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First Fluorescent Ferrocenyl Compound as Multiresponsive Calcium-Sensing Device. NMR, Electrochemical, and Photophysical Preliminary Investigations in CH_3CN

Jérôme Maynadié,[†] Béatrice Delavaux-Nicot,*,[†] Suzanne Fery-Forgues,[‡] Dominique Lavabre,[‡] and René Mathieu[†]

Laboratoire de Chimie de Coordination du CNRS, UPR 8241, 205, Route de Narbonne, F-31077, Toulouse Cedex 04, France, and Laboratoire des Interactions Moléculaires et Réactivité Chimique et Photochimique, UMR 5623 au CNRS, Université Paul Sabatier, 118 Route de Narbonne, F-31062, Toulouse Cedex, France

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A new ferrocene receptor binds a calcium guest via complex processes involving the whole unsaturated core of the ligand. Complexation induces significant changes in the ligand properties, as evidenced by the unprecedented cation sensing observed both by electrochemistry and fluorescence spectroscopy.

Compounds that undergo a change in their physical properties upon complexation are relevant to the development of molecular sensing and switching devices.[1] In particular, redox-active receptor molecules and especially those based on ferrocene are used most exclusively for ion electrochemical analysis mainly in organic solvents and sometimes in aqueous media.[2] In parallel, extensive studies on ion recognition by fluorescent sensors have demonstrated the usefulness of this technique in a wide range of applications.[3] (In particular, there are a large number of excellent Ca^{2+} fluorophores available commercially; see, for example, refs 3b,c.) However, despite the development of these two subjects, few examples of fluorescent ferrocenyl ion sensors have been described, probably because ferrocene derivatives are known to be efficient fluorescence quenchers.[4] Moreover, molecules that contain two distinct signaling units will be the keystone of new families of ion chemosensors potentially usable by two different and complementary techniques. The fabrication of these types of systems and their integration into different supports (e.g., matrixes, electronically conducting polymeric supports, optical fibers, and so forth) will probably lead to novel prototype molecular sensory devices of commercial usage.[4a,2b] It is important to point out that electrochemical sensors containing ferrocene are of particular interest, as they offer the possibility to modulate ion–receptor interaction according to redox state; for example, electrostatic interactions can be switched on by the oxidation of ferrocene to ferricinium. The modulation or control of the photophysical properties of a fluorescent moiety incorporated in such a molecule is a fascinating challenge for modern chemistry.[5]

In an early publication,[4b] we established that new electroactive and efficient fluorescent species containing only ferrocene as a metallic moiety could be obtained. Here, we report on the electrochemical and optical ion-sensing properties of **1** and show that this compound really behaves as a new type of multiresponsive calcium-sensing device which has the rare advantage of displaying several clear macroscopic events upon addition of this analyte.

Electrochemical tests were performed with **1** (10^{-3} M) in acetonitrile, in the presence of alkali and alkaline earth cations. In Figure 1a, the wave observed at $E_{pa} = 1.03$ V for **1** ($E_{1/2} = 1.01$ V) was attributed to the (Fe^{II}/Fe^{III}) couple oxidation process.[4b] Two distinguishable oxidation peaks situated at $E_{pa} = 0.70$ and 0.88 V showed that a complex

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* To whom correspondence should be addressed. E-mail: delavaux@lcc-toulouse.fr.

[†] Laboratoire de Chimie de Coordination du CNRS.

[‡] Laboratoire des Interactions Moléculaires et Réactivité Chimique et Photochimique.

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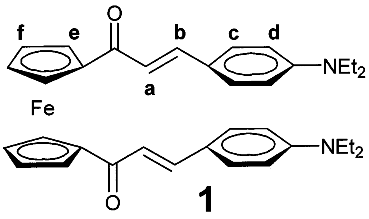

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oxidation process occurred for the organic parts of the molecule before the Fe oxidation process.

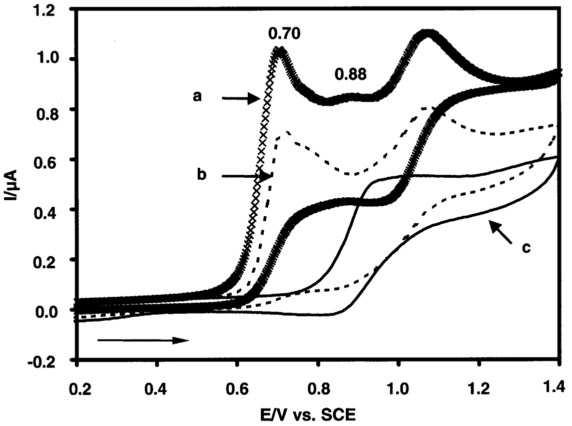

Figure 1. Cyclic voltammograms of (a) **1**, (b) **1** + 1 equiv of $Ca(CF_3SO_3)_2$, and (c) **1** + 2 equiv of $Ca(CF_3SO_3)_2$. Experimental conditions: Pt electrode (1 mm) in 0.1 mol L^{-1} solution of Et_4NBF_4 in CH_3CN, at 100 mV s^{-1}, ligand concentration 10^{-3} M.

Compound **1** was not sensitive to the presence of Li^+, Na^+, or K^+ and poorly sensitive to Ba^{2+}. However, stepwise addition of up to 2 equiv of $Ca(CF_3SO_3)_2$ to a solution of compound **1** resulted in a clear evolution of the voltammogram (Figure 1c). The ferrocene wave shifted to 0.89 V, the presence of calcium being thus heralded by an unexpected cathodic shift of $\Delta E_{1/2} = -120$ mV. In addition, the disappearance of both waves corresponding to the organic oxidation process and to the reduction process (at $E_{pa} = -1.71$ V), respectively, indicated that the whole organic conjugated parts of the molecule were also strongly affected by the presence of the salt. However, further addition of salt (until 10 equiv) had no significant effect. Generally, in ferrocenyl compounds containing organic aza fragments, the iron(II) oxidation process precedes the oxidation process of the aza fragments, and addition of metal cation induces a classical positive shift of the iron potential.[2] In compound **1**, the opposite is observed. Calcium interaction probably induces an important electronic reorganization of the molecule leading to an unusual cathodic shift of the iron potential. A series of theoretical calculations and experiments are underway to validate this explanation. However, to our knowledge, this is the first report of such intriguing electrochemical behavior involving Ca^{2+} cation.

NMR and UV−vis spectroscopy experiments were performed to have further insight into the interactions between the ligand and the cation. Considering the ^{13}C NMR spectra, 2D NMR analyses highlighted remarkable variations when 2 equiv of salt was added to compound **1**. The olefinic carbons CH_b and the CO groups moved from 142.06 and 191.61 ppm to 148.35 and 194.87 ppm, respectively. The NEt_2 groups were the only groups not to be affected by this interaction under these conditions. The complexation process was further studied by ^1H NMR spectroscopy (Figure 2) showing that the most pronounced downshift (maximum value: $\Delta(\delta H) = 0.41$ ppm) occurred for the H_b protons. Figure 2 confirms that the whole unsaturated core of the molecule including the Cp rings contributes to the electronic interaction with the cation. The electrostatic attraction between Ca^{2+} and the negative electron density of the carbonyl group is the key point of this interaction. This is in line with an influential role of the double bond and the participation of the CO groups in the Ca^{2+} interaction.[6] Considering now the nonclassical shape of the curves and the tendency for the H_b, H_c, and H_e resonances to be maximum before 1 equiv, these results suggest that multiple equilibria are involved (vide infra).

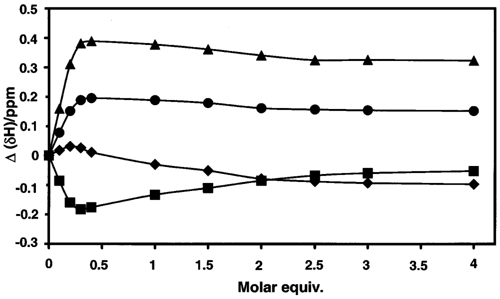

Figure 2. Chemical shift variations of the H_a (◆), H_b (▲), H_c (■), and H_e (●) protons of **1** (4.28×10^{-3} M), versus the molecular equiv of $Ca(CF_3SO_3)_2$, in CD_3CN. H_d and H_f are omitted for clarity.

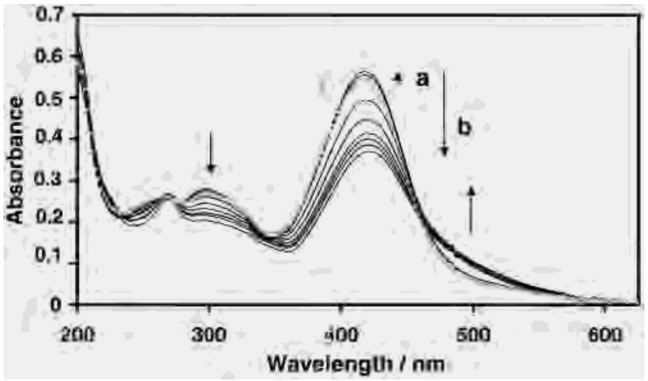

Figure 3. Absorption spectra of **1** (1.25×10^{-5} M) in acetonitrile before (gray line) and after addition of $Ca(CF_3SO_3)_2$. From top at 416 nm to bottom at 422 nm, $[Ca(CF_3SO_3)_2]$ (M): 1.3×10^{-5}, 2.5×10^{-5}, 0, 5.0×10^{-4}, 1.0×10^{-3}, 1.5×10^{-3}, 2.0×10^{-3}, 2.5×10^{-3}, 3.0×10^{-3}.

Regarding the absorption properties, **1** (1.25×10^{-5} M) alone in acetonitrile gave orange solutions. The absorption spectrum (Figure 3) exhibited an intense long-wavelength band at $\lambda_{max} = 416$ nm mainly identified as a charge-transfer (CT) band resulting from the displacement of the electron density from the donor amino group toward the acceptor carbonyl group. In the presence of calcium salt, the reddening of the solution observed corresponded to an increase in the

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absorbance around 500 nm, assigned to the interaction of the carbonyl group with a cation.[6] Other modifications of the spectrum were observed. In particular, the intensity of the CT band slightly increased until 1 equiv of salt was added (arrow a). Then, upon subsequent addition of salt (arrow b), it slowly decreased while λ_{max} shifted from 416 to 422 nm. Moreover, it should be noticed that no isosbestic points were observed, confirming that more than one equilibrium is involved in solution. Absorption spectroscopic data displayed in Figure 3 were processed, according to a method described in the literature.[6b,7] Good fits were obtained by taking into account the existence of three species of different stoichiometries: **1**M, (**1**)$_2$M, and (**1**)M$_2$, where M is the metal cation. The corresponding association constants were $(3.2 \pm 0.3) \times 10^3$ M^{-1}, $(2.0 \pm 1) \times 10^6$ M^{-1}, and $(1 \pm 0.8) \times 10^3$ M^{-1}, respectively, pointing out the stability of sandwich complex (**1**)$_2$M. The treatment of the NMR data is consistent with these stoichiometries. To have experimental proof of the existence of these species from an additional technique, mass spectra were recorded with samples of **1** containing 0.6 and 2 equiv of salt. The positive FAB technique using an MNBA matrix reveals peaks at 777 [**1**M − $CF_3SO_3^-$], 1115 [(**1**)M$_2$ − $CF_3SO_3^-$], and 1365 [(**1**)$_2$M − $CF_3SO_3^-$], confirming that strong interactions exist between one or two molecules and $Ca(CF_3SO_3)^+$.

In the absence of salts, the emission spectrum of **1** in acetonitrile displayed only one band with a maximum at $\lambda = 560$ nm, independent of the excitation wavelength. In the presence of salt, **1** (3×10^{-6} M) was excited at $\lambda = 348$ nm to minimize the effect of absorption variations. Figure 4 shows that a two-step behavior was observed: First, the emission intensity increased until the Ca^{2+} concentration reached 2 equiv (arrow a), and then it decreased slowly (arrow b). Above 2.5 mM Ca^{2+}, the decrease went faster, leading to total fluorescence quenching for a calcium concentration of 4.5 mM. These significant trends, associated with the excited state of **1**, indicated that **1** behaves as a fluorescent probe providing a different and noticeable response over a wide range of Ca^{2+} concentrations.

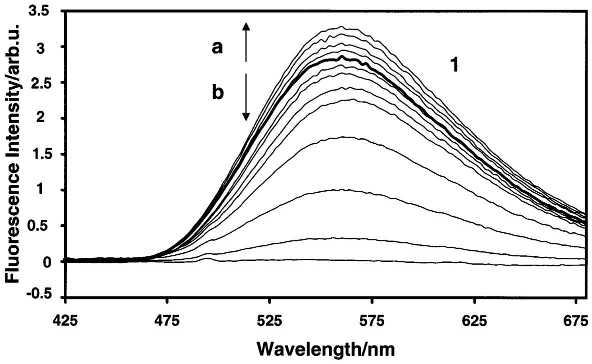

Figure 4. Fluorescence titration spectra of **1** (3.0×10^{-6} M) with $Ca(CF_3SO_3)_2$. From top to bottom at 560 nm, [$Ca(CF_3SO_3)_2$] (M): 6.0×10^{-6}, 1.2×10^{-5}, 3.0×10^{-5}, 5.0×10^{-5}, 0, 5.0×10^{-4}, 1.0×10^{-3}, 2.5×10^{-3}, 3.0×10^{-3}, 3.5×10^{-3}, 4.0×10^{-3}, 4.3×10^{-3}, 4.5×10^{-3}.

Compound **1** is a rare example of a molecule containing two different signaling units, for example, redox and fluorescent. As we previously envisaged in our precedent publication,[4b] we bring now the experimental evidence that it is also a new and original ferrocenyl probe for both the electrochemical and optical detection of $Ca(CF_3SO_3)_2$. It was also shown that the whole unsaturated core of the ligand is involved in the binding processes which mainly occur via the CO function and in its vicinity. In the range of concentrations considered, several identified species compete. Consequently, our future research efforts will concentrate on the complete understanding of the unusual properties of this compound, and on the development of testing methods for the recognition ability of **1** and its derivatives toward other ions and in other media. These preliminary results are already promising in regards to the obtainment of ferrocenyl multiresponsive sensing devices incorporating redox and fluorescent units.

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