behaviour of **36** and **37**, by using cyclic voltammetry, showed that they responded electrochemically to a narrow range of cations, comprising Mg^{2+}, Zn^{2+} and Ni^{2+}. Upon addition of these cations to a solution of the free ligands, a new redox peak appears in the CV, which is shifted 310–350 mV. By contrast, no perturbation of the CV curves was observed upon addition of Li^+ and Ca^{2+}cations.

Of particular significance is the fact that the protonated species [**36**·HBF_4], readily prepared as a crystalline solid in almost quantitative yield by addition of 1 equiv. HBF_4 to a solution of **36** in dichloromethane, can function as a selective electrochemical sensor for hydrogen sulfate, which promotes a significant cathodic perturbation in the CV of this protonated ligand.

Ferrocenophane **39** was also used for the preparation of the 1,5-difunctionalized [5] ferrocenophane derivatives **40**, by simple treatment with the corresponding organolithium derivative.[47]



40

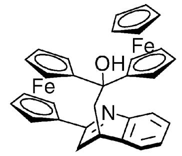
a: R = Ph
b: R = 3-pyridyl
c: R = Fc
d: R = 2-pyridyl

It is worth noting that derivatives **40** act as electrochemical sensors of Mg^{2+} ions: a new redox peak appears in the CVs, which is anodically shifted relative to the $E_{1/2}$ of the free receptors by 268–382 mV. Receptors **40a**, **40b** and **40c** are selective for Mg^{2+}, whilst **40d** is also responsive to Ca^{2+} ions (302 mV shift).

The electrochemical response observed for receptors **40a** and **40b** probably arises from Mg^{2+} coordination to the nitrogen atom of the dihydroquinoline ring and is almost identical to that observed upon protonation in the presence of HBF_4. However, for receptors **40b** and **40d**, which bear a pyridine ring, the positive shift upon coordination with Mg^{2+} is notably lower than that upon protonation, which is indicative that oxidation is facilitated by an additional coordination of the metal ion with the nitrogen atom of the pyridine ring.

Additional evidence for cation binding is provided by UV/Vis spectrophotometric data. Typically, upon addition of Mg^{2+}, as a chelating metal ion, into a dichloromethane solution of **40b**, the characteristic lowest-energy, spin-allowed d–d band of the ferrocene unit is perturbed when the complexation process takes place: the d–d band appearing at λ_{max} = 458 nm (ε = 1398 $M^{-1}cm^{-1}$) in the free receptor disappeared entirely and was replaced by a new band at λ_{max} = 520 nm (ε = 2674 $M^{-1}cm^{-1}$), accompanied by an increase in absorbance. Furthermore, the colour of the dichloromethane solution of **40b** changes from orange to purple, which can be used for "naked-eye" detection of Mg^{2+} in the presence of Ca^{2+}. A Job's plot experiment between **40b** and $Mg(ClO_4)_2$ in dichloromethane at 25 °C revealed a 1:1 stoichiometry. Thus, compound **40b** constitutes an example of a dual electrochemical/optical Mg^{2+} ion sensor.

The new strained asymmetric diferrocene derivative **41**,[48] also available from [5]-ferrocenophane **39**, has also been described. One of the most interesting structural attributes of this [5]-ferrocenophane is the presence of two ferrocene redox-active moieties in proximity to the cation-binding dihydroquinoline site.



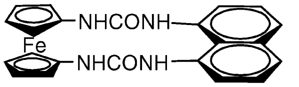
41

Evaluation of its metal-recognition properties demonstrate that compound **41** acts as a highly specific electrochemical and optical Mg^{2+} ion sensor, as revealed by spectroscopic and electrochemical techniques. In the presence of Mg^{2+}, a new redox peak that is anodically shifted relative to the $E_{1/2}$ of the free receptor ($\Delta E_{1/2}$ = 340 mV) appears in the CV.

This coordination process has an effect also on the UV/Vis spectrum of **41**, because ferrocene-based ligands show characteristic perturbations on their LE bands upon complexation. The UV/Vis spectrum of **41** exhibits a prominent HE band at λ_{max} = 319 nm (ε = 8240 $M^{-1}cm^{-1}$), assigned to a ligand-centred π–π* electronic transition (l–π*), together with a less energetic and weaker LE band at λ_{max} = 464 nm (ε = 1195 $M^{-1}cm^{-1}$), attributed to a MLCT process ($d_{\pi-\pi*}$) that is responsible for the bright orange colour of this compound. Addition of Mg^{2+} ions into a solution of **41** in dichloromethane caused a progressive appearance of a new, more intense, LE band, which was redshifted by 76 nm, assigned to MLCT ($d_{\pi-\pi*}$) transitions in the complexed ligand and responsible for a change of colour from orange (neutral proligand) to deep purple (complexed ligand). The HE band was also redshifted, although only very little. By contrast to the above behaviour, compound **41** does not show any significant sensing activity in the presence of Ca^{2+} or alkaline ions. Then, this colour change can be used for "naked-eye" detection of Mg^{2+} even in the presence of Ca^{2+}.

The bathochromic shift of the LE band and the remarkable increase in its molar absorptivity are consistent with an increase in electronic interaction in the resulting complex, as the complexation process through the C=N–C group implies a lowering of the energy gap between the d_π orbitals of the iron atom (HOMO) and the π* orbital of the acceptor group (LUMO). This observation agrees with the appearance of an irreversible reduction wave in the CV of the complexed form of **41**, which is not observed for the proligand and might be attributed to the reduction of the now highly polarized endocyclic C=N double bond. The complexation process in which the binding site (C=N–C) interacts with the cation gives rise to a more stabilized π* orbital in the C=N group, which acts as the acceptor in the MLCT process. Consequently, the oxidant character of this group is enhanced, and the charge-transfer process from the ferrocenyl group (which acts as the donor group) to the acceptor unit is the favoured route upon cation binding.

In the 1,3,7,9-tetraaza[9]ferrocenophane **42** the redox activity of the ferrocene group, the photoactive behaviour of the naphthalene ring and the anion-binding ability of the urea group are combined.[49] The presence of this structural motif, in which two signalling subunits are directly attached by two putative anion-binding sites, yields a combined fluorescence- and redox-based sensor for F^- and $H_2PO_4^-$ anions in a single molecule. Thus, the reversible one-electron wave, corresponding to the free receptor ($E_{1/2}$ = –0.350 V vs. Fe/Fe$^+$), is shifted upon stepwise addition of F^- ($\Delta E_{1/2}$ = –0.190 V) and $H_2PO_4^-$ ($\Delta E_{1/2}$ = –0.125 V) anions, the BEF being 1628 for F^- and 130 for $H_2PO_4^-$.

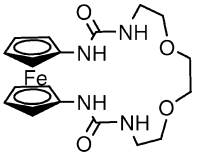


42

Assessments of the anion affinities also came from observing the extent to which the fluorescence intensity of **42** was affected in the presence of anions. The study of the fluorescence behaviour of compound **42** was carried out in dmf ($c = 5 \times 10^{-5}$ M), and the spectrum shows two weak, well-resolved naphthalene-like emission bands with maxima at 362 and 380 nm, when excited at 310 nm, with a quantum yield $\Phi_0 = 0.016$, measured with respect to naphthalene as standard ($\Phi = 0.23 \pm 0.02$). The absorption spectrum between 250 and 350 nm is dominated by the broad naphthalene band with a maximum at 310 nm. Upon addition of F^- or $H_2PO_4^-$ ions, an emission enhancement was observed, although the magnitude of the fluorescence enhancement factor was much smaller for $H_2PO_4^-$ (Φ = 0.05, threefold) than for F^- (Φ = 0.21, 13 fold). Upon recognition, no remarkable anion-binding-induced changes in the absorption spectrum could be detected. Unlike many fluorescent chemosensors for F^-, the fluorescence is "switched on" rather than "switched off" upon recognition. This fact could be of interest, because in the sensing processes fluorescence enhancement, rather than quenching, is usually preferred in order to observe a high signal output.

On the other hand, the behaviour as heteroditopic receptor of 1,3,12,14-tetraaza-6,9-dioxo[14]ferrocenophane **43**, in which both the bis(urea) and the crown ether motifs present in the ansa bridge are built at the same time by using 1,1′-bis(isocyanato)ferrocene and 3,6-dioxo-1,8-diaminooctane, has also been reported.[50] Electrochemical studies upon addition not only of anions but also of metal ions were carried out. This study revealed that receptor **43** showed electrochemical response upon the stepwise addition of F^- and of AcO^-, giving rise to a clear "shifting behaviour" in which the second redox wave was shifted by $\Delta E_{1/2}$ = –0.08 V for F^- and $\Delta E_{1/2}$ = –0.11 V for AcO^-. A "two-wave behaviour" ($\Delta E_{1/2}$ = –0.22 V) was observed upon addition of $H_2PO_4^-$, which allows the calculation of the BEF factor, indicating that the complexation to the reduced form of the receptor is 5287 times more difficult than that to the oxidized one.

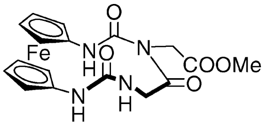
Anion-binding properties of **43** were also evaluated by ^{1}H NMR spectroscopy: the response of this receptor upon addition of several anions provided evidence for the anion-recognition event when F^-, AcO^- or $H_2PO_4^-$ anions were used, in the form of downfield shifts observed for the urea protons during the titration with those anions. Titration isotherms obtained from these chemical shifts were fitted to a 1:1 binding model (receptor/anion) for the F^-, AcO^- and $H_2PO_4^-$ anions.



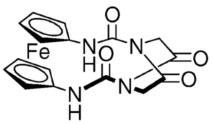
43

Titration experiments with the addition of Li^+, Na^+ and K^+ cations to an electrochemical solution of **43** demonstrate that only the addition of Li^+ gives a clearly observable, separate redox wave anodically shifted in relation to that of the free receptor ($\Delta E_{1/2}$ = 65 mV) and due to the formation of the complexed species [**43**·Li^+]. The CV obtained upon addition of F^- and $H_2PO_4^-$ to an electrochemical solution of the species [**43**·Li^+] showed that the first molar equivalent of these anions have no affinity for the urea residues present in the complex [**43**·Li^+]. However, addition of 1.5 equiv. F^- or $H_2PO_4^-$ anions to the complex [**43**·Li^+] promotes the appearance of the redox peak ascribed to the free receptor **43**. Moreover, further additions of F^- (up to 3 equiv.) or $H_2PO_4^-$ (up to 4 equiv.) to such an electrochemical solution induced a cathodic shift of the redox peak, the magnitude of this redox potential being the same as that observed when those anions were added to the free receptor **43**. These results indicate that the added anions are apparently able to stoichiometrically bind the Li^+ cation, avoiding being bound by the urea groups present in the [**43**·Li^+] host. It is also worth mentioning that a similar behaviour was observed upon addition of the appropriate amounts of Li^+ to the complexed species [**43**·F^-] and [**43**·$H_2PO_4^-$].

1, 3, 6, 8-Tetraaza[8]ferrocenophanes **44** and **45** were also directly prepared from 1,1′-bis(isocyanato)ferrocene and glycine methyl ester.[51] The binding and recognition abilities of these new ligands, bearing a ferrocene unit substituted at the 1- and 1′-positions by two urea groups, towards various anions were evaluated by electrochemical and spectral analysis. These studies revealed that these highly functionalized, nitrogen-rich [8]ferrocenophanes can have applications as spectral and electrochemical selective sensors for F^- and $H_2PO_4^-$ anions.



44



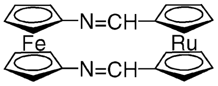
45

The binding constants of compounds **44** and **45** with such anions, as their TBA^+ salts, were determined by using ^{1}H NMR spectroscopic titration methods to follow the chemical shift change of the NH protons. The binding modes in the complexes formed have also been discussed on the basis of theoretical calculations.

[*m*,*n*]-Ferrocenophanes

[2,2]-Ferrocenophanes

Mixed diaza[2,2]ferrocenoruthenocenophanes **46** and **47**, bearing an aldimine functionality connecting both metallocene units, have been described.[52] These new heterometallocenophanes exhibit interesting cation-sensing properties and show high selectivity for Zn^{2+} ions. The metal–ligand transition band in the absorption spectra of these compounds is redshifted by about 100 nm only in the presence of Zn^{2+} ions. This change in the absorption spectra is accompanied by a dramatic colour change from pale red to deep green, which demonstrates the ability of these compounds to behave as colorimetric chemosensors for highly selective "naked-eye" detection of Zn^{2+} ions (detection limits of 6.0×10^{-6} and 5.8×10^{-6} M, for **46** and **47**, respectively) and over some other cations, including the strong competitor Cd^{2+}.



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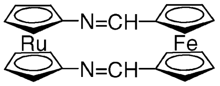
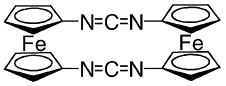


47

[3,3]-Ferrocenophanes

Tetraaza[3,3]homo- and heterometallocenophanes **48**[53] and **49**[52] have also been reported. Although these derivatives do not display any ion-sensing properties, they have been used for the study of intramolecular electronic processes as well as for the preparation of an extremely nitrogen-rich [2,2]bis[3,3]ferrocenophane in which the organometallic fragments are linked by four guanidine moieties.[53]



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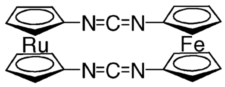

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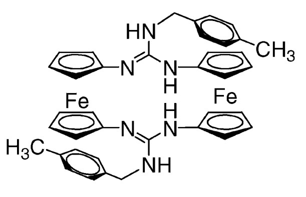

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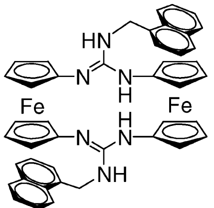

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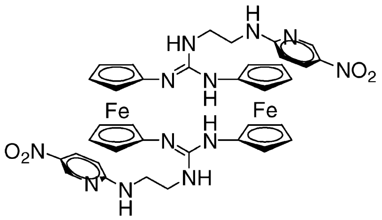

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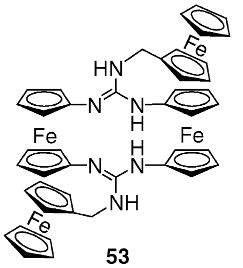


53

The receptors **50**–**53** having a [3.3]ferrocenophane framework in which two ferrocene subunits, with similar electronic environments, are linked through two substituted guanidine moieties have been prepared by the reaction of bis(carbodiimide) **48** with primary amines.[54]

This architecture is exceptionally "tunable", because a variety of "legs" may be appended to the basic [3.3]ferrocenophane scaffold to give a wide range of signalling units. These receptors show remarkable ion-sensing properties due to the presence of a redox active unit (ferrocene) and an amphoteric binding site (guanidine). The DPVs of receptors **50**–**52** in dmso/H_2O (4:1, v/v) display two one-electron oxidation peaks in the range $E_\mathrm{p}^1 = -390$ to -350 mV and $E_\mathrm{p}^2 = -90$ to -120 mV vs. the Fe $^{\mathrm{II}}$/Fe$^{\mathrm{III}}$ redox couple, whereas the DPV of receptor **53**, in dmso, exhibits three well-resolved peaks: two one-electron oxidation peaks at –440 and –150 mV, and another one with a potential at +50 mV vs. the Fe $^{\mathrm{II}}$/Fe$^{\mathrm{III}}$ redox couple, which is actually due to two closely overlapping one-electron transfer processes corresponding to the oxidation of the peripheral ferrocenes. In contrast to most ferrocene-based redox sensors reported, which rely on changes in the oxidation potential of the ferrocene, in the newly designed receptors, not only the occurrence of two oxidation peaks but also the magnitude of the ΔE_p (250–280 mV for receptors **50**–**52** and ΔE_p = 290 and 200 mV for receptor **53**) allows the different perturbations of the two oxidation peaks of this structural motif upon complexation to be used, for the first time, as a redox-ratiometric measurement of the binding event.

In this nitrogen-rich structural motif, the guanidine bridges act as multipoint binding sites for anions, cations and amino acids. In fact, they allow the sensing not only of the F^-, AcO^-, HSO_4^-, $H_2PO_4^-$ and $HP_2O_7^{3-}$ anions, but also of the amino acids L-Glu, L-Trp, L-Leu and L-Phe through two different oxidation-peak perturbations, in a highly polar environment. Additionally, the monoprotonated form of this structure is able to selectively sense Cl^- and NO_3^- by redox-ratiometric measurements.

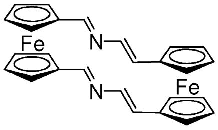
The metal-recognition properties of the guanidino-ferrocenophane receptors **50**–**52** towards Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Cd^{2+} and Zn^{2+} ions have also been evaluated by electrochemical analysis in dmso/CH_2Cl_2 (3:2, v/v). The electrochemical results obtained demonstrate that voltammograms of such hosts are only affected when Zn^{2+} cations are added. Such addition promotes a dramatic decrease in intensity of the first oxidation peak, while no perturbation of the second oxidation peak is observed.

Because of the presence of the naphthalene ring, receptor **51** is able to act as a fluorescent chemosensor of Zn^{2+}, Ni^{2+} and Cd^{2+} cations. When the complexes were formed, there was a pronounced redshift along with an increase in intensity of the naphthalene monomer emission. Furthermore, proton-induced complexation of **51** provides a versatile means of sensing selectively NO_3^- by fluorescence emission quenching.

The UV/Vis data obtained in dichloromethane for the bis(guanidyl) ferrocenophane receptors **50**–**53** are consistent with most ferrocenyl chromophores in that they exhibit two charge-transfer bands in the visible region: a prominent absorption band with a maximum at 363 nm, which can safely be ascribed to ligand-centred π–π* electronic transitions (l–π*), together with another lower-energy, weaker absorption band, which is produced either by a Fe^{II} d–d transition[24] or by a MLCT process ($d_{\pi-\pi*}$). Therefore, the anion-recognition properties of these bis(ferrocene) ligands, in dichloromethane, towards the F^-, Cl^-, AcO^-, NO_3^-, HSO_4^-, $H_2PO_4^-$ and $HP_2O_7^{3-}$ anions have also been described by using UV/Vis spectroscopy. No changes were observed in the UV/Vis spectra of receptors **50**, **51** and **53** upon addition of the above-mentioned anions, even in a large excess. However, in receptor **52**, the presence of different nitrogen functionalities allow the colorimetric sensing of F^-, AcO^-, $H_2PO_4^-$ and $HP_2O_7^{3-}$ anions. In fact, addition of such anions induces a redshift of the LE band of the free ligand and an important increase in molar absorptivity. This new band is responsible for a change of colour and has been used for the "naked-eye" detection of these anions.

[4,4]-Ferrocenophanes

An exciting challenge that has been less explored is the design of redox-switchable ligands that are not only able to bind (namely, a shift in the $E_{1/2}$ value upon metal complexation) but are also able to act as actuators through the progressive electrochemical release of the metal cation (that is, the binding constant upon electrochemical oxidation is decreased). This is an unfamiliar area in ferrocene-based ligands, and the abrupt decrease in Na^+ cation binding strength upon electrochemical oxidation of a pentaoxa[13]-ferrocenophane has only been described in an earlier report.[55] In this context, a new highly preorganized molecular system **54** has been reported. In this receptor, two ferrocene subunits that have dissimilar electronic environments are linked through a conjugated double bridge which comprises a putative cation-binding site.[56]



54

The metal-recognition properties of ferrocenophane **54** were evaluated by electrochemical and optical analysis. The cyclic voltammetry and Osteryoung square-wave voltammetry (OSWV) analyses of **54** show two well-resolved, quasi-reversible one-electron oxidations in a 1:1 ratio at formal potentials of +0.44 and +0.89 V vs. decamethylferrocene (dmfc). The first reversible oxidation process arises from the oxidation of the ferrocene unit at the 4-position of the two bridges, while the second is associated with the oxidation of the ferrocene unit at the 1-position. Whereas no perturbation of the voltammograms was observed upon addition of Ca^{2+}, Li^+, Na^+ and K^+ ions, even in a large excess, a significant modification was observed upon addition of Mg^{2+} ions. In contrast, the second oxidation wave was apparently not perturbed upon the addition of Mg^{2+} ions. This particular behaviour is the characteristic of a large equilibrium constant for the binding of Mg^{2+} by the neutral receptor. The fact that the second oxidation process of complex $[Mg_2\cdot\mathbf{54}]^{4+}$ practically occurs at the same potential as that observed for the free ligand **54** suggests that the complex is disrupted after the first monoelectronic oxidation of complex $[Mg_2\cdot\mathbf{54}]^{4+}$ and the second oxidation really takes place on the uncomplexed mono-oxidized species $\mathbf{54}^+$. Demonstration of the electrochemically mediated control of the successive trapping and expulsion of Mg^{2+} ions, as well as the ability of compound **54** to transport this cation through a liquid membrane in which the switchable activation/deactivation of the ligand is carried out electrochemically, has also been reported.

The UV/Vis spectrum of **54** is characterized by a very strong absorption band at 331 nm (ε = 17200 $\mathrm{M}^{-1}\,\mathrm{cm}^{-1}$), which is assigned to a high-energy, ligand-centred π–π* electronic transition, and a weaker, lower-energy band at 500 nm (ε = 1600 $\mathrm{M}^{-1}\,\mathrm{cm}^{-1}$), which is attributed to a MLCT process (d–π*). Such spectral characteristics confer an orange colour to the neutral ferrocenophane **54**. The addition of increasing amounts of $Mg(ClO_4)_2$ to a solution of **54** in CH_2Cl_2 caused a progressive appearance of a band at 350 nm (ε = 19900 $\mathrm{M}^{-1}\,\mathrm{cm}^{-1}$) and a new more intense band, located at λ = 520 nm (ε = 3700 $\mathrm{M}^{-1}\,\mathrm{cm}^{-1}$) and the complete disappearance of the initial band at 500 nm. The new band is redshifted by 20 nm and is responsible for the change of colour from orange (neutral ferrocenophane **54**) to deep purple (complexed ferrocenophane $[Mg_2\cdot\mathbf{54}]^{4+}$). This colour change can be used for a "naked-eye" detection of Mg^{2+}, even in the presence of Ca^{2+}.

Conclusions

The examples described in this review show how the reversible Fe^{II}/Fe^{III} redox couple in aza-substituted ferrocene receptors bearing an additional signalling unit may be used not only to control the binding strength between two or more interacting species but also to satisfy multisignal sensing purposes. Interesting links between redox-switched binding processes and remarkable changes in the emission and/or absorption spectra are described. Recent developments in the design of organic–inorganic hybrid materials suggest that many of the effects observed in solution for such probes appear to be perfectly reproducible, which bodes well for future applications. Thus, future research should be directed to rethink classical models of ferrocene-based molecular sensors in order to develop new highly selective and specific sensing receptors having structures that are as simple as possible but can be applied to solve real-world problems in the fields of medicine, biology or environmental sciences.

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