

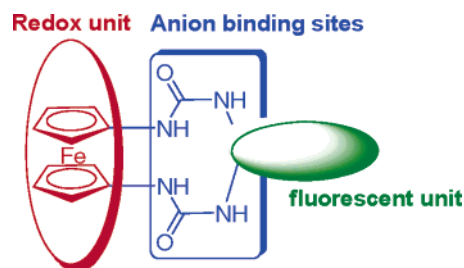
Ferrocene-Based Ureas as Multisignaling Receptors for Anions[†]

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Received March 2, 2006



The synthesis of structurally new types of ferrocene-based ureas, in which the ferrocene moiety is simultaneously attached to two urea groups, have been prepared directly from 1,1'-bis(isocyanato)ferrocene **1**. Homoditopic receptors **2a–e** show spectral and electrochemical anion-sensing action: they display a selective downfield shift of the urea protons and a cathodic shift of the ferrocene/ferrocinium redox couple with hydrogen phosphate and fluoride anions. In addition, receptor **2d** based on an unprecedented tetraaza[9]ferrocenophane architecture, shows spectral, electrochemical, and selective fluorescent responses to fluoride anion.

Introduction

Since anions are ubiquitous and play important roles in many biological and chemical systems, the field of synthetic anion receptors chemistry is one of the fastest growing disciplines within the general context of supramolecular chemistry.¹ One successful approach for preparing anion hosts involves the formation of molecular architectures which contain redox,

chromogenic, or fluorogenic groups that are covalently or noncovalently linked to the receptor moiety, thus enabling the electrochemical, colorimetric, and fluorimetric sensing of anions with both temporal and spatial resolution.

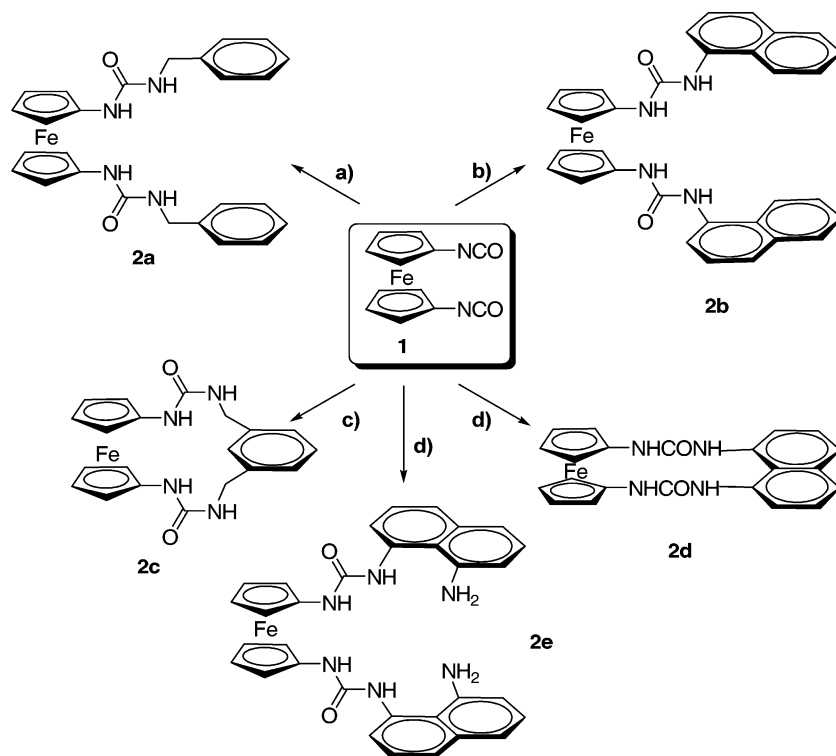
The nature of the anion–receptor interaction is a matter of choice for the designer; anion–receptor based solely on hydrogen bonding seems to be particularly challenging by the perspective of achieving a good selectivity using interactions that strongly depend on the direction and distance.

Urea is an attractive building block for anion receptors because it contributes two relatively strong hydrogen-bonding sites.² The two 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 oxianion 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,³ and new insights into the nature of urea–anion interactions providing structural criteria for the deliberate design of anion

[†] Dedicated to our friend Prof. M. Moreno Mañas, in memoriam.

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SCHEME 1. Synthesis of Receptors 2^a

^a Reagents: (a) benzylamine; (b) 1-aminonaphthalene; (c) *m*-xylylenediamine; (d) 1,8-diaminonaphthalene.

selective receptors containing two or more urea binding groups have also been recently reported.⁴ There are, however, few examples of urea/ferrocene redox-active anionophores.⁵

Generally, anion recognition motifs are often structurally complicated and require an elaborate and sophisticated synthetic process. Therefore, the development of simple and easy-to-make chemosensors for anions is strongly desired. From this perspective, we decided to study a series of new type of anionophores by combining the redox activity of the ferrocene moiety with the strong hydrogen-bonding ability of the urea group. An interesting feature of our synthetic approach for the preparation of these receptors is that 1,1'-bis(isocyanato)ferrocene, prepared from the corresponding 1,1'-ferrocene dicarboxylic acid, via its

acyl azide,⁶ is used as common building block. Despite its rich functionality, the chemistry of this difunctionalized ferrocene derivative remains almost unexplored because only its conversion into 1,1'-bis(isocyanato)ferrocene⁷ and nitrogen-rich ferrocenophanes have been reported.^{5d, 8}

Here, we present the synthesis and anion coordination properties of a new kind of simple ferrocene-based urea receptors bearing in its molecule one or two signaling units linked through two urea groups either linearly or joined through a ferrocenophane framework.

Results and Discussion

Synthesis. Reaction of 1,1'-bis(isocyanato)ferrocene **1** with the appropriate primary amine (1:2 molar ratio) allowed isolation of the 1,1'-bis(ureido)ferrocenes **2a** and **2b** in 80% and 75% yields, respectively (Scheme 1), whose ¹H and ¹³C NMR, elemental analysis, and mass spectra were consistent with the proposed structures.

The easy access to the above-mentioned 1,1'-difunctionalized ferrocene derivatives from **1** prompted us to check the reaction with diamines in order to evaluate the suitability of this reaction in achieving homoditopic [*m*]ferrocenophanes bearing two urea groups. In agreement with our expectations, we have found that this reaction afforded the tetraaza[*m*]ferrocenophanes **2c** and **2d**, although their formation is strongly dependent both on the 1/diamine molar ratio and on the reaction conditions. So, by using *m*-xylylenediamine or 1,8-diaminonaphthalene in a 1:1

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TABLE 1. Voltammetric and Complexation Data of Ligands **2**, Obtained in DMSO at 278 K

receptor A ^a	$E_{1/2}$ (V) free	$E_{1/2}$ (V) complex	$\Delta E_{1/2}$ (mV)	min equiv ^b	max equiv ^c	R/A ^d	K_{as}
2a ·F ⁻	-0.320	-0.480	-160	0.1	3	1:2 ^e	$7.2 \times 10^5 \text{ M}^{-2}$
2a ·H ₂ PO ₄ ⁻	-0.320	-0.462	-142	0.25	3	1:1 ^e	$5.6 \times 10^3 \text{ M}^{-1}$
2b ·F ⁻	-0.330	-0.540	-208	0.1	2.25	1:2 ^e	$4.0 \times 10^6 \text{ M}^{-2}$
2b ·H ₂ PO ₄ ⁻	-0.330	-0.420	-90	0.1	1	1:1 ^e	$2.1 \times 10^4 \text{ M}^{-1}$
2c ·F ⁻	-0.398	-0.510	-112	0.25	2	2:1 ^f	$3.3 \times 10^6 \text{ M}^{-2}$
						1:1	$4.9 \times 10^4 \text{ M}^{-1}$
2c ·H ₂ PO ₄ ⁻	-0.398	-0.471	-76	0.25	1.5	2:1 ^f	$3.0 \times 10^4 \text{ M}^{-2}$
2d ·F ⁻	-0.350	-0.540	-190	0.1	2	1:2 ^e	$8.5 \times 10^4 \text{ M}^{-2}$
2d ·H ₂ PO ₄ ⁻	-0.350	-0.475	-125	0.1	2	1:1 ^e	405 M^{-1}
2e ·F ⁻	-0.342	-0.402	-60	0.25	2	1:1 ^e	$3.7 \times 10^3 \text{ M}^{-1}$
	0.034 ^g	-0.340	-374 ^h				
2e ·H ₂ PO ₄ ⁻	-0.342	-0.450	-108	0.25	2	1:1 ^e	$4.4 \times 10^4 \text{ M}^{-1}$
	0.034 ^g	-0.298	-332 ^h				

^a Anions added as their tetrabutylammonium salts. ^b Minimum equivalents of salt required to give a detectable electrochemical response. ^c Maximum equivalents required to saturate the voltammetric response. ^d Stoichiometries (receptor/anion) of the complexes formed. ^e Obtained by EQNMR analysis of the ¹H NMR titration data. ^f Obtained by using isothermal titration calorimetry (ITC). ^g E_p of the irreversible wave. ^h ΔE_p .

molar ratio and under high dilution conditions the main products obtained were the corresponding tetraaza[*m*]ferrocenophanes **2c** and **2d** in 70 and 68% yield, respectively. Interestingly, by using an excess of 1,8-diaminonaphthalene (1:4 molar ratio) and under normal dilution conditions, the corresponding 1,1'-bis(ureido)-ferrocene **2e**, having two naphthalene fluorophore subunits, was mainly obtained in 73% yield. Remarkably, the ¹H and ¹³C NMR spectra of compounds **2c** and **2d** reveal high symmetry, only showing one set of signals for the two ureido substituents placed at the 1 and 1' positions of the ferrocene moiety.

Anion-Sensing Properties. At first, the electrochemical properties of receptors **2** as its own as well as in the presence of variable concentrations of F⁻, Cl⁻, Br⁻, AcO⁻, NO₃⁻, HSO₄⁻, and H₂PO₄⁻ as guest anionic species were investigated using cyclic (CV) and differential pulse (DPV)⁹ voltammetries. Each free receptor exhibited a reversible one-electron redox wave,¹⁰ typical of a ferrocene derivative, at the halfwave potential values shown in Table 1, calculated versus the ferrocenium/ferrocene (Fc⁺/Fc) redox couple and which are identical to those obtained from the corresponding DPV peaks.

Titration studies with addition of those anions, as their tetrabutylammonium salts (TBA⁺), to an electrochemical solution of receptors **2** ($c = 10^{-3} \text{ M}$) in the appropriate solvent, containing 0.1 M [*n*-Bu₄N]ClO₄ as supporting electrolyte, demonstrate that while addition of F⁻ and H₂PO₄⁻ anions to receptors **2a–d** promotes remarkable responses, indicating the interaction of the urea binding sites with these anions, addition of Cl⁻, Br⁻, AcO⁻, NO₃⁻, and HSO₄⁻ anionic species had no effect on the CV and DPV of these receptors, even when present in a large excess.

Nevertheless, the results obtained on the stepwise addition of substoichiometric amounts of the appropriate guest anionic species revealed two different electrochemical behaviors, depending on the receptor and anion used, which reflects either a typical “two wave behavior”, with the appearance of a second wave at more negative potentials, together with the correspond-

ing to the free receptor and which is due to the anion complexed species, or a “shifting behavior”, in which a second redox wave, negatively shifted compared to the free receptor, appears.¹¹ Moreover, for the receptor–anion combinations studied showing a “two wave behavior”, only 0.1 equiv of anion was needed to give a clearly observable separated redox wave, from the complexed species, while for the systems showing a “shifting behavior” a minimum of 0.25 equiv of the anion is required to give an observable electrochemical response.

In general, for receptor–anion systems exhibiting “two wave behavior”, both half-wave potentials can be obtained from the voltammetric data as both redox couples are simultaneously detected and then the binding enhancement factors (BEF)¹² could be calculated. This factor indicates the times that the complexation in the reduced form of the receptors is more difficult than that in the oxidized one. From the results showed in Table 1, is notable that while the addition of H₂PO₄⁻ anion to the receptors **2a**, **2c** and of F⁻ anion to **2c**, shows a voltammetric response typical of a “shifting behavior”, clean “two wave behavior” responses were seen in the other homoditopic receptor–anion combinations studied.

The responses of receptors **2** upon addition of F⁻, Cl⁻, Br⁻, AcO⁻, NO₃⁻, HSO₄⁻, and H₂PO₄⁻ anions have also been investigated by ¹H NMR titration, providing further evidence for the anion-binding event. Thus, titration isotherms obtained by using the computer program EQNMR¹³ and generated from the change in chemical shift of the host urea protons upon addition of the appropriate anions were used to fit the binding model receptor–anion and the derived association constants (Table 1).

Quantum chemical calculations at the DFT¹⁴ level of theory (see the Supporting Information) on the simplest open ferrocenyl-bisurea **3** as model compound were performed to help explaining the preferred binding modes upon interaction with both F⁻ and H₂PO₄⁻ anions, as well as the magnitude of the host–guest complexation. Receptor **3** itself shows a preferential

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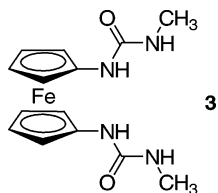
(10) The criteria applied for reversibility was a separation of $\approx 60 \text{ mV}$ between cathodic and anodic peaks, a ratio of 1.0 ± 0.1 for the intensities of the cathodic and anodic currents I_c/I_a , and no shift of the half-wave potentials with varying scan rates.

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geometry for the free ligand (see the Supporting Information) with both urea sidearms arranged to form an intramolecular complex by means of two unequal hydrogen bridge bonds between a carbonyl O atom and both NH groups ($d_{O\cdots HN} = 2.028$ and 2.302 Å, WBI 0.020 and 0.005) in the complementary urea moiety in a six-membered chelate fashion. With respect to the noninteracting conformer of C_i symmetry, this represents a stabilization electronic energy of -5.07 kcal/mol that must be enough compensated by the interaction with a guest for the complex formation. For this model compound **3**, the complexation of F^- anion occurs in a C_2 symmetrical mode (see the Supporting Information) with all four urea H atoms directed inward and yielding two pairs of hydrogen bonds ($d_{F\cdots HN} = 1.691$ and 1.729 Å, WBI 0.079 and 0.064) that give rise to a high complexation energy (see Table 1 in the Supporting Information). The interaction with a second equivalent of F^- has little effect on the complexation energy and keeps the C_2 symmetry in the most stable conformation (see the Supporting Information), but with every F atom strongly interacting mainly with only one urea group ($d_{F\cdots HN} = 1.508$ and 1.666 Å, WBI 0.145 and 0.094). On the contrary, complexation of the less polarizing $H_2PO_4^-$ anion occurs with little deformation of the ligand that weakens the convergent intramolecular hydrogen bonds ($d_{O\cdots HN} = 2.183$ and 2.690 Å, total WBI 0.024) in order to approach the remainder divergent NH and CO urea groups that form a six contact points array with the anionic guest, mainly consisting in weak hydrogen bonds with two PO ($d_{PO\cdots HN} = 1.763$ and 1.812 Å, WBI 0.071 and 0.059) and one POH group ($d_{POH\cdots OC} = 1.905$ Å, WBI 0.037), yielding a moderate complexation energy (see the Supporting Information).

In this context, the behavior of the urea/ferrocene ligand **2a** as a versatile redox active receptor has been studied by electrochemical measurements. Compound **2a** 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 $H_2PO_4^-$ anions as their tetrabutylammonium salts revealed its capability for acting as electrochemical sensor for those anions. In fact, upon addition of F^- a two-wave response, with the appearance of 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 changes markedly and a typical shifting behavior, with the appearance of a new negatively shifted wave, was observed, $\Delta E_{1/2} = -142$ mV being the maximum shift obtained when 3 equiv of $H_2PO_4^-$ was added ($E_{1/2} = -0.462$ V) (see the Supporting Information). 1H NMR titration experiments were also used to monitor the anion recognition process. Thus, upon addition of aliquots of F^- and $H_2PO_4^-$ anions the urea protons were clearly downfield shifted, demonstrating that these protons are involved in the ligand–anion binding event (see the Supporting Information). 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. The calculated

association constants using the EQNMR program were 7.2×10^5 M^{-2} for F^- and 5.6×10^3 M^{-1} for $H_2PO_4^-$.

The binding and recognition abilities of the homoditopic ferrocenophane receptor **2c**, bearing a *m*-xylylene unit connecting the two urea groups at the 1 and 1' positions of the ferrocene moiety, were also evaluated by electrochemical and isothermal titration calorimetry (ITC) analysis. The CV response of **2c** in DMSO showed an electrochemically reversible one-electron oxidation process at $E_{1/2} = -0.398$ V vs Fc^+/Fc . Electrochemical anion-sensing experiments demonstrate that only the stepwise addition of F^- and $H_2PO_4^-$ promotes a cathodic shift of the ferrocenium/ferrocene redox couple. The maximum shift was obtained when 2 equiv of F^- ($\Delta E_{1/2} = -112$ mV) or 1.5 equiv of $H_2PO_4^-$ ($\Delta E_{1/2} = -76$ mV) were added (Table 1) (see the Supporting Information). Notably, the presence of the other anions had no effect on the voltammetric response, even when present in a large excess.

The limited solubility of receptor **2c** in DMSO- d_6 prevented 1H NMR spectroscopy-based titrations. To overcome such problems, efforts were made to determine the anion affinities of this receptor by means of other, more sensitive methods. Isothermal titration calorimetry (ITC) provides useful insight into the nature of the binding interactions, and the advantages of this method for studying anion recognition properties have been recently reported.¹⁵ ITC experiments were carried out by adding aliquots of the appropriate anion ($c = 1.4 \times 10^{-2}$ M) to a solution of **2c** ($c = 1 \times 10^{-3}$ M) at 298 K in DMSO. In the case of adding F^- , the titration curve showed two inflection points around 0.5 and 1.0 equiv of anion added, which confirms the formation of complexes with 2:1 and 1:1 (receptor/anion) stoichiometries (see the Supporting Information). When $H_2PO_4^-$ anion was added, the titration curve showed an inflection point around 0.5 equiv of anion added which evidenced the formation of a 2:1 complex. The titration data were fitted to a 1:1 or a 2:1 binding model using a nonlinear least-squares fitting procedure. The corresponding association constants are listed in Table 1.

Anion-binding properties of receptors **2b**, **2d**, and **2e** bearing two photoactive naphthalene groups connected to the ferrocene unit by two urea moieties were evaluated by both electrochemical and fluorescence analysis. It is worth mentioning that the fluorescence response of the acyclic receptor **2b** 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 behavior despite the formation of stable complexes. Nevertheless, its electrochemical anion-sensing behavior was determined by CV experiments in DMSO containing 0.1 M TBAClO₄ as supporting electrolyte. The results obtained by the stepwise addition of F^- anion (as its TBA⁺ salt) 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 the corresponding to the free receptor ($E_{1/2} = -0.330$ V vs Fc^+/Fc). Its position with respect to the wave corresponding to the uncomplexed receptor ($\Delta E_{1/2} = -210$ mV)¹⁶ reflects a more favorable oxidation process for the ferrocene moiety in the complexed species due to the presence

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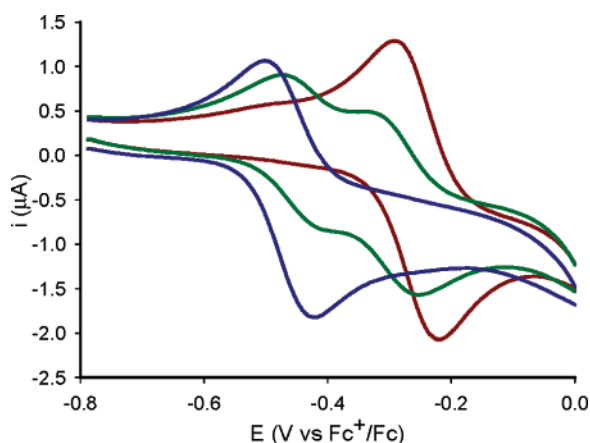


FIGURE 1. CV response of receptor **2b** (10^{-3} M) in DMSO before (red) and after addition of 1 (green) or 2.2 (blue) equiv of F^{-} ; supporting electrolyte, 0.1 M (*n*-Bu₄N)ClO₄; scan rate, 100 mV s⁻¹.

in close proximity of a negatively charged anion center. The current of the new redox couple increases until 2.2 equiv of the guest fluoride anion is added. At this point, the reversible wave corresponding to uncomplexed receptor **2b** disappears (Figure 1). This “two-wave behavior” is diagnostic of a large value for the equilibrium constant for F^{-} binding by the neutral receptor **2b** with a BEF of 3312, which means that the complexation in the reduced form of the ligand **2b** 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 **2b** a similar effect was observed with a $\Delta E_{1/2} = -90$ mV (BEF = 25) the CV data showing that 1 equiv is required to achieve the disappearance of the redox wave due to the uncomplexed receptor (see the Supporting Information). It is noteworthy that the presence of other anions (Cl^{-} , Br^{-} , AcO^{-} , HSO_4^{-} , and NO_3^{-}) in solution had no effect on the CV even in high concentrations.

Titration experiments using 1H NMR spectroscopy in DMSO-*d*₆ following the chemical shift change of the urea protons were used to determine the binding constants of **2b** with both F^{-} (Figure 2) and $H_2PO_4^{-}$ anions. During the titration experiment, all of the NH urea signals are shifted downfield ($\Delta\delta = +2.22$ and 2.09 ppm for F^{-} and $\Delta\delta = +1.83$ and +1.51 ppm for $H_2PO_4^{-}$) indicating that all these protons participate in an authentic hydrogen-bonded complex.¹⁷ Titration isotherms obtained from these changes in the chemical shifts of the host NH signals were fitted nicely to a 1:2 and 1:1 (receptor/anion) binding model for F^{-} and $H_2PO_4^{-}$ anions, respectively, the corresponding association constants being 4.0×10^6 M⁻² for F^{-} and 2.1×10^4 M⁻¹ for $H_2PO_4^{-}$.

Compound **2d** is the most rigid of the homoditopic anion receptors considered in this study, in which the redox activity of the ferrocene group, the photoactive behavior of the naphthalene ring, and the anion-binding ability of the urea group are combined. The presence of this structural motif in which two signaling subunits are directly attached by two putative anion-binding sites could yield a combined fluorescence- and

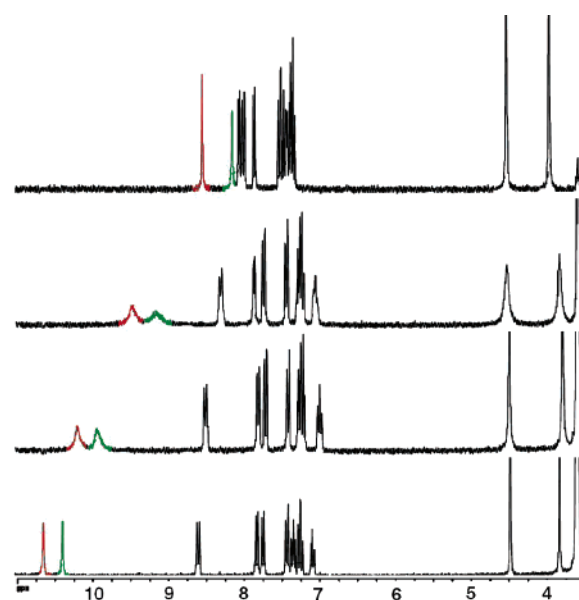


FIGURE 2. 1H NMR spectral changes observed for the urea protons of **2b**, in DMSO-*d*₆, after the addition of (a) 0, (b) 0.8, (c) 1.6, and (d) 2.8 equiv of F^{-} .

redox-based sensor in a single molecule. The electrochemical anion-binding properties of **2d** were determined by CV in DMSO. Thus, on stepwise addition of F^{-} (as its TBA⁺ salt), a clear evolution of the reversible one-electron wave, corresponding to the free receptor, from $E_{1/2} = -0.350$ V vs Fe/Fe⁺ to $E_{1/2} = -0.540$ V vs Fe/Fe⁺ ($\Delta E_{1/2} = -0.190$ V) was observed, the maximum perturbation of the CV being obtained when 2 equiv of F^{-} anion was added. This “two-wave behavior” is diagnostic of a large value for the equilibrium constant for fluoride binding by the neutral receptor **2d**. Similar “two-wave behavior” was also found when 2 equiv of $H_2PO_4^{-}$ was added: $E_{1/2} = -0.475$ V vs Fe/Fe⁺ ($\Delta E_{1/2} = -0.125$ V) (see the Supporting Information). The BEF are 1628 for F^{-} and 130 for $H_2PO_4^{-}$, respectively. As was mentioned above, the presence of Cl^{-} , Br^{-} , HSO_4^{-} , NO_3^{-} , and AcO^{-} anions had no effect on the CV, even when present in large excess. These findings underscore the selectivity of receptor **2d** for F^{-} and $H_2PO_4^{-}$ anions in a relatively polar solvent (DMSO), where hydrogen-bonding interactions between the urea functional groups and the anions are usually weakened by competing solvent molecules.

The binding constants of **2d** with several guest anions were determined by the titration methods using 1H NMR spectroscopy in DMSO-*d*₆ following the chemical shift change of the NH protons. Namely, addition of aliquots of the F^{-} anion to a solution of the receptor **2d** caused a chemical shift change of the NH protons of the receptor until 2 equiv of the anion was added ($\Delta\delta = +1.57$ and +2.03 ppm), indicating that all four protons participate in the formation of the hydrogen-bonded complex, whose calculated association constant was $K_a = 8.5 \times 10^4$ M⁻² (error < 10%) (see the Supporting Information) with the resulting binding curve nicely fitting to a 1:2 stoichiometry of the complex. Further additions of the anion did not promote any significant change in those chemical shifts.

Addition of 1 equiv of $H_2PO_4^{-}$ as a guest anion resulted in a lower downfield shift ($\Delta\delta = +1.08$ and +1.42 ppm) of the NH resonances, which is also consistent with the formation of a hydrogen-bonded complex. The resulting binding curve clearly

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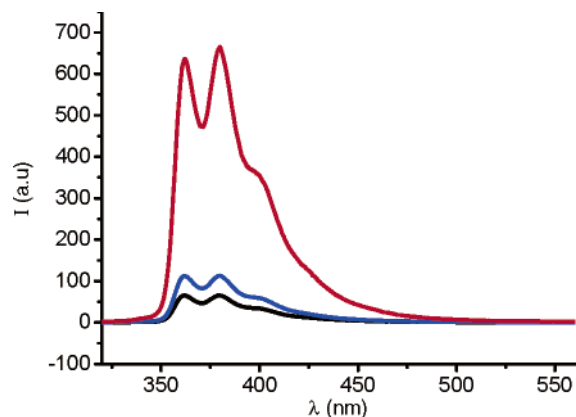


FIGURE 3. Fluorescent emission of **2d** ($c = 5 \times 10^{-5}$ M in DMF) upon addition of tetrabutylammonium fluoride (red) and dihydrogenophosphate (blue) ($\lambda_{\text{exc}} = 310$ nm).

demonstrated the 1:1 stoichiometry of the complex, and the association constant was 405 M^{-1} (error < 10%). With Cl^- , Br^- , HSO_4^- , NO_3^- , and AcO^- anions, there were no chemical shifts changes for the NH peaks, even when up to 10 equiv of these anions were added.

Assessments of the anion affinities also came from observing the extent to which the fluorescence intensity of **2d** was affected in the presence of anions. The study of the fluorescence behavior of compound **2d** was carried out in DMF ($c = 5 \times 10^{-5}$ M) and shows a weak well-resolved naphthalene-like emission bands with a maximum at 362 and 380 nm, respectively, when excited at 310 nm, and with a quantum yield $\Phi_0 = 0.016$, measured with respect to naphthalene as standard ($\Phi = 0.23 \pm 0.02$).¹⁸ The absorption spectrum between 250 and 350 nm is dominated by the broad naphthalene band with a maximum at 310 nm. Upon addition of various anions as TBA^+ salts in a 20-fold excess, no change in the emission spectra could be observed for Cl^- , Br^- , and HSO_4^- . However, a strong fluorescence enhancement factor of 13 was obtained in the presence of F^- with a quantum yield of $\Phi = 0.21$. Similar emission enhancement was observed upon the addition of H_2PO_4^- ion ($\Phi = 0.05$), although the magnitude of such enhancement (3-fold) was much smaller than for F^- ion (Figure 3). 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 sensing processes, fluorescence enhancement, rather than quenching, is usually preferred in order to observe a high signal output.

The sensing of a fluoride anion, the smallest anion, has attracted growing attention because of its important role in numerous biological processes.¹⁹ The conventional approaches for the binding of fluoride anion have used either the specific strong affinity of a boron atom toward the fluoride anion or designed hydrogen bonding with the fluoride anion. These binding events have been converted into an electrochemical²⁰ or fluorescent change²¹ or, more directly, a colorimetric change detectable by the naked eye.²² Despite the development of these classical single-signaling approximations, there is a paucity of

use of multichannel signaling fluoride selective chemosensors.²³ The receptor **2d**, however, based on an azaferrocenophane structure bearing two urea groups as linkers between the redox-active (ferrocene) and fluorescent (naphthalene) signaling subunits, shows both fluorescent and electrochemical anion-sensing action: it displays a selective fluorescent enhancement factor of 13 and a remarkable cathodic shift of the ferrocene oxidation wave (190 mV) with fluoride anions.

The calculated global minimum for the **2d**· 2F^- complex exhibits all four acidic urea protons involved in the binding process, but following an asymmetric pattern in contrast to the behaviour shown for the **3**· 2F^- model complex.²⁴ The most acidic urea proton—at one of the naphthalene-linked NH groups (as evaluated by simple comparison of either Mulliken or natural charges on such hydrogen atoms in the free ligand **2d**)—is attached to one F atom ($d_{\text{F}\cdots\text{H}} = 1.018 \text{ \AA}$, WBI 0.509), the corresponding naked N atom forming hydrogen bridge bonds with both the latter H atom ($d_{\text{N}\cdots\text{HF}} = 1.527 \text{ \AA}$, WBI 0.195) and the related naphthalene-linked NH group ($d_{\text{N}\cdots\text{HN}} = 2.015 \text{ \AA}$, WBI 0.028) in the other urea moiety. Both urea subunits are also connected by the other two NH groups that are hydrogen bridge bonding the second F^- anion ($d_{\text{F}\cdots\text{HN}} = 1.367$ and 1.640 \AA , WBI 0.205 and 0.095) in an almost linear fashion (angle $\text{F}\cdots\text{H}\cdots\text{N} = 168.0$ and 159.2° , respectively) (Figure 4). Even after the required remarkable ligand reorganization from the uncomplexed C_2 -symmetric geometry (see the Supporting Information), the highly negative calculated change in energy

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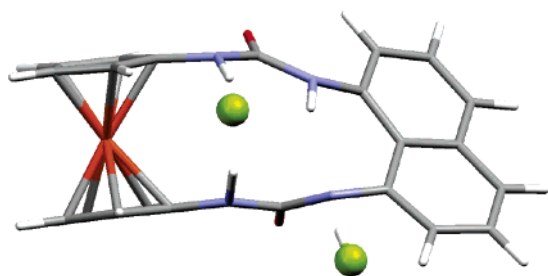


FIGURE 4. Calculated structure (B3LYP/6-31G*) structure for the $2\mathbf{d}\cdot 2\mathbf{F}^-$ complex. Fluorine atoms are represented as green-yellow balls.

upon complexation (see Table 1 in the Supporting Information) is consistent with the above-mentioned high association constant for this complex. As a consequence, this rigid geometry of $2\mathbf{d}\cdot 2\mathbf{F}^-$, in which the HOMOs are involved in fluoride binding, leads to the efficiency of the photoinduced electron transfer (PET) process, present in the uncomplexed receptor $2\mathbf{d}$, being reduced, thus explaining the observed strong fluorescence enhancement.

The binding and electrochemical recognition of anionic guests by the difunctional “urea-amine” receptor $2\mathbf{e}$ has also been studied. This novel receptor $2\mathbf{e}$ presents the characteristic structural features of incorporating a redox center 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.²⁵ The recognition of anions in solution by $2\mathbf{e}$ was investigated by means of both electrochemical and fluorescent 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 (see the Supporting Information). The electrochemical response of $2\mathbf{e}$ upon addition of Cl^- , Br^- , AcO^- , NO_3^- , and HSO_4^- anions show identical CV compared to that of the free receptor, indicating that the presence of those anions has little effect on its electrochemical response. 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 behavior”, with the appearance of a second wave at more negative potentials, together with the corresponding free receptor ($\Delta E_p = -374$ mV for F^- and $\Delta E_p = -332$ 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 behavior”, 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) (Figure 5) (see also the Supporting Information), indicating that coordination of an anionic guest to the urea group close to the ferrocene group facilitates its oxidation.

It has already been reported that difunctional mixed amide-amine receptors show two different modes of anion binding²⁶

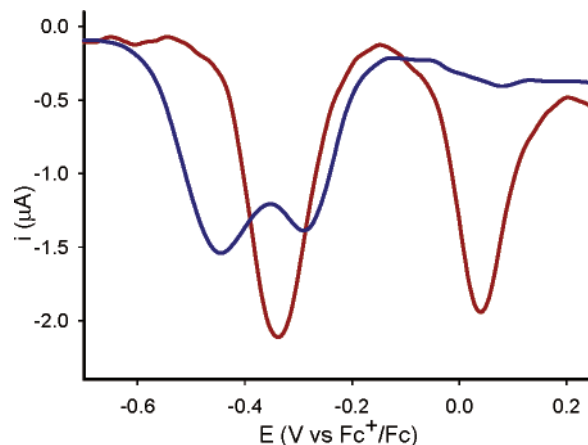


FIGURE 5. DPV response of compound $2\mathbf{e}$ (10^{-3} M) in DMSO before (red) and after (blue) addition of 2 equiv of H_2PO_4^- ; supporting electrolyte, 0.1 M (*n*-Bu₄N)ClO₄; scan rate, 0.004 V s⁻¹; pulse width, 50 ms; amplitude, 50 mV.

depending on the acidic characteristics of the anion used. Thus, for nonacidic guests, such as F^- , the binding mode is based on the receptor-donating hydrogen bonds from the urea (and probably to a lesser extent amino) group to the guest. For the moderately strong 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 recognition of F^- and H_2PO_4^- anions by receptor $2\mathbf{e}$ in DMSO-*d*₆ solution was also investigated by ¹H NMR titrations. Substoichiometric additions of those anions promote a large perturbation of the primary amino group present in the difunctional receptor, causing total disappearance when 0.5 equiv of anions was added. Further additions, up to 2 equiv, causes a clear downfield shift of the urea protons ($\Delta\delta = +1.11$ and $+1.69$ ppm for F^- —and $\Delta\delta = +0.80$ and $+0.38$ ppm for H_2PO_4^-) proving the recognition event between the receptor and anion (see Supporting Information). EQNMR analysis based on the results obtained by analyzing the changes in chemical shifts of the urea protons during the recognition process indicate a 1:1 binding model and associations constants of 3.7×10^3 M⁻¹ for F^- and 4.4×10^4 M⁻¹ for H_2PO_4^- .

The presence of a naphthalene unit within the structure of receptor $2\mathbf{e}$ prompted us to study its recognition capability by fluorimetric analysis. Thus, the fluorescence spectra of $2\mathbf{e}$ excited at $\lambda = 330$ nm in DMF show a weak emission bands 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 avoids the receptor enhancement fluorescence upon coordination with the corresponding anions.

Conclusions

In summary, we describe the first members of a potentially large class of easy-to-synthesize neutral ferrocene-based urea

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receptors and examined their binding properties toward various guest ions using spectral, electrochemical, and fluorescence techniques. Our synthetic methodology, which allows the preparation of a wide variety of ferrocene-based ureas, either acyclic or ferrocenophane-based cyclic architectures, with the ferrocene unit directly linked to two urea groups, is based on the reaction of the 1,1'-bis(isocyanato)ferrocene **1** with amino or diamino compounds. Selective binding to hydrogenphosphate and fluoride anions was observed for all of these ferrocene-based ureas. Remarkably, the new receptor 1,3,7,9-tetraaza[9]-ferrocenophane **2d**, obtained from the reaction with 1,8-diaminonaphthalene, exhibits not only a high selectivity for fluoride ion over other anions with dramatic fluorescent enhancement but also a special electrochemical recognition with remarkable cathodic shift of the ferrocene oxidation wave.

Experimental Section

General Methods. All reactions were carried out under N₂ and using solvents which were dried by routine procedures. Column chromatography was performed with the use of a column of dimensions 60 × 4.5 cm and of silica gel (60 A C.C. 70–200 μm, sds) as the stationary phase. The following abbreviations for stating the multiplicity of the signals in the NMR spectra were used: s (singlet), bs (broad singlet), d (doublet), t (triplet), bt (broad triplet), st (pseudotriplet), dt (double triplet), m (multiplet), q (quaternary carbon). The FAB⁺ mass spectra were recorded using 3-nitrobenzyl alcohol as a matrix. CV and DPV voltammograms were performed with a conventional three-electrode configuration consisting of platinum working and auxiliary electrodes and a SCE reference electrode. The experiments were carried out with a 10⁻³ M solution of sample in DMSO containing 0.1 M (n-C₄H₉)₄ClO₄ (**WARNING, CAUTION: potential formation of highly explosive perchlorate salts or organic compounds**) as supporting electrolyte. All of the potential values reported are relative to the Fc⁺/Fc couple at room temperature. Deoxygenation of the solutions was achieved by bubbling nitrogen for at least 10 min and the working electrode was cleaned after each run. The cyclic voltammograms were recorded with a scan rate increasing from 0.05 to 1.00 V s⁻¹, while the DPV were recorded at a scan rate of 4 mV s⁻¹ with a pulse high of 10 mV and a step time of 50 ms. Typically, receptor (1 × 10⁻³ mol) was dissolved in solvent (5 mL) and TBAP (base electrolyte) (0.170 g) added. The guest under investigation was then added as a 0.1 M solution in appropriate solvent using a microsyringe, while the cyclic voltammetric properties of the solution were monitored. Ferrocene was used as an external reference both for potential calibration and for reversibility criteria. Under similar conditions the ferrocene has E^o = 0.390 V vs SCE and the anodic peak-cathodic peak separation is 67 mV. Microcalorimetric titrations were carried out using an isothermal titration calorimeter, and they were performed as follows: a solution of the receptor in DMSO (c = 1 × 10⁻³ M) was prepared and it was titrated with the appropriate alkylammonium salt at 25 °C. The original heat pulses were normalized using reference titrations carried out using the same salt solution but pure solvent, as opposed to the solution containing the receptor.

Theoretical Calculations. Calculated geometries were initially optimized with the Gaussian 03²⁷ package at the DFT level of theory by using the B3LYP functional²⁸ (Becke's three parameters hybrid functional²⁹ with the Lee–Yang–Parr correlation functional³⁰) and the 3-21G* basis set. The obtained structures were then refined with tight convergence criteria at the final B3LYP/6-31G* level. For **2d**, **3•F⁻**, and **3•2F⁻**, the final refinement was performed by imposing the resulting C₂ symmetry obtained in the unconstrained low-level calculations. The interaction studies between **2d**, or **3** and the appropriate ions were carried out at the B3LYP/6-31G* level after global minimum search in the B3LYP/3-21G* potential

energy surface. Reported total electronic energies are uncorrected for the ZPVE (zero point vibrational energy) and computed in the gas-phase. Ligand strain energies (L_{strain}) were computed as the difference between the uncorrected total electronic energy of the free ligand in its most stable conformation and that of the frozen ligand conformation in the complex after removing the guest atoms and restoring the initial distances (as in the free ligand) to the bonds of atoms involved in guest binding (typically N–H or C=O bonds). Solvent (chloroform or DMSO) effects were calculated as SPE calculations on the gas-phase optimized geometries, using the Tomasi's PCM (polarizable continuum model) formalism.³¹ Bond orders were characterized by the Wiberg's bond index³² (WBI) and calculated at the B3LYP/6-311G** level with the natural bond orbital (NBO) method as the sum of squares of the off-diagonal density matrix elements between atoms, as formulated in terms of the natural atomic orbital (NAO) basis set. Atomic charges were obtained from SPE calculations at the B3LYP/6-311G** level using either the Mulliken³³ population analysis or the NBO method.

General Procedure for the Preparation of 1,1'-Bis(N-substituted)ureido]ferrocenes. To a solution of 1,1'-bis(isocyanato)ferrocene **1** (0.1 g, 0.37 mmol) in freshly distilled dry THF (15 mL) was added dropwise a solution of the appropriate amine (1.11 mmol) in the same solvent (5 mL) under nitrogen. The solution was stirred for 3 h at room temperature, and the resulting yellow solid was filtered, washed with diethyl ether, and recrystallized from the adequate solvent to give the appropriate 1,1'-disubstituted ferrocene derivative.

2a: 80%; mp 208–212 °C dec from DMSO; IR (Nujol; cm⁻¹) 3329, 3290, 1630, 1594, 1255, 1040, 938, 800; ¹H NMR (200 MHz, DMSO-*d*₆): δ 3.76 (st, 4H), 4.19 (d, 4H, ³J = 5.6 Hz), 4.25 (st, 4H), 6.35 (t, 2H, ³J = 5.6 Hz), 7.17–7.28 (m, 10H), 7.50 (s, 2H); ¹³C NMR (50 MHz, DMSO-*d*₆) δ 43.2 (CH₂), 61.8 (CH), 64.8 (CH), 97.9 (q), 127.0 (CH), 127.4 (CH), 128.6 (CH), 141.0 (q), 156.3 (q); EIMS *m/z* (relative intensity) 482 (M⁺, 5), 375 (11), 349 (14), 242 (97). Anal. Calcd for C₂₆H₂₆FeN₄O₂: C, 64.74; H, 5.43; N, 11.61. Found: C, 65.01; H, 5.22; N, 11.38.

2b: 75%; mp 225–228 °C dec from DMSO; IR (Nujol; cm⁻¹) 3344, 3269, 1643, 1568, 1466, 1385, 1342, 1261, 1051, 825; ¹H NMR (300 MHz, DMSO-*d*₆) δ 4.10 (st, 4H), 4.71 (st, 4H), 7.34 (t, 1H, ³J = 7.8 Hz), 7.38 (dt, 1H, ³J = 6.9 Hz, ⁴J = 1.2 Hz), 7.45 (dt, 1H, ³J = 6.9 Hz, ⁴J = 1.2 Hz), 7.50 (d, 1H, ³J = 8.4 Hz), 7.84 (d, 1H, ³J = 7.8 Hz), 7.98 (d, 1H, ³J = 8.4 Hz), 8.02 (d, 1H, ³J = 7.8 Hz), 8.49 ppm (s, 2H); ¹³C NMR (75.3 MHz, DMSO-*d*₆) δ 61.2 (CH), 64.6 (CH), 116.3 (CH), 121.0 (CH), 122.1 (CH), 125.3

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(CH), 125.6 (CH), 125.7 (CH), 128.2 (CH), 133.6 (q), 134.6 (q), 153.2 (q); MS (FAB⁺) *m/z* (relative intensity) 555 (35, M⁺ + 1). Anal. Calcd for C₃₂H₂₆FeN₄O₂: C, 69.32; H, 4.73; N, 10.11. Found: C, 69.51; H, 4.55; N, 10.38.

General Procedure for the Preparation of Tetraaza[m]-ferrocenophanes. To a solution of 1,1'-bis(isocyanato)ferrocene **1** (0.1 g, 0.37 mmol) in freshly distilled dry THF (80 mL) was added dropwise a solution of an equimolar amount of the appropriate diamino compound in the same solvent (80 mL) under nitrogen. The solution was stirred at room temperature for 4 h and the solvent removed under vacuum giving a residue which was chromatographed on a silica gel column, using CH₂Cl₂/CH₃OH (9:1) as eluent to give the corresponding ferrocenophane which was crystallized from the adequate solvent.

2c: 70%; mp 202–205 °C dec from DMSO; IR (Nujol; cm⁻¹) 3297, 3208, 1647, 1548, 1247, 1211, 1035, 1014, 812; ¹H NMR (200 MHz, DMSO-*d*₆) δ 3.87 (bs, 4H), 4.26 (d, 4H, ³*J* = 6.2 Hz), 4.40 (bs, 4H), 6.23 (bt, 2H), 6.99–7.17 (m, 3H), 7.35 (s, 1H), 7.51 (s, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 41.8 (CH₂), 60.5 (CH), 62.2 (CH), 98.7 (q), 122.6 (CH), 123.5 (2 × CH), 126.9 (CH), 141.0 (q), 155.4 (q); MS (FAB⁺) *m/z* (relative intensity) 405 (70, M⁺ + 1). Anal. Calcd for C₂₀H₂₀FeN₄O₂: C, 59.42; H, 4.99; N, 13.86. Found: C, 59.17; H, 4.76; N, 13.59.

2d: 68%; mp 177–179 °C from DMSO; IR (Nujol; cm⁻¹) 3360, 3263, 1665, 1600, 1493, 1374, 1067, 1035, 852, 804, 750; ¹H NMR (200 MHz, DMSO-*d*₆) δ 3.81 (bs, 4H), 4.08 (bs, 2H), 4.89 (bs, 4H), 7.25 (d, 2H, ³*J* = 7.0 Hz), 7.43 (t, 2H, ³*J* = 7.0 Hz), 7.67–7.76 (m, 4H), 8.48 (s, 2H); ¹³C NMR (50 MHz, DMSO-*d*₆) δ 57.9 (CH), 60.9 (CH), 62.2 (CH), 63.3 (CH), 97.7 (q), 124.4 (CH), 125.2 (CH), 125.7 (CH), 134.0 (q), 135.7 (q), 153.8 (q); EIMS *m/z* (relative intensity) 426 (100, M⁺), 399 (3), 268 (100), 158 (54). Anal. Calcd for C₂₂H₁₈FeN₄O₂: C, 61.99; H, 4.26; N, 13.14. Found: C, 61.74; H, 4.30; N, 13.38.

Preparation of 1,1'-Bis(8-amino-1-naphthylureido)ferrocene 2e. To a solution of 1,1'-bis(isocyanato)ferrocene **1** (0.1 g, 0.37 mmol) in freshly distilled dry THF (15 mL) was added dropwise a solution of 1,8-diaminonaphthalene (1.5 mmol) in the same solvent (15 mL) under nitrogen. After the mixture was stirred at room temperature for 4 h, the solvent was reduced under reduced pressure to 10 mL, and then Et₂O (20 mL) was added. The orange solid formed was filtered and recrystallized from CH₂Cl₂/Et₂O (2/10) to give **2e** in 73% yield: mp 210–213 °C dec; IR (Nujol; cm⁻¹) 3479, 3375, 3325, 3254, 1652, 1614, 1559, 1446, 1378, 1252, 1170, 1033, 950, 824; ¹H NMR (300 MHz, DMSO-*d*₆) δ 3.93 (bs, 4H), 4.48 (bs, 4H), 5.51 (s, 4H), 6.67 (t, 2H, ³*J* = 7.2 Hz), 7.04–7.14 (m, 6H), 7.37 (d, 2H, ³*J* = 8.2 Hz), 7.54 (d, 2H, ³*J* = 7.2 Hz), 8.51 (s, 2H), 9.16 (s, 2H); ¹³C NMR (75.3 MHz, DMSO-*d*₆) δ 61.7 (CH), 64.6 (CH), 97.5 (q), 112.5 (CH), 118.2 (q), 118.8 (CH), 119.5 (CH), 123.8 (CH), 125.1 (CH), 126.0 (CH), 135.7 (q), 136.1 (q), 144.5 (q), 153.7 (q); MS (FAB⁺) *m/z* (relative intensity) 585 (100, M⁺ + 1). Anal. Calcd for C₃₂H₂₈FeN₆O₂: C, 65.76; H, 4.83; N, 14.38. Found: C, 65.51; H, 5.02; N, 14.64.

Acknowledgment. We gratefully acknowledge the grants from MEC-Spain (CTQ2004-02201) and Fundación Séneca (CARM-Spain) (PB/72/FS/02).

Supporting Information Available: Electrochemical data upon addition of anion guests; ¹H NMR and ITC titration experiments; binding profiles; calculated structures, energies, and Cartesian coordinates. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO0604540