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pH-Driven Cu^{2+} Translocation in Ferrocene-Containing Ligands

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The ligands **L1**H_4, **L2**H_2, and **L3**H_4 have been synthesized, featuring two, one, and two ferrocene-functionalized diamino-diamido compartments, respectively. The coordination chemistry of the ligands towards Cu^{2+} has been fully characterized by means of potentiometric and spectrophotometric titrations, which allowed us to determine the protonation constants of the ligands, the formation constants of their complexes, and their coordination geometry. **L1**H_4 and **L2**H_2 feature additional diaminopyridine and bis(aminoquinoline) binding sites, respectively, and are capable of the pH-driven translocation of two and one Cu^{2+} cations, respectively. Electrochemical experiments (CV) coupled with pH-metric titrations demonstrate that while the coordination of Cu^{2+} to the compartments more distant from ferrocene (Fc), i.e. diaminopyridine in **L1**H_4 and bis(aminoquinoline) in **L2**H_2 leaves the oxidation potential of Fc unchanged, the translocation of the Cu^{2+} cation(s) inside the diamino-diamido compartment(s) is signaled by a peculiar lowering of the Fc oxidation potential.

Introduction

The controlled translocation of metal cations is a recent development of coordination chemistry in solution based on the concepts elaborated by supramolecular chemistry,[1] and is at the edge of one of the hot topics of nanotechnology, i.e. molecular machines and controlled motions at the molecular level.[2]

However, few papers have been published so far in this field. As a first example, the chemically promoted redox-driven translocation of one iron cation inside a polytopic ligand was reported by the group of Shanzer in 1995,[3a] and the same author reported the redox-controlled translocation of one copper cation in 2002.[3b]

Using a different approach, we are involved in a long-term research effort concerning the translocation of transition metal cations in aqueous solutions driven by the variation of a classical bulk property, i.e. pH.[4,5] This approach has also been exploited by a few other groups.[6] Recent results obtained by our group include the simultaneous pH-driven translocation of two Cu^{2+} cations inside large macrocyclic ligands containing two dioxo232 and two diaminopyridine binding sites, and functionalized either with a benzyl[7] or a propargyl[8] unit on the central carbon of the malonic amide groups. For the latter examples, the pH-driven double translocation process can be summarized as follows: at slightly acidic or neutral pH values, the two Cu^{2+} cations reside in the diaminopyridine compartments (Scheme 1: $[\mathbf{BZ}H_4Cu_2]^{4+}$ blue, λ_{max} = 660 nm, and $[\mathbf{PG}H_4Cu_2]^{4+}$ blue, λ_{max} = 660 nm) but when the pH is raised enough, the two dioxo232 compartments lose their amido protons and the Cu^{2+} cations move inside the very effective diamino-diimido binding units to form a neutral complex ($[\mathbf{BZ}Cu_2]$ and $[\mathbf{PG}Cu_2]$ in Scheme 1). The overall molecular shape and Cu^{2+} coordination number and geometry in the neutral complexes depend on the bulkiness of the substituent: the slim propargyl allows folding and apical coordination of one pyridine to each Cu^{2+} cation (square-pyramidal geometry, purple, λ_{max} = 575 nm), while the bulky benzyl prevents folding, resulting in square-planar Cu^{2+} cations (pink, λ_{max} = 515 nm). Visual and instrumental recognition of the double movement is based on the color change.

In this paper we report a double pH-driven Cu^{2+} translocation inside the ligand **L1**H_4, whose backbone is identical to that of **BZ**H_4 and **PG**H_4 but features two ferrocene (Fc) groups instead of benzyl and propargyl moieties. For sake of comparison the Fc-containing **L2**H_2 and **L3**H_4 ligands, which are capable of single Cu^{2+} translocation and inclusion of two Cu^{2+} cations with no translocation, respectively, on changing pH, have also been studied. As Fc is reversibly oxidizable and its potential is significantly influenced by nearby charges or dipoles, the study of the Fc redox potential as a function of the absence/presence and position of Cu^{2+} cation(s) in these new systems has two goals: i) obtaining an electrochemical signal, as an alternative to color[4,7,8] or fluorescence changes,[4,5] that can be

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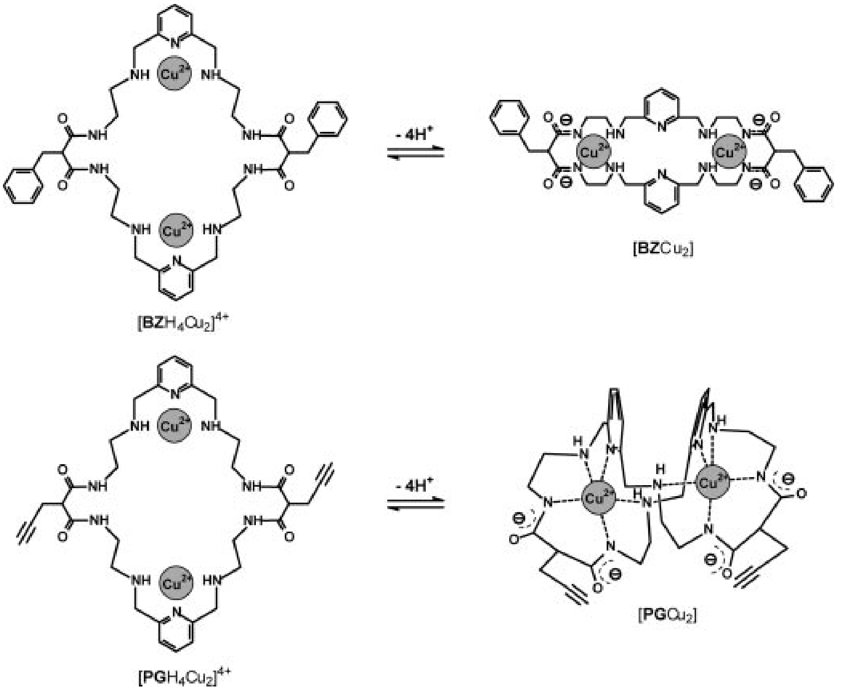
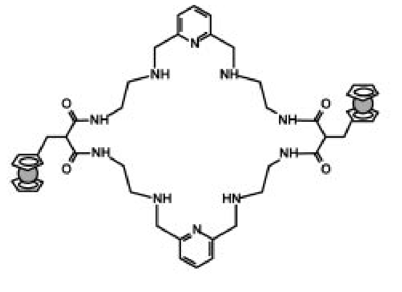
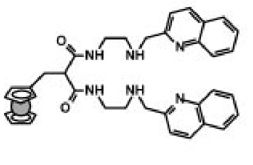


Scheme 1. Pictorial representation of pH-driven double Cu^{2+} translocation (upper equilibrium, ref.[6]) and pH-driven double Cu^{2+} translocation plus folding (lower equilibrium, ref.[7]) in ligands **BZ**H_4 and **PG**H_4.

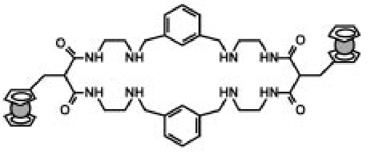
used to monitor the position(s) of the cation(s) inside the ligands; and ii) evaluating how a change in the overall charge and in the charge distribution upon Cu^{2+} translocation can electrostatically influence the space region occupied by ferrocenes. These are linked to a long-term research project of ours concerning the grafting of ligands on Si surfaces,[9] which may be achieved by surface reactions of the propargyl groups[10] and is thus accessible for ligands like **PG**H_4.



L1H_4



L2H_2



L3H_4

Accordingly, we report here the full characterization in aqueous solution of ligands **L1**H_4, **L2**H_2, and **L3**H_4 and of their copper complexes, by means of the determination of the protonation and complexation constants of the forms present in the pH range 2–12. The pH values between which double and single Cu^{2+} translocation takes place in **L1**H_4 and **L2**H_2, respectively, are determined. The nature and the coordination geometry of the pertinent copper complexes are investigated by UV/Vis spectroscopy. Finally, electrochemical (CV) investigations on the Fc redox potential have been carried out in aqueous solution as a function of pH, in the presence and in the absence of Cu^{2+}, to determine the effect of the metal cations and of their positions on the Fc oxidation potential.

Results and Discussion

Copper Complexes in Aqueous Solution and pH-Driven Translocation

The protonation and complexation constants of the ferrocene-containing ligands **L1**H_4, **L2**H_2, and **L3**H_4 were determined by means of potentiometric titrations in a water/dioxane (1:4, v/v) mixture due to the hydrophobic nature of the ferrocene molecule, which does not allow solubilization of the three ligands in pure water. Titrations were carried out automatically by addition of base to solutions containing first ligand only plus excess acid (for the determination of the protonation constants) and then to solutions containing ligand, the pertinent quantity of $Cu(CF_3SO_3)_2$ (2, 1, and 2 equiv. in the case of **L1**H_4, **L2**H_2, and **L3**H_4, respectively), and excess acid. The log*K* (protonation and complexation) values were obtained by elaboration of the emf vs. volume of added base data obtained by means of the Hyperquad program suite.[11] Experimental conditions and details are described in the Experimental Section. The calculated logarithmic protonation constants data are collected in Table 1.

Table 1. Logarithmic step protonation constants for ligands. Uncertainties are indicated in parentheses.[a]

	$\log K_1$	$\log K_2$	$\log K_3$	$\log K_4$
L1H_4	8.78(0.01)	7.77(0.01)	6.91(0.01)	6.15(0.02)
L2H_2	7.98(0.01)	6.78(0.01)	3.35(0.02)	
L3H_4	7.89(0.01)	7.80(0.01)	6.87(0.02)	6.04(0.02)

[a] Data obtained in dioxane/water (8:2, v/v), 0.05 M $NaNO_3$, T = 25 °C.

The number and $\log K$ values of the found protonation steps are in agreement with those already described for similar ligands in the same solvent mixture.[4,5] The formation constants of the copper complexes of the three ligands and the relative equilibria are reported, as logarithmic values, in Tables 2 (**L1**H_4 and **L3**H_4) and 3 (**L2**H_2) The distribution diagrams in Figure 1 (parts A–C), in which the percentage of each species (with respect to total ligand) is expressed as a function of pH, can be drawn from the data in all these tables.

From Figure 1 (A) it can be seen that the system containing ligand **L1**H_4 and Cu^{2+} in a 1:2 molar ratio allows the efficient translocation of the two Cu^{2+} cations.

The species [**L1**H_4Cu_2]$^{4+}$ (see Scheme 2) contains the neutral ligand and two copper cations, each of which is chelated to the tridentate diaminopyridine units. The large formation constant of this species (24.12 log units) reflects the chelating nature of the two donor sets and the coordination of two Cu^{2+} cations, and is in good agreement with the values already found for the analogous species [**BZ**H_4Cu_2]$^{4+}$ and [**PG**H_4Cu_2]$^{4+}$ (Scheme 1, $\log K$ = 25.31[7] and 25.30,[8] respectively). This species is the prevalent one in a large pH range (i.e. between pH 3 and 7), and accounts for over 95% at $3.7 < pH < 5.9$. Its formulation was confirmed by mass spectrometry (ESI) with solutions containing ligand and $Cu(CF_3SO_3)_2$ in a 1:2 stoichiometry and with the pH set at between 4 and 5. Peaks were observed for [**L1**H_4Cu_2 – H]$^{3+}$, [**L1**H_4Cu_2 + CF_3SO_3]$^{3+}$, and [**L1**H_4Cu_2 + $2CF_3SO_3$]$^{2+}$ (*m/z* 368, 369; 418, 419; and 701, 703 respectively). In the analogous complexes [**BZ**H_4Cu_2]$^{4+}$ and [**PG**H_4Cu_2]$^{4+}$, each Cu^{2+} cation was found to be five-coordinate (diaminopyridine chelate + two water molecules) with a trigonal-bipyramidal geometry on the basis of the visible absorption spectra. A d–d absorption band centered at 670 nm (ε = 190 $M^{-1}cm^{-1}$) can also be observed for [**L1**H_4Cu_2]$^{4+}$ when spectra are taken at $3.7 < pH < 5.9$, despite the absorption band of ferrocene in the visible range (λ_{max} = 440 nm, ε = 186 $M^{-1}cm^{-1}$). Figure 2 shows a spectrum taken for this species at pH 5.1. The solution has a green color due to the combination of blue (band at 670 nm) and yellow-orange (ferrocene band at 440 nm).

Table 3. Formation constants of the Cu^{2+}-containing species for the ligand featuring one dioxo232 compartment. Column 1 reports the relative equilibrium for each value relative to a generic diamido ligand LH_2. Uncertainties are indicated in parentheses.[a]

	L2H_2
$LH_2 + Cu^{2+} \leftrightharpoons [LH_2Cu]^{2+}$	10.90(0.01)
$[LH_3]^+ + Cu^{2+} \leftrightharpoons [LH_3Cu]^{3+}$	14.86(0.01)
$LH_2 + Cu^{2+} + H_2O \leftrightharpoons [LH_2Cu(OH)]^+ + H^+$	5.04(0.01)
$LH_2 + Cu^{2+} \leftrightharpoons [LCu] + 2H^+$	–2.56(0.02)

[a] Data obtained in dioxane/water (8:2, v/v), 0.05 M $NaNO_3$, T = 25 °C.

On increasing the pH above 6, the two hydroxide species [**L1**$H_4Cu_2(OH)$]$^{3+}$ and [**L1**$H_4Cu_2(OH)_2$]$^{2+}$ are formed by deprotonation of the coordinated water molecules. A pK_a of 7.19 and 8.68 may be calculated for the first and second deprotonation steps. These values are too large to suggest bridging of OH^- between the two Cu^{2+} cations.[12] The d–d absorption band of coordinated copper does not change significantly on passing from [**L1**H_4Cu_2]$^{4+}$ to [**L1**$H_4Cu_2(OH)$]$^{3+}$ and [**L1**$H_4Cu_2(OH)_2$]$^{2+}$ (a shift of λ_{max} to 675 nm and a lowering of ε to 160 are observed), similarly to the analogous complexes of **BZ**H_4 and **PG**H_4.[7,8] When the pH is raised to above 9.8 the solution takes a brown-purple color due to the neutral species [**L1**Cu_2], which is the prevalent one at $pH > 10.8$ (> 95% at $pH > 11.3$). In this species the two Cu^{2+} cations have translocated inside the diamino-diimido compartments (see Scheme 2). Mass spectra measured at $pH > 11.3$ display the peak for [**L1**Cu_2 + H]$^+$ (*m/z* 1101, 1103). The interpretation of the UV/Vis spectrum of this species is complicated by the presence of the ferrocene band. While the band at 670 nm disappears when [**L1**Cu_2] is formed (see part A of Figure 1, black triangles, for an Abs_{670} vs. pH plot), the band for this species falls under the Fc absorption, as can be seen in Figure 2 for a spectrum taken at pH 11.5. The effect of the formation of [**L1**Cu_2] is to shift the apparent absorption maximum of Fc to longer wavelengths and to increase the intensity of the band. Subtracting the spectrum at pH 5.1 from that at pH 11.5 gives the profile shown in the inset of Figure 2, which gives an indication that the absorption maximum of [**L1**Cu_2] is closer to 515 nm (absorption of [**BZ**Cu_2][7]) than to 575 nm (absorption of [**PG**Cu_2][8]). This

Table 2. Formation constants of the Cu^{2+}-containing species for the ligands featuring two dioxo232 compartments. Column 1 reports the relative equilibrium for each value relative to a generic tetra-amido ligand LH_4. Uncertainties are indicated in parentheses.[a]

	L1H_4	**L3**H_4
$LH_4 + 2Cu^{2+} \leftrightharpoons [LH_4Cu_2]^{4+}$	24.12(0.01)	10.63(0.01)
$LH_4 + 2Cu^{2+} + H_2O \leftrightharpoons [LH_4Cu_2(OH)]^{3+} + H^+$	16.93(0.02)	–1.23(0.02)
$LH_4 + 2Cu^{2+} + 2H_2O \leftrightharpoons [LH_4Cu_2(OH)_2]^{2+} + 2H^+$	8.25(0.02)	
$LH_4 + 2Cu^{2+} \leftrightharpoons [LCu_2] + 4H^+$	–13.17(0.02)	–14.89(0.03)

[a] Data obtained in dioxane/water (8:2, v/v), 0.05 M $NaNO_3$, T = 25 °C.

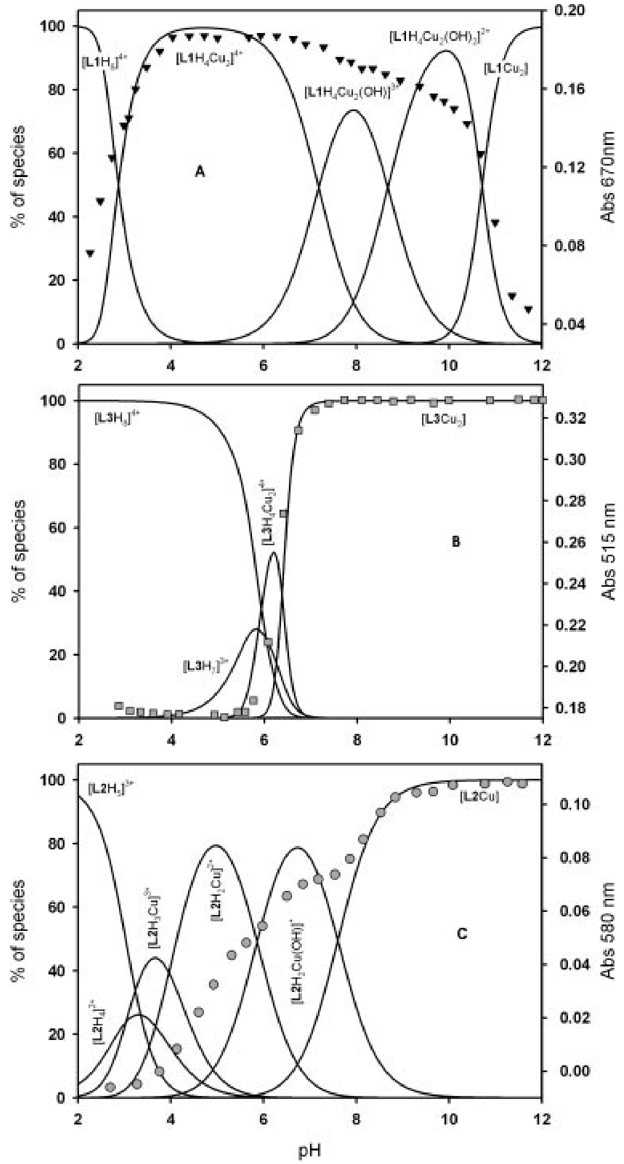
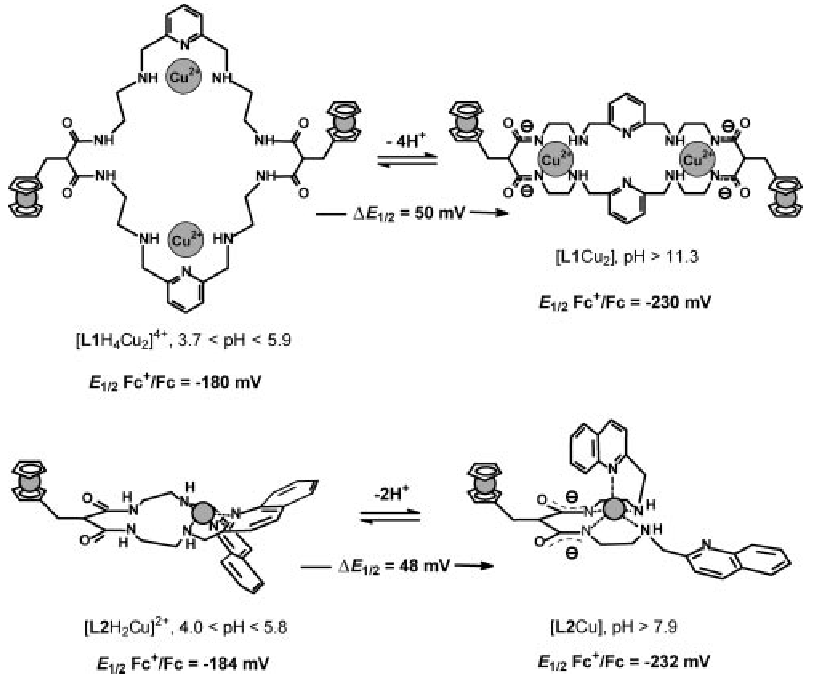


Figure 1. Distribution diagrams for the three systems, expressed as percentage of species (with respect to total ligand) vs. pH. Each diagram has been calculated for a 10^{-3} M ligand concentration. The species relative to each curve are reported on the diagram. A: **L1**H_4 + $2Cu^{2+}$; black triangles indicate the absorbance at 670 nm (i.e. at λ_{max} for [**L1**$H_4Cu_2]^{4+}$) vs. pH. B: **L3**H_4 + $2Cu^{2+}$; grey squares indicate the absorbance at 515 nm (i.e. at the expected maximum of absorption for the Cu^{2+}-centered d–d transition) vs. pH. C: **L2**H_2 + Cu^{2+}; grey circles indicate the absorbance at 580 nm (i.e. at λ_{max} for [**L2**Cu]) vs. pH.

fits well with a structure in which each Cu^{2+} is square planar, as shown in Scheme 2, which is indeed what would be expected if we consider the bulkiness of the ferrocene group, which should prevent the folding of the ligand structure and thus not allow apical coordination of Cu^{2+} by the pyridine moiety.[8]

According to these findings, translocation of the Cu^{2+} cations from the diaminopyridine compartments to the diamino-diimido ones (and vice versa) can occur as shown in Scheme 2, i.e. by changing the pH between two values chosen in the range 3.7–5.9 and >11.3. The movement is reversible and can be performed repeatedly, as confirmed by adding first excess base to a solution at pH 4.0 and then the same quantity of acid 10 times: the recorded spectra for [**L1**$H_4Cu_2]^{4+}$ and [**L1**Cu_2] are superimposable, apart from a negligible lowering of the intensity due to dilution. Kinetic characterization of the translocation process is beyond the scope of this paper. However, it can be noticed that the process is relatively fast: an instantaneous (i.e. not progressive) color change was observed visually upon addition of acid or base, and even though only a few seconds were needed to add the acid or base and transfer a sample of the bulk solution to a cuvette, the sequence of constant absorption spectra obtained subsequently indicated that the translocation process was already complete. In this connection, the question may be raised whether the cation translocation is an *intra*- or an *inter*molecular process. Careful kinetic measurements would be needed to give a reliable answer to this question, and again these are outside the scope of this paper. However, the hypothesis that the movement is intramolecular can be put forward. First of all it should be stressed that the probability of the translocation process is much higher between two compartments belonging to the same ligand molecule than between two compartments of different ligand molecules (binding of Cu^{2+} to the starting compartment means that the receiving compartment belonging to the same molecule would feel an enormously increased local concentration of Cu^{2+}). Moreover, kinetic studies carried out on closely related systems always show the intramolecular nature of the cation translocation processes.[4a,5]

It is interesting to compare these findings with those found for the non-translocating system containing the macrocyclic bis-dioxo232 ligand **L3**H_4 and Cu^{2+} in a 1:2 molar ratio. In this case, the structure of the ligand does not allow chelation and formation of stable Cu^{2+} complexes, apart from the square-planar, neutral bis-Cu^{2+} species [**L3**Cu_2], which is obtained by the release of the four amido protons. Accordingly, the distribution diagram (Figure 1, B) is dominated by the tetraprotonated, nonmetalated species [**L3**$H_8]^{4+}$ and by [**L3**Cu_2], which is prevalent at pH > 6.2 and accounts for more than 95% at pH 6.8. Indeed, a species in which two Cu^{2+} cations interact with the free ligand, i.e. [**L3**$H_4Cu_2]^{4+}$, is observed with a very low formation constant (10.63 log units), and may be representative of the coordination of each Cu^{2+} to a single amine nitrogen. This species forms in low quantities and in a limited pH range (it goes over 5% only between pH 5.6 and 6.5, reaching a maximum of around 50%) and is not competitive with respect to [**L3**Cu_2]. As a consequence, no translocation is possible in this system and formation of the neutral, square-planar species [**L3**Cu_2] is anticipated, on the pH axis, with respect to what is found for [**L1**Cu_2]. In particular, [**L3**Cu_2] goes over 95% at pH > 6.8, while [**L1**Cu_2] goes over 95% at pH > 11.3, with a dramatic shift of 4.5 pH units. As regards the UV/Vis spectra, at acidic pH values this system displays only the ferrocene absorption (λ_{max} = 440 nm, ε = 210 $M^{-1}cm^{-1}$, orange color) in the visible



Scheme 2. Pictorial representation of pH-driven double Cu^{2+} translocation and pH-driven single Cu^{2+} translocation plus folding in ligands **L1**H_4 and **L2**H_2. The change in the Fc oxidation potential, which depends on the position(s) of the Cu^{2+} cation(s), is also evidenced.

range, as can be seen in part B of Figure 2 (spectrum measured at pH 4.0). At the pH values in which the formation of [**L3**Cu_2] begins, the Fc band shifts to longer wavelengths, increases in intensity, and gains a shoulder due to the intrinsic absorption of Cu^{2+} inside the diamino-diimido compartments (the solution takes a brown-purple color). Above pH 7 a series of superimposable spectra are obtained. Figure 2 (part B) also shows a spectrum recorded at pH 8.5. The inset B of Figure 2 displays the profile obtained by subtracting the spectrum recorded at pH 4.0 from that recorded at pH 8.5: noticeably, a curve similar to the inset A of Figure 2 is obtained, which can be considered a further indication of the square-planar nature of Cu^{2+} in [**L1**Cu_2]. Moreover, plotting the absorbance at 515 nm vs. pH gives a profile (Figure 1 B, grey triangles) that perfectly superimposes the profile of the percentage of [**L3**Cu_2] vs. pH.

Finally, the behavior of the system containing **L2**H_2 and one equivalent of Cu^{2+} was examined. In this case, the structure of the ligand allows only single Cu^{2+} translocation. Indeed, the ligand resembles two very similar ones that we have already studied, in which a benzyl group[4b] or a propargyl group[8] are present instead of $FcCH_2$ in the same position. In both cases, a single pH-driven Cu^{2+} translocation is possible from the bis(aminoquinoline) compartment to the diamino-diimido one, and vice versa. However, translocation is accompanied by an overall folding of the system as the Cu^{2+} cation coordinated in the diamino-diimido compartment is also apically coordinated by quinoline. We have recently demonstrated that this kind of translocation + folding process always takes place when Cu^{2+} moves in open (i.e. non-cyclic) ligands of this kind, independently of the nature of the substituent on the central carbon of the malonic amide group.[8] Accordingly, we would expect a behavior like that sketched in Scheme 2 for **L2**H_2/Cu^{2+}, and this is confirmed by the experimental results. Calculation of the potentiometric titrations and formation constants allows us to draw the distribution diagram for this system (Figure 2, C). [**L2**H_2Cu]$^{2+}$ is the species in which the Cu^{2+} cation is coordinated by the two bis(aminoquinoline) chelating units (plus one water molecule), as has already been found for the systems based on similar benzyl- and propargyl-containing ligands.[4b,8] It forms at pH values above 3 and is prevalent between 4.0 and 5.8, reaching a maximum of 80% at pH 5.1. In the UV/Vis spectra (Figure 2 C, spectrum taken at pH 5.2), beside the ferrocene absorption (somewhat masked by the strong quinoline absorption band, which has a shoulder in the visible range), a d–d transition is observed at 660 nm (ε = 90 $\text{M}^{-1}\,\text{cm}^{-1}$), typical of trigonal-bipyramidal Cu^{2+} in these kind of complexes.[4b,8] At a pH between 4 and 6 the solution has a green color due to a combination of the ferrocene absorption and the Cu^{2+} d–d transition. Mass spectra (ESI) reveal the expected peaks at *m/z* 730, 732 for [**L2**H_2Cu-H]$^+$ and at *m/z* 880, 882 for [**L2**H_2Cu + CF_3SO_3]$^+$. On raising the pH the monohydroxide species [**L2**$H_2Cu(OH)$]$^+$ forms, with Cu^{2+} remaining in the bis(aminoquinoline) compartment, thanks to the deprotonation of coordinated water. The absorption spectrum of this species is similar to that of [**L2**H_2Cu]$^{2+}$. What is observed is a moderate shift of the absorption maximum towards shorter wavelengths and no perceivable change in the color of the solution. The solution color changes when the pH is raised over 7 and [**L2**Cu] forms in significant amounts. This species is that in which Cu^{2+} has translocated into the diamino-diimido compartment. It becomes prevalent above pH 7.9 and accounts for over 95% at a pH above 9.5. At this pH or higher, the

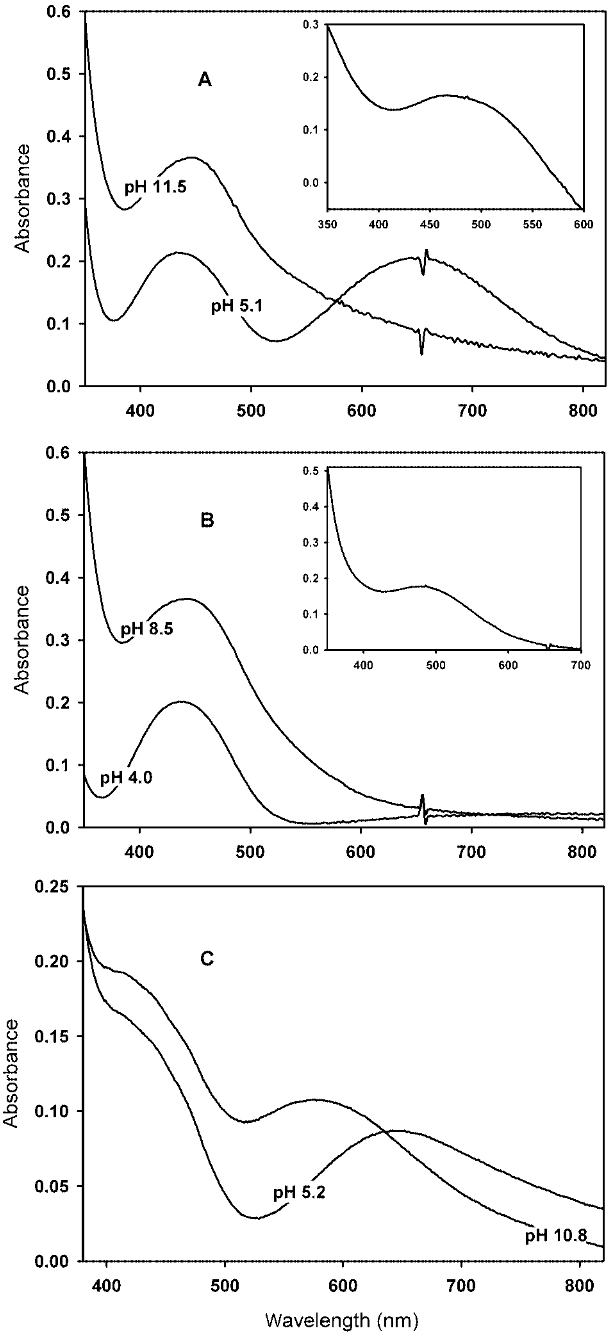


Figure 2. A: absorption spectra for the system **L1**H_4 + 2Cu^{2+} at 1.1×10^{-3} M ligand concentration; the spectrum recorded at pH 5.1 belongs to [**L1**H_4Cu_2]$^{4+}$, the spectrum recorded at pH 11.5 belongs to [**L1**Cu_2]. Subtraction of the spectrum at pH 5.1 from the spectrum at pH 11.5 is shown in the inset. B: Absorption spectra for the system **L3**H_4 + 2Cu^{2+} at 1.0×10^{-3} M ligand concentration; the spectrum recorded at pH 4.0 belongs to [**L3**H_8]$^{4+}$ and the very weak and large band (between 600 and 900 nm) is due to free Cu^{2+} (not complexed at this pH value, see also Figure 1, B), i.e. it is the d–d transition of the solvated cation; the spectrum recorded at pH 8.5 belongs to [**L3**Cu_2]; the subtraction of spectrum at pH 4.0 from spectrum at pH 8.5 is shown in the inset. C: Absorption spectra for the system **L2**H_4 + Cu^{2+} at 1.0×10^{-3} M ligand concentration; the spectrum recorded at pH 5.2 belongs to [**L2**H_2Cu]$^{2+}$, the spectrum recorded at pH 10.8 belongs to [**L2**Cu].

solution display a green/brown color and the UV/Vis spectra show that the Cu^{2+} d–d band has shifted to 580 nm (ε = 110 $M^{-1}cm^{-1}$). This is the typical value for a pentacoordinate, square-pyramidal Cu^{2+} cation inside a diamino-diimido compartment and apically coordinated by quinoline.[4b,8] (Figure 2 C, spectrum taken at pH 10.8). By means of a coupled pH-metric/spectrophotometric titration it is possible to obtain a plot of the absorbance at 580 nm vs. pH (part C of Figure 1, grey circles), which shows superimposition with the relevant percentage of species vs. pH curves. The observed step profile of Abs_{580} vs. pH is due to the fact that both [**L2**H_2Cu]$^{2+}$ and [**L2**$H_2Cu(OH)$]$^{+}$ also have a significant absorbance at 580 nm. The ESI mass spectra show a peak at *m/z* 730, 732 for [**L2**Cu + H]$^{+}$. Accordingly, single Cu^{2+} translocation plus folding can take place, as illustrated in Scheme 2. The reversibility of the backwards and forwards movements was checked by preparing a solution of [**L2**H_2Cu]$^{2+}$ at pH 5.2 and adding first excess strong base and then the same quantity of strong acid for ten cycles, always obtaining superimposable spectra for [**L2**H_2Cu]$^{2+}$ and [**L2**Cu], with a negligible effect due to dilution.

The Effect of the Translocation Process on the Ferrocene Oxidation Potential

A huge number of multicomponent molecular systems that contain Fc and one or more binding units are capable of electrochemically signaling the coordination of metal cations to the binding units or the protonation of the donor atoms of the latter. The proximity of M^{n+} (or, for example, of NH_2^{+}) makes the oxidation potential of Fc increase due to obvious electrostatic repulsion effects between the positive charge and ferricinium.[13]

We first examined the effect of protonation of the amine groups on the Fc oxidation potential in our ligands in the absence of metal cations. Each ligand was dissolved in the same solvent used for complexation studies (dioxane/water, 4:1 v/v) to a 10^{-3} M concentration, with 0.1 M $NaNO_3$ as the background electrolyte, and a series of CV experiments were carried out spanning the 2–12 pH interval by means of addition of excess standard HNO_3 and microadditions of standard NaOH. Quite interestingly, the oxidation potential of Fc does not change significantly with protonation, even at the lower limit of the examined interval, i.e. pH 2. At the more acidic pH values the found $E_{1/2}$ values are –175, –178, and –170 mV for the species [**L1**H_8]$^{4+}$, [**L2**H_5]$^{3+}$, and [**L3**H_8]$^{4+}$ respectively (potential values referenced to Ag/Ag^{+} electrode; see Exp. Sect. for details), while at more basic values the measured values are –182, –184, and –180 mV for **L1**H_4, **L2**H_2, and **L3**H_4, respectively (reversible waves are found in all cases, with a peak separation of around 120 mV at a scan rate of 400 $mV\,s^{-1}$). These values are close to the average for a mono-alkyl-substituted ferrocene, and the absence of significant changes on protonation is indeed not unexpected as it has already been demonstrated that a distance of more than three carbon atoms between ferrocene and the group changing its charge makes any electrostatic effects almost negligible.[14] However it is worth stressing that even in +4 charged systems as $[\mathbf{L1}H_8]^{4+}$ and $[\mathbf{L3}H_8]^{4+}$ the peripheral ferrocene moieties do not experience any significant change (<10 mV) in the potential of their oxidation process.

After obtaining these data we examined the effect on the Fc oxidation potential of the presence/absence of Cu^{2+} cations, and of their translocation, in the three ligands by means of coupled pH-metric titrations and electrochemical measurements. We coupled pH-metric titrations and CV measurements by adding base to acidic solutions containing ligand + $2Cu^{2+}$ ($\mathbf{L1}H_4$ and $\mathbf{L3}H_4$) or ligand + Cu^{2+} ($\mathbf{L2}H_2$). In the case of the double translocating system $\mathbf{L1}H_4/2Cu^{2+}$ at the pH values at which $[\mathbf{L1}H_4Cu_2]^{4+}$, $[\mathbf{L1}H_4Cu_2(OH)]^{3+}$, and $[\mathbf{L1}H_4Cu_2(OH)_2]^{3+}$ exist, the $E_{1/2}$ for Fc^+/Fc oxidation remains constant at –180 mV vs. Ag^+/Ag (reversible, peak separation = 120 mV at a scan rate of 400 $mV\,s^{-1}$), i.e. roughly the same value observed both for the free and the protonated ligand. This clearly indicates that when the Cu^{2+} cations are located in the diamino-pyridine compartments they are too far from Fc to exert any significant effect on it. On the other hand, when the pH is raised enough (>9.8) to translocate the two Cu^{2+} cations inside the deprotonated dioxo232 compartments and form $[\mathbf{L1}Cu_2]$, a significant shift in the Fc redox potential is observed, with $E_{1/2}$ decreasing to a final value of –230 mV vs. Ag^+/Ag (reversible, peak separation = 120 mV at a scan rate of 400 $mV\,s^{-1}$), obtained at pH values above 11.2, i.e. where $[\mathbf{L1}Cu_2]$ accounts for more than 95% of the species present in solution. A nice superimposition of the $E_{1/2}$ vs. pH profile is observed with the formation curve of $[\mathbf{L1}Cu_2]$, as shown in Figure 3. It should be noted that the *lowering* of the oxidation potential of ferrocene due to the presence of a nearby metal cation is unusual but not new, as has already been reported in a ligand containing ferrocene and a simple dioxo232 ligand.[15] The overall charge in the complex is zero, but in each Cu^{2+}/diamino-diimido compartment a dipole is formed by Cu^{2+} and the two negative charges (delocalized between the oxygen atoms and the conjugated imido nitrogens) that points its negative end towards the region of space in which the ferrocene moiety is located.

The same kind of result is found for the single Cu^{2+} translocating system $\mathbf{L2}H_2/Cu^{2+}$. At the pH values in which Cu^{2+} is in the bis(aminoquinoline) compartment (up to pH 6) the observed $E_{1/2}$ for Fc oxidation is –184 mV (i.e. roughly the same as for the free or protonated ligand), while a negative shift is observed when the pH is raised and $[\mathbf{L2}Cu]$ begins to form. A final value of –232 mV vs. Ag^+/Ag is observed at pH 9.5 or higher ($[\mathbf{L2}Cu] > 95\%$).

Accordingly, this behavior allows electrochemical signaling of the pH-driven translocation of the Cu^{2+} cations. Moreover, this result gives a clear indication that the two different positions in which the Cu^{2+} cations can be located should have sharply different effects (e.g. as regards electrical capacity) on a surface to which $\mathbf{L1}H_4$ and $\mathbf{L2}H_2$ ligands are grafted by reaction of a HC≡C–CH_2– group bound to the same carbon bearing the $FcCH_2$ substituent. Finally, it should be mentioned that, obviously, the same negative shift effect is observed for the $\mathbf{L3}H_4/2Cu^{2+}$ system. However, as in this case no species exists to any significant degree in which the Cu^{2+} cations are located on the ligand, except $[\mathbf{L3}Cu_2]$, a shift in the ferrocene $E_{1/2}$ is observed on going from the protonated ligand (–180 mV) to the $[\mathbf{L3}Cu_2]$ complex (–224 mV), i.e. it is not due to a translocation process.

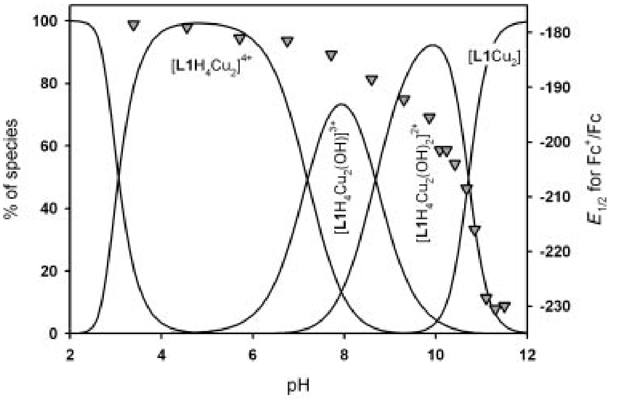


Figure 3. Distribution diagram for the system $\mathbf{L1}H_4/2Cu^{2+}$ at 10^{-3} M ligand concentration, with superimposed (grey triangles) $E_{1/2}$ values for the Fc^+/Fc couple as a function of pH, showing the negative shift that occurs on changing the position of the copper cations from the diaminopyridine to the diamino-diimido units.

Conclusions

Two new ligands have been studied in which double and single pH-driven Cu^{2+} translocation has been demonstrated to take place. Due to the bulkiness of the ferrocene group, in the macrocyclic and double translocating system ($\mathbf{L1}H_4/2Cu^{2+}$), translocation to the diamino-diimido compartments produces an authentic square planar Cu^{2+} complex. On the other hand, in the open ligand and single translocating system ($\mathbf{L2}H_2/Cu^{2+}$) translocation to the diamino-diimido compartment results in a five-coordinate Cu^{2+} center, with one quinoline folding to coordinate copper in one of its apical positions. From an electrochemical point of view, positioning of the Cu^{2+} cations in the compartments that are more distant from the Fc unit does not influence its redox potential at all. However, translocation inside the diamino-diimido compartments influences the oxidation of the ferrocene groups, which becomes easier by around 50 mV, thus allowing electrochemical signaling of the pH-driven translocation process. The unusual negative shift of the Fc oxidation potential on complexation of Cu^{2+} in the diamino-diimido compartment reflects the formation of a dipole that has its negative end pointing towards the region of space in which the ferrocene is located. Beside adding an electrochemical tool for signaling cation translocation processes, this work also gives an indication that, if molecules with the same structure as those studied here could be grafted on a conducting surface through the covalent binding of groups located in the same position as ferrocene, the surface could change its properties (e.g. impedance) upon translocation of the Cu^{2+} cation(s).

Experimental Section

Synthesis: The syntheses of the three ligands use N^1,N^3-bis(2-aminoethyl)-2-(ferrocenylmethyl)malonamide (Ferrocene-methyldioxo232) as the starting material, which was prepared according to a literature procedure.[15] 2-Quinolinecarboxaldehyde and 2,6-pyridinedicarboxaldehyde were purchased from Aldrich and used without further purification.

L1H_4**:** 2,6-Pyridinedicarboxaldehyde (134 mg, 1 mmol) was dissolved in 60 mL of CH_3CN. Ferrocene-methyldioxo232 (386 mg, 1 mmol) dissolved in 40 mL of CH_3CN was then added dropwise over a 2 h period under nitrogen and the mixture was kept under magnetic stirring overnight. An orange brown product (the tetraimino macrocycle) was collected by suction filtration, dissolved in methanol, and reduced with excess $NaBH_4$ (600 mg for each mol of C=N, considering 100% yield from the previous step), which was added in small portions, at room temperature, to avoid foaming. After the addition, the mixture was heated at reflux for 2 h, then cooled to room temperature and the solvent evaporated on a rotary evaporator. Water (100 mL) was added to the crude semisolid mixture, and the hydrolyzed suspension was extracted with three 30-mL portions of CH_2Cl_2. The organic portions were gathered, dried with $MgSO_4$, filtered, and the solvent removed on a rotary evaporator to give a yellow solid (237.5 mg, 0.243 mmol, 47.1% yield). ESI-MS: *m/z* 979 [**L1**H_4 + H]$^+$. ^{1}H NMR (DMSO): δ = 7.94 (t, 4 H, CO-N*H*-CH_2), 7.68 (t, 2 H, py-H), 7.24 (d, 4 H, py-H), 4.11 (s, 10 H, H of ferrocene), 4.02 (s, 4 H, H of ferrocene), 4.00 (s, 4 H, H of ferrocene), 3.4–3.0 [m, 14 H, amine protons + CO-C*H*(*R*)-CO + CO-NH-C*H₂*], 2.74 (d, 4 H, Fc-C*H₂*-CH), 2.50 (m, C*H₂*-NH-CH_2 + DMSO) ppm. $C_{50}H_{62}Fe_2N_{10}O_4\cdot CH_2Cl_2$ (1063.7): calcd. C 57.63, H 6.07, N 13.18; found C 57.58, H 6.05, N 13.15.

L2H_2**:** Quinoline-2-carboxaldehyde (628.7 mg, 4 mmol) was dissolved in 20 mL of ethanol. Ferrocenemethyl-dioxo232 (772 mg, 2 mmol) was dissolved in 30 mL of ethanol and added dropwise at room temperature, with magnetic stirring, under nitrogen. After 18 h the solution (containing the diimine) was treated in situ with excess $NaBH_4$ (600 mg for each mol of C=N). The subsequent workup was identical to that of **L1**H_4. A brown oily product was obtained, which was transformed into a yellow solid after repeated washing with diethyl ether (1.21 g, 90% yield). ESI-MS: *m/z* 669 [**L2**H_2 + H]$^+$. ^{1}H NMR (DMSO): δ = 8.5–7.5 (m, 14 H, quinoline protons and CO-N*H*-CH_2), 4.2–3.8 (m, 13 H, H of ferrocene and NH-C*H₂*-quinoline), 3.2 (m, 5 H, CO-CHR-CO and CO-NH-C*H₂*), 2.8 (d, 2 H, Fc-C*H₂*-CH), 2.6 (t, 4 H, C*H₂*-NH-CH_2) ppm. $C_{38}H_{40}FeN_6O_2\cdot H_2O$ (686.6): calcd. C 66.47, H 6.16, N 12.24; found C 66.44, H 6.18, N 12.21.

L3H_4**:** The synthesis of this ligand followed the same procedure described for **L1**H_4, but with isophthalaldehyde instead of 2,6-pyridinedicarboxaldehyde. The product was obtained as a yellow solid in 60.6% yield. ESI-MS: *m/z* 977 [**L3**H_4 + H]$^+$. ^{1}H NMR (DMSO): δ = 7.86 (s, 4 H, CO-N*H*-CH_2), 7.15–7.25 (m, 8 H, H of the phenyl rings), 4.10 (s, 10 H, H of ferrocene), 4.02 (s, 4 H, H of ferrocene), 3.99 (s, 4 H, H of ferrocene), 3.61 (s, 8 H, NH-C*H₂*-arene), 3.35 (broad, 4 H, amine protons), 3.2–3.0 [m, 10 H, CO-C*H*(*R*)-CO + CO-NH-C*H₂*], 2.74 (d, 4 H, Fc-C*H₂*-CH), 2.50 (m, C*H₂*-NH-CH_2 + DMSO) ppm. $C_{52}H_{64}Fe_2N_8O_4\cdot 0.5CH_2Cl_2$ (1019.3): calcd. C 61.86, H 6.43, N 10.99; found C 61.89, H 6.45, N 11.02.

Potentiometric Titrations: Protonation equilibria for ligands **L1**H_4, **L2**H_2, and **L3**H_4 were studied in dioxane/water (8:2, v/v) made up to 0.05 M in $NaNO_3$, thermostatted at 25 °C, with a Radiometer automatic system (Titralab TIM900) under nitrogen. In a typical experiment, a volume of 20 mL of a 10^{-3} M ligand solution was treated with 1.0 M standard HNO_3 in a quantity corresponding to the mols of ligand multiplied by the number of basic groups (amines + quinolines or pyridines) and augmented by two. Titrations were run by adding 20-μL portions of standard 0.1 M NaOH and collecting 80–100 points for each titration. Complexation equilibria were studied by means of titrations run under the same conditions, except that the starting solutions also contained $Cu(CF_3SO_3)_2$ in a 1:1 (**L2**H_2) or 2:1 (**L1**H_4 and **L3**H_4) molar ratio with respect to the ligand. Prior to each potentiometric titration, a titration according to the Gran method[16] was run to determine the $E°$ of the glass electrode in the chosen conditions. Protonation data (emf vs. volume of added base) were processed with the Hyperquad package[11] to determine protonation constants.

Spectrophotometric Titrations: Coupled spectrophotometric–pH-metric titrations were run with a procedure and under conditions similar to that described for potentiometric titrations. However, in this case, standard base was added manually by means of a 10- or 20-μL Rainin Pipet-Lite pipette. After each addition, a portion of the solution was transferred into a quartz cuvette and its absorption spectrum recorded. After recording the spectrum, the solution was transferred back to the bulk solution. The spectra recorded after each addition were associated with a pH value measured in the bulk solution by means of a glass electrode.

Electrochemistry: Cyclic voltammetric measurements were carried out in a three electrode cell, using a platinum electrode as the working electrode, a silver/silver ion electrode as the reference [clean silver wire into an electrolyte containing silver ion. The electrode filling solution was dioxane/water (8:2, v/v) made up to 7×10^{-3} M in $AgNO_3$, with 0.1 M $NaNO_3$ as the background electrolyte]. Dioxane/water (8:2, v/v) was used as solvent, made up to 0.1 M in $NaNO_3$. Ligand + metal solutions were at concentrations $\geq 5\times10^{-4}$ M. pH was regulated by means of microadditions of standard acid or base, and checked with a glass electrode dipped in the electrochemical solution before measurements. Scan rates were in the 200–400 mV s^{-1} range.

Instrumentation: Mass spectra were recorded with a Finnigan MAT TSQ 700 instrument, and NMR spectra with a Bruker AMX 400. Spectrophotometric measurements were performed with a diode array HP 8452A spectrophotometer or a Varian CARY 1000 SCAN spectrophotometer. The pH-metric titrations were made with a Radiometer TitraLab 90 titration system. Electrochemistry was obtained with a BAS100B/W instrument.

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