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Remarkable enhancement of Ca^{2+} affinity using a redox-switchable coordinating group†

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Redox-switchable coordinating groups hold significant promise for metal purification, detection, and the design of stimuli-responsive materials. However, existing designs often involve complex structures where a redox-active metal interferes with the target metal interaction. In this study, we demonstrate the use of a simple organic motif, namely 2-nitropyridine, as a redox-switchable coordinating group. This group was conjugated with a diaza-crown ether to yield a ligand for Ca^{+2} coordination. Under normal conditions, this ligand demonstrates weak metal interactions attributed to the electronic properties of the nitro groups. However, upon reduction, it transitions to a radical anion state with a strong affinity for Ca^{+2}. Notably, the required redox potential shifts depending on the metal ion present in the solution, dictated by the charge density of the complexed ion. This behavior facilitates the recognition of various metal ions in a solution, opening possibilities for applications in biological or industrial sensing.

Introduction

Responsive materials are poised at the forefront of scientific research and technological innovation,[1] offering the potential to revolutionize domains like medicine, electronics, and energy storage.[2–4] These versatile materials exhibit adaptability in response to external stimuli like pH, light, or redox potential. Notably, redox-responsive materials are particularly significant in industry for their capability to employ electrons as a versatile trigger, offering promising applications across various domains.[5]

A specific category of redox-responsive materials encompasses those equipped with redox-switchable coordinating groups.[6] These groups exhibit a remarkable ability to selectively bind or release metals in direct response to changes in electrical potential. To date, the structural diversity of redox-switchable coordinating groups is quite limited. Most examples are grounded in metal complexes, where the oxidation state of the metallic center significantly influences the donor capacity of adjacent atoms for the target metal.[6–11] A variation of this strategy has been recently published where an *ortho*-substituted *closo*-carborane was applied for the reversible capture of uranyl ions.[12] Other notable examples include redox-responsive groups capable of releasing metals, such as Ca^{2+}, upon oxidation.[13–15]

Building upon the pioneered work by Kaifer *et al.*, where nitrobenzyl groups were employed as redox-switchable entities to enhance the affinity of crown ethers for sodium,[16] herein we explore the application of 2-nitropyridine as a redox-switchable coordinating group for recognizing Ca^{2+}. The Ca^{2+} ion plays a key role in several physiological processes including the signaling pathways of the nervous system.[17] Electrochemical sensors represent the most promising alternative to overcome several limitations of luminescence sensors, to allow real-time monitoring of Ca^{2+} in live brains.[18,19]

In its native state, the nitro moiety manifests limited coordinating capacity, accompanied by its electron-withdrawing characteristics, which concurrently diminish the Lewis basicity of the pyridine. However, upon reduction, the nitro moiety might undergo a transformative process, evolving into its radical anion form. This transition would endow 2-nitropyridine with the attributes of a robust bidentate coordinating group, facilitating effective metal binding. Significantly, thanks to its chemical simplicity and remarkable stability, this

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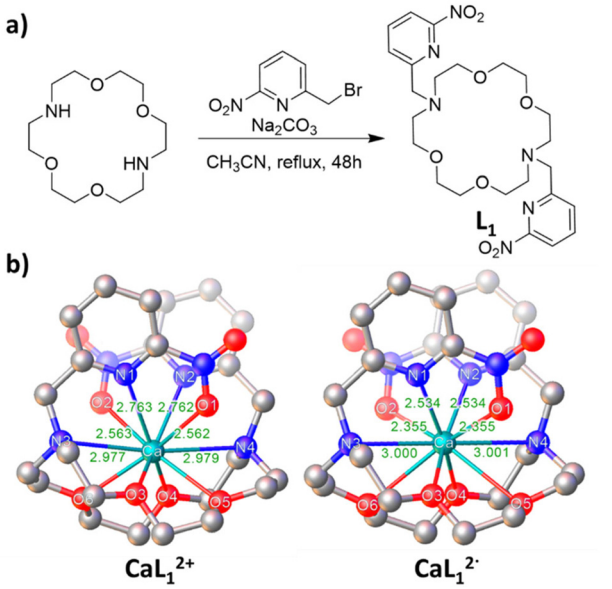

Fig. 1 (a) Synthesis of L_1. (b) DFT models illustrating the complexation of L_1 to Ca^{2+} in its oxidized form, CaL_1^{2+}, and upon the formation of the radical anion in both nitro-pyridine, *i.e.*, $CaL_1^{2\cdot}$.

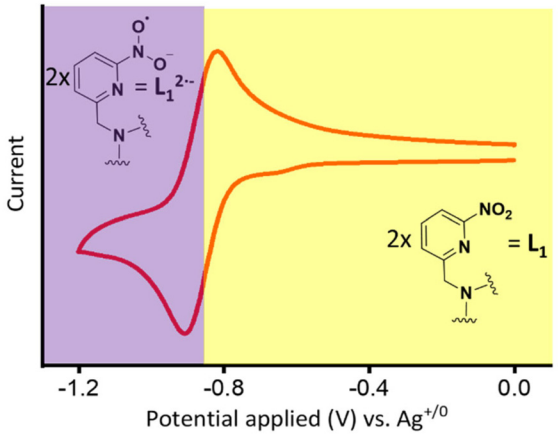

Fig. 2 Cyclic voltammogram for L_1 (1 mM) in acetonitrile with 0.1 M of NBu_4PF_6 as supporting electrolyte. The signal was recorded with a glassy carbon electrode (scan rate of 500 mV s^{-1}).

group can be effortlessly incorporated into the targeted chemical framework, offering a direct pathway for the development of novel redox-switchable ligands.

To check our hypothesis, we decided to couple 2-nitropyridine to a diaza-crown ether (Fig. 1). Crown ethers are extensively applied as building blocks in the field of supramolecular chemistry due to their unique capabilities to recognize metal cations.[20] They have a distinct cavity size and charge distribution that allows for selective recognition of a metal cation with a specific dimension. This ligand was inspired in MACROPA, a well-known chelator containing pyridinecarboxylate groups, which was developed for selective complexation of large metal ions.[21–24]

Results and discussion

Design, synthesis and electrochemical characterization of receptor L_1

A primary advantage of 2-nitropyridine is its chemical simplicity. Numerous commercially available analogs of this molecule simplify their direct incorporation into the desired platform. Specifically, L_1 was prepared in quantitative yield by treating 4,13-diaza-18-crown-6 with 2-(bromomethyl)-6-nitropyridine in acetonitrile in the presence of sodium carbonate as base (reflux, 48 h, Fig. 1a). We envisaged that the poor coordinating ability of the pendant arms will result in weak binding to alkaline and alkaline-earth cations, while electrochemical reduction will result in strong coordination of the pendant arms after formation of the radical anion form. DFT studies supported this design, as the CaL_1^{2+} complex is characterized by a weak coordination of the 2-nitropyridine units, with Ca–N and Ca–O distances of 2.763 and 2.563 Å, respectively. These distances decrease dramatically upon reduction of the system, amounting to 2.543 (Ca–N) and 2.385 Å (Ca–O) in $CaL_1^{2\cdot}$ (Fig. 1b, see ESI† for computational details).

The cyclic voltammogram (CV) of an acetonitrile solution of L_1 (0.1 M NBu_4PF_6) shows a single electrochemically *quasi*-reversible reduction occurring at a $E_{1/2}$ value of −864 mV *versus* the silver couple (Ag^+/Ag^0, Fig. 2). According to literature, the reduction of the nitro group attached to aromatic compounds is strongly influenced by the nature of the solvent.[25] In aprotic solvents, nitrobenzene can undergo up to two consecutive one-electron reduction steps, yielding the radical anion and the dianion successively (Scheme S1†).[26] Both steps are reversible, however the dianion tends to react rapidly with solvent, electrolytes or impurities. Analyzing (eqn (S1)†) the CV of L_1 with the Randles–Sevcik equation, gives an electron number of 1.6 e^- for the standard equation, and 1.9 e^- for the equation with parameters corrected by Matsuda.[27] This is consistent with the expected behavior of nitro groups in acetonitrile,[28] and thus a two-electron reaction can be unequivocally assumed, with each nitropyridine group contributing one electron. With this insight, we can infer that the observed *quasi*-reversible process is attributed to the formation of a dianion with one electron on each nitrobenzene. Additionally, the presence of a singular redox couple suggests that both active redox groups are sufficiently separated in space, ensuring that the reduction of the first group, yielding $L_1^{\cdot-}$, does not influence the subsequent reduction leading to the formation of $L_1^{2\cdot-}$.

Electrochemical response of L_1 in the presence of Ca^{2+} and affinity constants

The CV of L_1 was replicated following the addition of 1 equiv. of calcium trifluoromethanesulfonate [$Ca(OTf)_2$]. Strikingly, the resulting CV profile significantly deviates from that of L_1 in the absence of metal (Fig. 3a). The primary distinction arises from the observation of two *quasi*-reversible redox

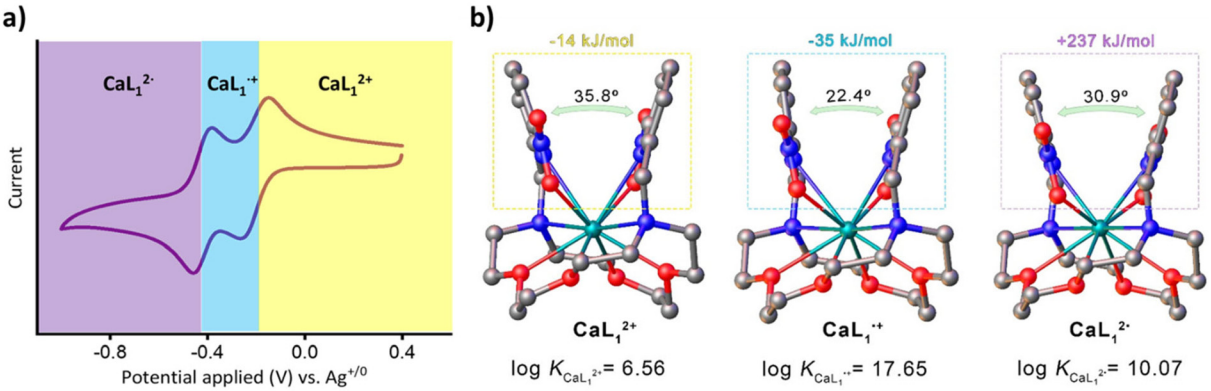

Fig. 3 (a) Cyclic voltammogram of an acetonitrile solution of L_1 (1 mM) in the presence of one equivalent of calcium trifluoromethanesulfonate. NBu_4PF_6 (0.1 M) was used as supporting electrolyte and the signal was recorded with a glassy carbon electrode (scan rate of 500 mV s^{-1}). (b) DFT simulations of the three complexes observed on the cyclic voltammogram, showcasing the angles between the nitropyridines in each scenario. The DFT interaction energy between the nitropyridines within each structure in gas phase is displayed atop. At the bottom, the experimental affinity constants for Ca^{2+} with each oxidation state of L_1 are provided.

couples rather than one. We propose that, unlike the scenario in the absence of the metal, the interaction with the Ca^{2+} ion forces the two nitropyridine groups into proximity, leading to repulsion between the radical anions and hindering the second reduction.

The second notable distinction pertains to the $E_{1/2}$ values, which exhibit a noteworthy anodic shift potential. Specifically, the $E_{1/2}$ value for the initial reduction is −208 mV, and for the subsequent reduction, it is −416 mV. Thus, the initial reduction shifted by 0.656 V respect to L_1 in the absence of metal. This substantial variance is associated with the distinct affinity constants of $L_1^{2\cdot-}$, $L_1^{\cdot-}$, and $L_1^{\cdot}$ for Ca^{+2}. Thus, a UV-vis absorption spectrophotometric titration was applied to determine the affinity constant of L_1 for Ca^{2+} in the conditions applied in the CV experiments, specifically 0.1 M NBu_4PF_6 in acetonitrile at room temperature. The absorption spectrum of L_1 experiences significant changes upon addition of Ca^{2+}, with the absorption maximum at 278 nm undergoing a blue shift to 274 nm, with well-defined isosbestic points developing during the titration (Fig. S9, ESI†). The spectrophotometric data were successfully fitted to a 1 : 1 binding isotherm with a binding constant of $K = 3.6(1) \times 10^6$ M^{-1} using standard methods (see ESI† for details).[29] This value, along with the variation in reduction potentials observed in the presence of calcium, was utilized to derive the affinity constants of the reduced ligands with eqn (1):

$$E_{CaL} - E_L = \frac{RT}{F} \ln \frac{K_{CaL^{\cdot-}}}{K_{CaL}} \quad (1)$$

An analogous expression was employed to estimate the association constant of $L_1^{2\cdot-}$ (see ESI† for details). Previous studies used an analogous expression to estimate the stability of complexes when the metal ion is the redox-active species.[30,31]

$L_1^{\cdot-}$ showed the highest affinity constant for Ca^{2+}, attaining an extraordinary log K value of 17.65. The Ca^{2+} complexes with the highest stabilities are formed with anionic ligands such as $DOTA^{4-}$, reaching a log K value of 17.2.[32] To our knowledge, this signifies the highest reported affinity constant for this cation. For comparison, complexes with crown ethers and cryptates are characterized by log K values <7.0, although some Ca^{2+} cryptates were found to be particularly inert.[33] The structurally related $MACROPA^{2-}$ forms a Ca^{2+} complex with log K value of 5.25 in aqueous medium.[34] Regarding other redox-switchable hemilabile ligands, information on their affinities is frequently unreported. However, it is anticipated that the reduced form of these ligands would demonstrate a significantly lower affinity for this ion, attributed to their dependence on redox-active metals. In contrast to L_1, where the reduction induces the formation of strong coordinating groups, the reduction in other ligands occurs over a metal that is not directly coordinated with Ca^{+2}, leading to a reduction in electrostatic interaction.

Interestingly, the fully reduced form of L_1, denoted as $L_1^{2\cdot-}$, displays a lower affinity compared to the aforementioned intermediate, with a log K value of 10.07. The unexpected lower affinity of L_1^{2-} could be ascribed, at least in part, to the repulsion that arises between the two radical anions when they are in proximity and interacting with the metal. Indeed, the angle defined by the least square planes of the aromatic units in the DFT structure of CaL_1^{2+} (35.8°) decreases to 22.4° in $CaL_1^{\cdot+}$, suggesting attractive interactions among the two aromatic units in the latter. This interaction energy between the two arms was estimated by DFT to be ∼−35 kJ mol^{-1} in $CaL_1^{\cdot+}$. However, DFT predicts a very important repulsive interaction between the pendant arms in $CaL_1^{2\cdot}$ (+237 kJ mol^{-1}, Fig. 3b). DFT provides $\Delta G^{\circ}_{(sol)}$ values for the first and second reduction processes of −286 and −259 kJ mol^{-1}, in line with the CV data that shows that the first reduction is more favorable than the second. The energy difference among the two processes corresponds to a difference in potential of ΔE = 270 mV, in reasonable agreement with the experimental data of 208 mV. The

analysis of kinetic electrochemical parameters (Table S1†) also agrees with a process involving significant changes in conformational and solvation energies.[35]

The former findings suggest that a modified version of the $\mathbf{L_1}$ ligand, featuring a single redox-switchable coordinating group, is anticipated to display a solitary *quasi*-reversible redox couple upon coordination with Ca^{+2}, aligning closely with the initial reduction potential of $\mathbf{L_1}$. To test this hypothesis, we synthesized ligand $\mathbf{L_2}$, differing from $\mathbf{L_1}$ by the absence of one of the 2-nitropyridine moieties. As expected, $\mathbf{L_2}$ exhibited a single redox couple for both the molecule in the absence and presence of Ca^{+2} with $E_{1/2}$ values of −811 and −225 mV respectively (Fig. 4).

Electrochemical response of L_1 in the presence of different cations

To get further insights on the performance of $\mathbf{L_1}$ as redox-switchable ligand, we recorded CV experiments in the presence of equimolar quantities of additional redox-inactive mono- and di-positive metal ions, namely, Na^+, K^+, Ca^{2+}, Sr^{2+} and Ba^{2+}. All the cations exhibited a behavior akin to Ca^{2+}, with two distinct redox couples observed at potentials more positive than those recorded for the ligand in its original state (Fig. 5). As depicted in Fig. 5, among the Group 2 cations, Sr^{2+} exhibited $E_{1/2}$ values that closely resembled those of Ca^{2+} at −284 and −451 mV, followed by Ba^{2+}, with values of −341 and −494 mV. In contrast, alkali metals displayed values much more similar to the original ligand, with Na^+ at −580 and −811 mV and K^+, at −757 and −888 mV. On this basis, it can be concluded that, (i) in all cases, $\mathbf{L_1}^{\bullet-}$, has a larger affinity for the metals than the fully reduced $\mathbf{L_1}^{2\bullet-}$, and (ii) the impact of reduction on the affinity for the metals follows the order Ca^{+2} > Sr^{+2}, Ba^{+2} ≫ Na^+ > K^+. Akin to previously reported redox-switchable coordinating groups, this order correlates with the Lewis acidity of the cations, directly linked to the charge density of the metal ions. It has been shown that the Lewis acidity of metal ions correlates very well with the pK_a of the aquated ions,[36] which have been demonstrated to be very good descriptors of Lewis acidity.[37] Indeed, the plots of the observed $E_{1/2}$ values *versus* the pK_a data of the corresponding aqua-ions are linear, with the potential becoming more negative as the pK_a increases (Fig. S8, ESI†). The quality of the linear regression is particularly good for the first reduction wave (R^2 > 0.995). The poorer linear correlation of the second reduction wave (R^2 > 0.95) suggests that the repulsive effects among the two reduced nitropyridine groups depend significantly on the size of the metal ion.

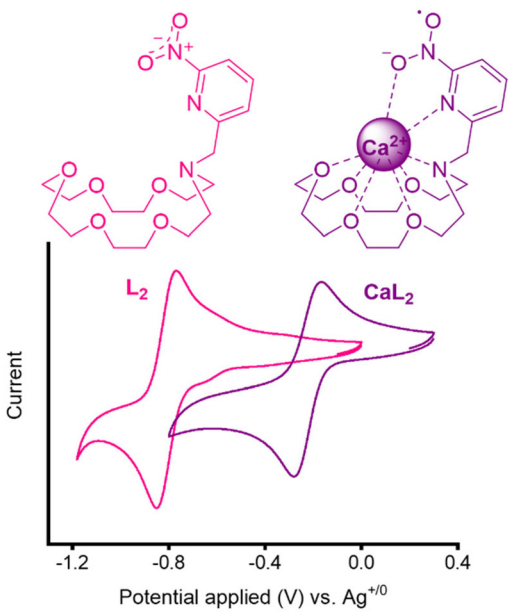

Fig. 4 Cyclic voltammogram of an acetonitrile solution of $\mathbf{L_2}$ (1 mM) in the absence and in the presence of one equivalent of Ca^{2+}. NBu_4PF_6 (0.1 M) was used as supporting electrolyte and the signal was recorded with a glassy carbon electrode (scan rate of 500 mV s^{-1}).

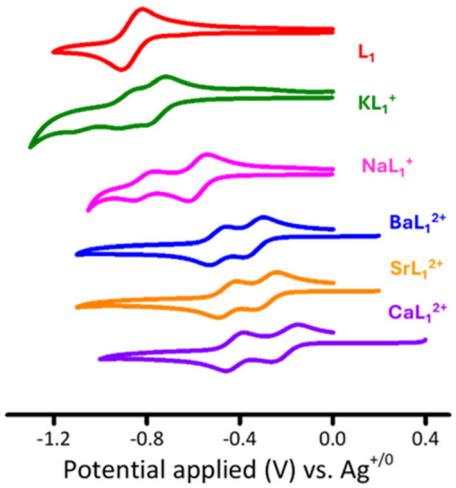

Fig. 5 Cyclic voltammogram of an acetonitrile solution of $\mathbf{L_1}$ (1 mM) with different alkaline and alkaline earth metals. NBu_4PF_6 (0.1 M) was used as supporting electrolyte and the signal was recorded with a glassy carbon electrode (scan rate of 500 mV s^{-1}).

Conclusions

In conclusion, our findings show that 2-nitropyridine effectively functions as a redox-switchable coordinating group. Its limited coordinating capabilities change dramatically upon reduction, forming a robust bidentate ligand. Leveraging its chemical simplicity, we integrated this group into a diaza-crown ether framework, yielding a redox-responsive ligand finely tuned for the biorelevant Ca^{2+} cation. This ligand allows attaining unprecedented affinity for Ca^{2+} upon its reduction (log K value of 17.65). The principles presented here will allow the design of electrochemical sensors for Ca^{2+} and other metal ions, which requires anchoring the electroactive ligand on the surface of electrodes.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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