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A Bis-guanidine-Based Multisignaling Sensor Molecule That Displays Redox-Ratiometric Behavior or Fluorescence Enhancement in the Presence of Anions and Cations

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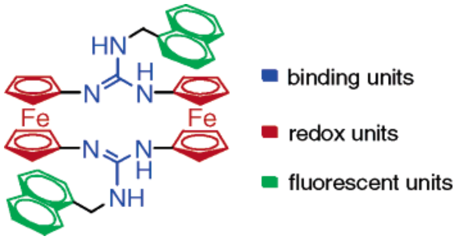
ABSTRACT



The guanidine bridge in the new structural motif [3,3]ferrocenophane acts as a dual binding site for anions and metal ions. Sensing of anions (Cl^-, F^-, NO_3^-, HSO_4^-, and $H_2PO_4^-$) takes place by redox-ratiometric measurements, whereas metal ion (Zn^{2+}, Ni^{2+}, and Cd^{2+}) recognition is achieved by fluorescence measurements.

Development of chemosensors capable of recognizing and sensing anions and cations is one of the most challenging fields from the viewpoint of organic and supramolecular chemistry. These multisite ligands, which are able to bind a single heteroditopic guest or simultaneously bind to a nonidentical guest, have been achieved by integrating cationic and anionic guest binding sites in a single molecule.[1]

The guanidine function due to its amphoteric nature has a rich history in biological[2] and artificial receptors.[3] The guanidinium group within a variety of molecular architectures forms strong noncovalent interactions with anionic groups through hydrogen-bonding and charge-pairing interactions. In addition, deprotonated guanidines (guanidinates) have the potential to develop into valuable ancillary ligands in coordination and organometallic chemistry,[4] although the straightforward coordination of neutral guanidines to metal centers remains comparatively underdeveloped,[5] and metal−guanidinyl complexes are barely known and unexplored.[6]

Ferrocene-based ligands have been found to be useful for incorporating redox functions into supramolecular complexes that bind and allow the electrochemical sensing of cations,[7] anions,[8] and neutral molecules[9] by a change in the oxidation potential of the ferrocene. Despite the rich chemistry of guanidines, as binding sites, and ferrocene, as redox signaling

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(1) For a review see: Kirkovits, G. J.; Shriver, J. A.; Gale, P.A-; Sessler, J. L. *J. Inclusion Phenom. Macrocycl. Chem*. **2001**, *41*, 69. For recent references, see: (a) Mahoney, M. J.; Beatty, A. M.; Smith, B. D. *J. Am. Chem. Soc*. **2001**, *123*, 5847−5848. (b) Miyaji, H.; Collison, S. R.; Prokés, J. H.; Tucker, R. *Chem. Commun*. **2003**, 64−65. (c) Otón, F.; Tárraga, A.; Velasco, M. D.; Molina, P. *Dalton Trans*. **2005**, 1159−1161.

(2) (a) Hannon, C. L.; Anslyn, E. V. In *Biorg. Chem. Front*. Duggas, H., Schmidtchen, F. P., Eds.; Springer, Berlin, 1993; Vol. 3, pp 193−255.

(3) Best, M. D.; Tobey, S. L.; Anslyn, E. V. *Coord. Chem. Rev*. **2003**, *240*, 3−15.

(4) Baily, P. J.; Pace, S. *Coord. Chem. Rev*. **2001**, *214*, 91−141.

(5) Coles, M. P. *Dalton Trans*. **2006,** 985−1001.

(6) Aioki, S.; Iwaida, K.; Hanamoto, N.; Shiro, M.; Kimura, E. *J. Am. Chem. Soc*. **2002**, *124*, 5256−5257.

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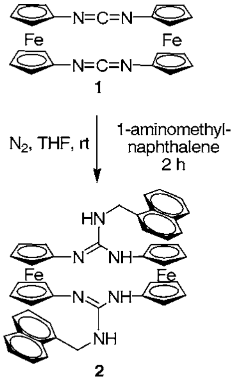
units, only one example, however, of guanidinylferrocene has been described.[10]

With these considerations in mind, we decided to combine in a highly preorganized system the redox activity of the ferrocene group with the photoactive behavior of the naphthalene ring and the binding ability of the guanidine group. Here, we report an extremely nitrogen-rich [3.3]-ferrocenophane in which the two ferrocene subunits, having similar electronic enviroments, are linked by two naphthalene-appended guanidine moieties. The presence of multiple binding sites in the design of a new structural motif, the multiresponsive character of the receptor, and the ability of the double-bridge to act as a favorable binding for anions and cations in the recognition event are most noteworthy.

Receptor **2** was prepared in good yield (75%) from 1,3,10,12-tetraaza[3.3]ferrocenophane[11] **1** and 1-aminomethylnaphthalene in THF at room temperature (Scheme 1). The binding and recognition ability of receptor **2** toward various anions was evaluated by differential pulse (DPV)[12] voltammetry.

Scheme 1. Synthesis of Ferrocenophane **2**



The DPV voltammogram of **2** in DMSO/H$_2$O (9:1, v/v) displays two one-electron oxidation peaks at $E^1_p = -0.35$ and $E^2_p = -0.09$ V vs Fe^{II}/Fe^{III} redox couple. So, in contrast to most ferrocene-based redox sensors reported that rely on changes in the oxidation potential of the ferrocene, in the designed ligand **2** not only the occurrence of two oxidation peaks but also the magnitude of the $\Delta E_{1/2} = 0.26$ V[13] allow that this new system could utilize variations at different redox potentials upon complexation, and consequently the first redox-ratiometric measurement could be made.

Preliminary electrochemical studies with various anions (F^-, Cl^-, AcO^-, NO_3^-, HSO_4^- and $H_2PO_4^-$) in the form of their corresponding tetrabutylammonium salts, revealed behavior that was quite different from the previous ferrocene-based anion receptors. For instance, the addition of increasing amounts of F^- and AcO^- anions caused the complete disappearance of the second oxidation peak whereas the first oxidation peak was apparently not perturbed. On the other hand, the addition of $H_2PO_4^-$ and HSO_4^- anions elicited different electrochemical responses. On stepwise addition of $H_2PO_4^-$, the first oxidation peak was slightly shifted *anodically* by +14 mV, whereas the second oxidation peak was remarkably shifted *cathodically* by −84 mV ($\Delta E_{1/2} = 0.16$ V). In contrast, in the presence of HSO_4^- anion the first oxidation peak was remarkably shifted *anodically* by +89 mV, whereas the second oxidation peak was slightly shifted *cathodically* by −13 mV ($\Delta E_{1/2} = 0.16$ V) (Figure 1). The presence of NO_3^- and Cl^- anions had no effect on the CV, even when present in large excess.

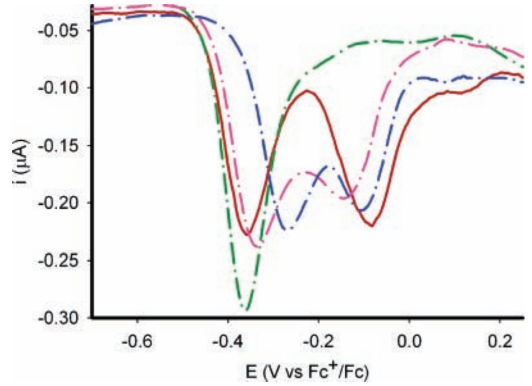


Figure 1. Evolution of the DPV of **2** (red) (1 mmol dm^{-3}) in DMSO/H$_2$O (4/1), [(*n*-Bu) $_4$N]PF$_6$ scanned at 0.1 V s^{-1} from −0.65 to 0.2 V, when F^- (green), $H_2PO_4^-$ (pink), and HSO_4^- (deep blue) anions were added.

Examining the relative perturbations at the two oxidation peaks on the addition of these guest anions yields two

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(7) For a review, see: (a) Beer, P. D.; Gale, P. A.; Chen, Z. *Coord. Chem. Rev.* **1999**, *185–186*, 3–36. For recent examples, see: (b) López, J. L.; Tárraga, A.; Espinosa, A.; Velasco, M. D.; Molina, P.; Lloveras, V.; Vidal-Gancedo, J.; Rovira, C.; Veciana, J.; Evans, D. J.; Wurst, K. *Chem.—Eur. J.* **2004**, *10*, 1815–1826. (c) Caballero, A.; Lloveras, V.; Tárraga, A.; Espinosa, A.; Velasco, M. D.; Vidal-Gancedo, J.; Rovira, C.; Wurst, K.; Molina, P.; Veciana, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1977–1981. (d) Caballero, A.; Martinez, R.; Lloveras, V.; Ratera, I.; Vidal-Gancedo, J.; Wurst, K.; Tárraga, A.; Molina, P.; Veciana, J. *J. Am. Chem. Soc.* **2005**, *127*, 15666–15667.

(8) For reviews, see: (a) Beer, P. D.; Gale, P. A. *Angew, Chem. Int. Ed.* **2001**, *40*, 486–516. (b) Gale, P. A. *Coord. Chem. Rev.* **2000**, *199*, 181–233. (c) Gale, P. A. *Coord. Chem. Rev.* **2001**, *213*, 79–128. For recent examples, see: (d) Otón, F.; Tárraga, A.; Velasco, M. D.; Espinosa, A.; Molina, P. *Chem. Commun.* **2004**, 1658–1659. (e) Otón, F.; Tárraga, A.; Espinosa, A.; Velasco, M. D.; Bautista, D.; Molina, P. *J. Org. Chem.* **2005**, *70*. 6603–6608.

(9) Westwood, J.; Coles, S. J.; Collison, S. R.; Gasser, G.; Green, S. J.; Hursthouse, M. B.; Light, M. E.; Tucker, J. H. R. *Organometallics* **2004**, *23*, 946–951 and references therein.

(10) Beer, P. D.; Drew, M. G. B.; Smith, D. K. *J. Organomet. Chem.* **1997**, *543*, 259–261.

(11) Tárraga, A.; Otón, F.; Espinosa, A.; Velasco, M. D.; Molina, P.; Evans, D. J. *Chem. Commun.* **2004**, 458–459.

(12) DPV removes the effect of electrode capacitive charging, resulting in measurements of only the Faradaic processes and hence in much higher signals than conventional voltammetries: Bard, A.; Faulkner, L. *Electrochemical Methods*, 2nd ed.; Wiley: New York, 2001.

(13) This value indicates that the mixed-valence compound **2**$^+$ is thermodinamically stabilised towards disproportionation to give **2** and **2**$^{2+}$ by the comproportionation constant of $K_c = 2.7 \times 10^4$. Spectroelectrochemical studies revealed that the mixed-valence compound **2**$^+$ shows a IVCT transition in the near-IR region ($\nu_{max} = 12186$ cm^{-1} with $\epsilon = 322$ M^{-1} cm^{-1}). Interestingly, this IVCT transition completely disappeared after addition of F^- and AcO^- anions.

interesting conclusions: (a) $H_2PO_4^-$ causes a large relative perturbation at the second oxidation peak, while HSO_4^- interacts more strongly at the first oxidation peak, and (b) the observation of *anodic* shifts in the first oxidation peak contrasts with previous examples of the binding of these oxoanions by ferrocene receptors where guests have been sensed through *cathodic* shifts in potential. Taking into account that HSO_4^- is considerably more acidic than $H_2PO_4^-$ and that the *anodic* shift of the first oxidation peak is higher for the HSO_4^- anion (+89 mV) than for $H_2PO_4^-$ anion (+14 mV), the observed electrochemical behavior is consistent with a guest-to-host proton-transfer reaction (*anodic* shift of the first oxidation peak) accompanied by hydrogen-bond formation and subsequent anion coordination (*cathodic* peak of the second oxidation peak).[14] These electrochemical results clearly revealed the advantage of the guanidino-ferrocenophane receptor **2** over the widely studied ferrocene-based receptors in which the presence of only one redox peak does not allow a dual redox peaks ratiometric measurement upon an anionic recognition process. Isothermal titration calorimetry (ITC) provides useful insight into the nature of the binding interactions, and 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 **2** ($c = 1 \times 10^{-3}$ 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. When $H_2PO_4^-$ and AcO^- anions were added, the titration curves showed an inflection point around 0.5 equiv of anion added, which evidenced the formation of a 2:1 complex. The association constants (K_{as}) calculated by nonlinear least-squares analysis were found to be $K_{21} = 1.3 \times 10^6$ and $K_{11} = 2.7 \times 10^5$ for F^- anion, 2.8×10^4 for $H_2PO_4^-$ anion, and 5.2×10^4 for AcO^- anion. It should be noted that, as yet, we have been unable to obtain reliable K_a values for HSO_4^- anion binding by ITC under the conditions used for the other anions.

The CV of the receptor **2** in dichloromethane shows two well spaced ($\Delta E_{1/2} = 0.45$ V) reversible one-electron oxidations peaks at −0.43 and 0.02 V vs Fe^{II}/Fe^{III} redox couple.[16] Upon protonation by addition of 1 equiv of HBF_4 in acetonitrile, the redox peaks were shifted *anodically* at −0.02 and 0.24 V, respectively ($\Delta E_{1/2} = 0.26$ V). This guanidinium receptor **2·H**$^+$ has also been used to investigate its ability to electrochemically sense anion binding. Upon addition of F^-, AcO^-, HSO_4^-, and $H_2PO_4^-$ anions two new redox peaks evolved, which were shifted *cathodically*. The evolving peaks appeared at virtually the same potential as that the free guanidine receptor **2**, indicating that a deprotonation has taken place.[17] However, the addition of NO_3^- and Cl^- elicited a different electrochemical response. In both cases, the two redox peaks are shifted *cathodically* by −50 and −130 mV respectively for NO_3^- ($\Delta E_{1/2} = 0.18$ V) and by −80 and −100 mV, respectively, for Cl^- ($\Delta E_{1/2} = 0.24$ V) (Figure 2). These findings are indicative of oxidation being facilitated by the proximate coordination of the anion to the guanidinium moiety, and underscore the selectivity of the guanidinium receptor **2·H**$^+$ for NO_3^- and Cl^- anions in dichloromethane, being the electrochemical changes higher for NO_3^- than for Cl^- anion. One of the current challenges in anion recognition chemistry involves the preparation of receptors that show high HSO_4^-/NO_3^- selectivity,[18] and one attractive feature of this new guanidinoferrocenophane structural motif is its ability to bind selectively HSO_4^- in the presence of NO_3^- anion.

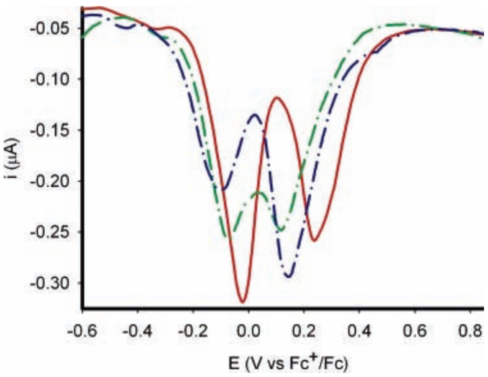

Figure 2. Evolution of the DPV of **2**·H^+ (red) (1 mmol dm^{-3}) in CH_2Cl_2 $[(n\text{-}Bu)_4N]PF_6$ scanned at 0.1 V s^{-1} from −0.6 to 0.8 V, when NO_3^- (green), or Cl^- (deep blue) anions were added.

Several trends have surfaced from the electrochemical study. First, neutral receptor **2** is able to recognize and discriminate F^-, AcO^-, HSO_4^-, and $H_2PO_4^-$ anions by using different variations of the two redox signals, in relatively polar solvent (DMSO/H_2O) where hydrogen-bonding interactions between the guanidine functional groups and the anions are usually weakened by competing solvent molecules. Second, the guanidinium receptor **2·H**$^+$ selectively sense NO_3^- and Cl^- anions in a less polar solvent. These findings underscore an unreported redox-ratiometric behavior to sense anions, which can be modulated in our case by simple protonation of the neutral receptor.

One of the most important attributes of receptor **2** is the presence of two ferrocene moieties in proximity to the cation binding guanidine groups. Therefore, the metal recognition

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(14) Beer, P. D.; Graydon, A. R.; Johnson, A. O. M.; Smith, D. K. *Inorg. Chem.* **1997**, *36*, 2112−2118.

(15) (a) Schmidtchen, F. P. *Org. Lett.* **2002**, *4*, 431−434. (b) Tobey, S. L.; Anslyn, E. V. *J. Am. Chem. Soc.* **2003**, *125*, 14807−14815. (c) Lee, C.-H.; Na, D.-D.; Yoon, D.-W.; Won, D.-H.; Cho, W. S.; Lynch, V. M.; Shevchuk, S. V.; Sessler, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 7301−7306. (d) Sambrook, M. R.; Beer, P. D.; Wisner, R. L.; Paul, R. L.; Cowly, A. R.; Szemes, F.; Drew, M. G. B. *J. Am. Chem. Soc.* **2005**, *127*, 2292−2302. (e) Sessler, J. L.; An, D.; Cho, W.-S.; Lynch, V. M.; Marquez, M. *Chem.—Eur. J.* **2005**, *11*, 2001−2011.

(16) This value gives a comproportionation constant of $K_c = 8.8 \times 10^7$. The absorption spectrum of the mixed-valence compound **2**$^+$, electrochemically generated shows a weak transition in the near-IR region ($\nu_{max} = 10570$ cm^{-1} with $\epsilon = 563$ M^{-1} cm^{-1}), which disappears after protonation.

(17) A control experiment with addition of K_2CO_3/H_2O to the final solution, which caused no further change in the redox behaviour, showed that this response was equivalent to deprotonation.

(18) Sessler, J. L.; Katayev, E.; Dan Pantos, G.; Ustynyuk, Y. A. *Chem. Commun.* **2004**, 1276−1277.

properties toward Li^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+} Cd^{2+}, and Zn^{2+} metal ions were evaluated by electrochemical and optical analysis. In DMSO, no perturbation of the DPV voltammogram of **2** was observed upon addition of Li^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, and Cd^{2+} metal ions.[19] However, a dramatic decrease in intensity of the first oxidation peak and no perturbation of the second oxidation peak was observed upon addition of Zn^{2+} ions.

The absorption spectrum of **2** shows an intense band at 283 nm attributed to the naphthalene units along with a very weak band at low energy centered at 441 nm, which can safely ascribed to metal-to-ligand charge transfer (LMCT) transition in the ferrocene moieties.[20] As expected receptor **2** displays a very weak fluorescence. The emission espectrum ($\lambda_{exc} = 310$ nm) exhibits a structureless band centered at 354 nm, due to the naphthalene monomer emission. Upon addition of small amounts of Zn^{2+} to the solution of receptor **2** in dichloromethane ($c = 5 \times 10^{-5}$ M), a pronounced red shift of 30 nm along with an intensity enhancement of the naphthalene monomer emission was observed (Figure 3). The final fluorescence enhancement factor (FEF) was 5 and the quantum yield ($\Phi = 0.070$) resulted in a 4-fold increase compared to that of the free receptor ($\Phi = 0.016$). The stoichiometry of the complex was determined by fluorogenic titration, and the results obtained indicate the formation of a 1:1 complex giving an association constant (K_a) of 5×10^4 M^{-1}. Similar results were obtained in the presence of Ni $^{2+}$ ($\Phi = 0.063$; FEF = 4; 1:1 complex stoichiometry and $K_a = 5.5 \times 10^4$ M^{-1}), and Cd^{2+} ($\Phi = 0.092$; FEF = 6; 1:1 complex stoichiometry and $K_{as} = 2.4 \times 10^4$ M^{-1}) metal ions.

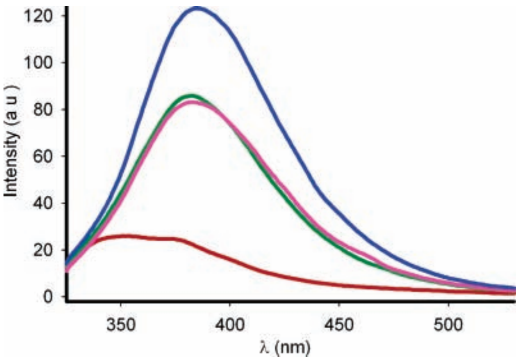

Figure 3. Changes in the fluorescence emission spectra of **2** (λ_{exc} = 310 nm) in CH_2Cl_2 ($c = 5 \times 10^{-5}$ mol dm^{-3}) (red) after addition of Ni^{2+}(3.5 equiv, green), Zn^{2+}(3 equiv, pink), and Cd^{2+}(4.5 equiv, deep blue) as triflate salts.

Interestingly, addition of 1 equiv of HBF_4 also produced an intensity enhancement of the naphthalene emission albeit lower ($\Phi = 0.043$ vs 0.016) than that originated by the above-mentioned metal ions. Remarkably, stepwise addition of NO_3^- anion to a solution of **2·H**$^+$ produced quenching of the emission ($\Phi = 0.020$), whereas addition of AcO^-, HSO_4^-, and $H_2PO_4^-$ anions, clearly induced deprotonation. Fluorogenic titration with NO_3^- anion indicates the formation of a 1:1 complex giving a $K_a = 51.2 \times 10^6$ M^{-1}.

In conclusion, we have designed a new multiproperties guanidinoferrocene based receptor, which represents the first redox-ratiometric chemosensor. It allows the sensing of F^-, AcO^-, HSO_4^-, and $H_2PO_4^-$ anions through two different oxidation peaks perturbations, and its monoprotonated form is able to selectively sense Cl^- and NO_3^- by redox-ratiometric measurements. Due to the presence of the naphthalene ring, receptor **2** is able to act as fluorescent chemosensor of Zn^{2+}, Ni^{2+}, and Cd^{2+} metal ions. Furthermore, proton-induced complexation provides a versatile means of sensing selectively NO_3^- via fluorescence emission quenching. This structural motif paves the way to the design of a new generation of homoditopic receptors able to sense both anions and cations.

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

Supporting Information Available: Spectral, electrochemical, optical, and fluorescence data of **2** and those obtained upon addition of metal ions and anions to **2**. Binding profiles and ITC titration plots.

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[19] Cu^{2+} and Hg^{2+} ions are not complexed by **2**, but instead, an intermolecular redox reaction takes place betwen them to give the dioxidized species **2**$^{2+}$.

[20] Barlow, S.; Bunting, H. E.; RIngham, C.; Green, J. C.; Bublitz, G. V.; Boxer, S. G.; Perry, J. W.; Maeder, S. R. *J. Am. Chem. Soc.* **1998**, *120*, 7511−7519.