Cooperative Recognition of Ni\(^{2+}\) Triggered by Fluoride Ions in Naturally Occurring \(\alpha\)-Hydroxyquinone Derivatives

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ABSTRACT: Perezone is a naturally occurring hydroxyquinone that has been deeply studied from different chemical aspects, such as therapeutic, electrochemistry, physical—chemical properties, or synthetic approaches that turn it an attractive template for new semisynthetic derivatives with a wide range of purposes. Herein, we describe a facile synthetic pathway to obtain new perezone derivatives by the addition of a pyrrole moiety that can be used for ion recognition. Compounds 2–4 showed the capability to interact with several anions and M\(^{2+}\) cations as separate events that result in colorimetric changes. Moreover, the compounds can behave as heteroditopic receptors. Besides, a previous interaction between fluoride ions and perezone derivatives triggered a successful recognition of M\(^{2+}\) ions, remarking Ni\(^{2+}\) as the most interesting phenomenon. These results project the compounds as potential colorimetric receptors for nickel ions in complex solutions.

INTRODUCTION

Chemical entities with supramolecular activity, such as molecular receptors, provide the building blocks for biological markers, molecular machines and smart polymers, among others. Recognition of chemical species is a fast-developing area in supramolecular chemistry due to its implications in pollution, materials, foods, drugs, and animal physiology.\(^1\)–\(^4\) In this sense, molecular recognition of biologically important anions is currently an expanding area in the field of supramolecular chemistry that has the continuous urgency for developing anion sensors for complex media such as blood, serum, drinking water, and other biological systems.\(^5\)–\(^7\)

Certain metallic species are in the spotlight of biological, chemical, and interdisciplinary studies by playing a pivotal role in many intra- and extracellular functions. However, these can only be monitored in vitro by using potentiometric single-ion selective sensors.

Even though most of the chemical sensing for cation recognition is focused on determining the biological activities of ions such as calcium (Ca), magnesium (Mg), iron (Fe), or copper (Cu), nocive effects of some metal cations remain in the shadow due to their apparent innocuousness, that is, in the cases of cobalt (Co), nickel (Ni), and chromium (Cr) that are used in prosthetics manufacturing because of their high mechanical stability and good biological compatibility, their corrosion products have been shown to provoke adverse biological responses. Highlighting nickel and nickel derivatives, it is also known that chronic exposure to these compounds can cause allergies, inflammatory processes, and prevalence of lung carcinoma; the general population consumes most of the nickel through food; the average daily intake of nickel from food in the United States is estimated to be 150–168 \(\mu\)g. A typical daily intake from drinking water is about 2 \(\mu\)g and from air is 0.1–1 \(\mu\)g. The general population is also exposed to nickel in nickel alloys and nickel-plated materials, such as coins, steel, and jewelry, and residual nickel may be found in soaps, fats, and oils.

Although sensing cationic ions has received more attention in supramolecular chemistry, recognition of anionic species has been emerging in the last 3 decades.\(^8\)–\(^10\)

Anions are essential to maintain the adequate functions of both biological and industrial processes and are often found as harmful pollutants.\(^11\) For instance, perchlorate ions are highly water-soluble environmental contaminants, so they can readily move to aqueous media, resulting in the contamination of groundwater and could also disrupt normal thyroid functions competing with iodide.\(^12\) It is also well known that chronic exposure to aqueous fluoride in concentrations above 1 ppm causes various diseases in organisms, such as dental and skeletal fluorosis, increased susceptibility to kidney disease, and cancer, as well as involvement in a delay of neurological development and reduced IQ in school-age children.\(^13\) Elusive anions such as fluoride can be recognized and captured by hydrogen bonding with protonated nitrogen groups.\(^14\) A class of ion receptors that always attract a great deal of interest...
are those that simultaneously coordinate both anionic and cationic guest species. A consequence of binding both cations and anions in the same receptor is a decrease in the energy cost of the recognition process.17 Like anion- and cation-sensing, ion-pair recognition also has multiple applications as sensors, membrane transport, salt solubilization, or extraction agents, to name a few.14,18,19

Recent reports in the area of anion recognition describe a wide variety of neutral, relatively simple-to-synthesize, and acyclic anion receptors based on pyrrole, indole, and amide groups and their combinations with remarkable anion-binding properties.20 Pyrrole can recognize anions due to its nature of donating the –NH hydrogen to electron pair receptors. The synthetic versatility of this heterocycle, as well as its ion-recognition capability, makes it attractive to be used in supramolecular chemistry, where typical examples are calixpyrroles and porphyrins.21 As a counterpart of anion recognizers, cation receptors have oxygen or nitrogen atoms with electron pairs available to be accepted by empty metal orbitals. The most well-known class of cation receptors includes the crown ethers, such as cryptands, podands, calixarenes, and hybrid species.22,23

Cation receptors containing non-ether groups, such as amides or carbonyl fragments, can also act as excellent cation guest recognizers.24,25 In particular, quinones have two carbonyl groups that could recognize cations via Lewis acid–base interactions; however, they have been poorly studied for such purposes, although they are of great interest in synthetic processes and biological systems. Anion–quinone interactions have been studied theoretically.26

Some quinones have been examined as cation or anion receptors,77–79 for example, benzoquinone has been reported to recognize an ion pair,80 the complex of calix-[4]-pyrrole and tetrachloroquinone interact by charge transfer, and the complex can recognize anions.31,32

A new anion receptor, dipyrrolyl quinone,33 which shows high fluoride specificity, has been described. This receptor presumably recognizes fluoride, both by an anion–π interaction with quinone and by hydrogen bonding with pyrrole. Modifications to pyrrolyl quinones, as well as to quinones, alter their electrochemical properties; the latter phenomenon was recently used for oxidative amidation of aromatic aldehydes.34

It is well known that the building of chemical entities is inspired by such elegant examples taken from natural sources and, in some cases, naturally occurring compounds are the nucleus of the new compounds, considering them as a template with multiple functions that allows the increment of the structure’s complexity and sharpens the specificity of the new receptor. Perezone 1 is a naturally occurring p-benzoquinone that shows antifeedant and phytotoxic activities,83 inhibition of ADP-induced platelet aggregation,84 promotion of the release of intramitochondrial Ca2+,85 and remarkable induction of cytotoxicity through the caspase-dependent or caspase-independent mechanism.86 Based on the premises that electron-withdrawing groups bound to pyrrolic compounds tend to increase the compound’s binding affinity toward anions, such as fluoride,87 and that quinones interact with ions, we have recently described the synthesis of (R)-2-hydroxy-6-methyl-3-(6-methyl-5-oxoheptan-2-yl)-5-(1H-pyrrolyl-2-yl)-cyclohexa-2,5-diene-1,4-dione 3, from perezone 1, designed as an ion-pair receptor.35 The behavior of 3 with inorganic salts motivated us to extend the study of compound 4, which in principle must increase the number of binding sites to evaluate it as a receptor of anions and cations. In this study, we report the heteroditopic receptor abilities of compounds 2–4 toward fluoride and nickel ions (Scheme 1).

### Scheme 1. Naturally Occurring Hydroxyquinone Perezone 1 and Its Semisynthetic Derivatives 2–4

![Scheme 1](https://doi.org/10.1021/acsomega.1c01420)

**RESULTS AND DISCUSSION**

Compound 2 was synthesized by the addition of pyrrole to perezone 1 using SiO2 as the acid promoter of the reaction, as reported previously for compound 3;40 the latter compound was used as a control for ion sensing. Dipyrromethane derivative 4 was obtained as a blue-violet amorphous solid by using a green approach to the condensation of (1H-pyrrolyl-2-yl)-4-oxo-perezone 3, with acetone catalyzed by dilute HCl (Scheme 2).41 Although the condensation of pyrrole with carbonyl compounds has been carried out with trifluoroacetic acid42 or Bi(NO3)3·5H2O43 to obtain dipyrromethanes or calix-[4]-pyrroles, in this case, the reaction proceeded with poor yields. The change of the catalyst for dilute HCl in aqueous media considerably increased the yield of the reaction. All compounds were characterized by different available analytical techniques, confirming their structures (Figures S1–S8). The supramolecular behavior of compounds 1–4 was analyzed to discriminate the effect of the side substituents of the hydroxyquinone–pyrrole adduct and the plausible synergism provided by dipyrromethane condensation.

Perezone 1 is an orange solid that has one broad transition band at λ_{max} = 408 nm, in accordance with previous reports on the starting material; this very broad, low-energy band at λ = 390–415 nm provides information about the molecule’s delocalization system and gives perezone its characteristic color; it may be the product of n–π* transition of the quinone carbonyl groups.84 Modifications to 1 at the quinonic moiety can be observed by the naked eye, as the pyrrolyl perezone derivatives 2–4 were all purple. The first comparison of compounds 1 and 2 is shown in Figure 1, where the UV/vis spectra are overlapped. As a first comparison, we can observe just one broad transition band at λ_{max} = 408 nm for the starting material 1 and a new absorption spectrum that shows a hypsochromic shift (from λ_{max} = 408 nm to λ_{max} = 360 nm) and a broad shoulder band that emerges at λ_{max} = 562 nm; the latter transition has been referred to as the ICT absorption...
band mediated by an intermolecular hydrogen bond with the pyrrole moiety.

Perezone derivatives 2 and 4 have been designed to recognize ion pairs and act as colorimetric sensors, as it was reported previously for compound 3, where color changes can be observed for several ion pairs; before using these compounds toward charged species, we compared the differences at their UV/vis absorption spectra, observing no other significant changes than a slight increase in absorbance and a bathochromic shift for the ICT transition band suffered by compound 4, as shown in Figure 2.

Compounds 2−4 were studied with a series of perchlorate salts including Li⁺, Cd²⁺, Ni²⁺, Hg²⁺, Pb²⁺, and Zn²⁺. No significant change was observed using Li⁺ and Hg²⁺, but the formation of a transition band at λ\text{max} = 459 nm is observed, which correlated with cation-host interaction (Figure S9). This effect (increment of absorbance at λ\text{max} = 459 nm) follows the order Ni²⁺ > Zn²⁺ > Pb²⁺ > Cd²⁺, as clearly shown by compound 3 evaluation that was taken as a model in Figure 3.

On the other hand, the compounds were tested as anion receptors, and after the addition of anions to a solution of each derivative, a change in the color from purple (λ\text{max} = 562 nm) to yellow (λ\text{max} = 408 nm) was observed with the more basic anions (Figures S10 and S11); such transition is the same as...
that for the starting material, which can be explained by the loss of conjugation with the pyrrole ring which then interacts with the anions, and this behavior is observed in three compounds. Compounds 2 and 3 showed a preference in the order of CN⁻ > F⁻ > OH⁻ > CH₃COO⁻ > N₃⁻ (Figures S10 and S11), but compound 4 showed a different pattern as follows: F⁻ > CN⁻ > CH₃COO⁻ > N₃⁻, as depicted in Figure 4. Job's plots for compounds 2–4 with fluoride showed a 1:1 stoichiometry (Figures S13–S15).

As mentioned above, receptors 3 and 4 were designed to stabilize interactions with the aliphatic carbonyl moiety, so it resulted in the necessity to demonstrate the role of this functional group. In this way, perezone 1 and pyrrolyl perezone derivatives 2 and 3 were evaluated with Ni²⁺ and F⁻. For compound 1, it is known that α-hydroxyquinones act as weak acids, the pK₆ value of which was calculated as <6, showing –OH deprotonation in alkaline solutions 45–47 which translated into a strong bathochromic shift (from λₘₐₓ = 400 to 550 nm). The oxynionic form is derived from internal proton donors such as the (–OH) group at the C2 position, which, in the presence of strong bases, give a purple color, with the intensity being directly proportional to the amount of perezone.48 No appreciable interaction is observed in the UV/vis spectra when a solution of nickel perchlorate was added. It is noteworthy that the bathochromic effect has been appreciated by other authors with topaqunione (a 6-substituted 2-hydroxy-1,4-p-benzoquinone) when it was reacted in the presence of a base, indicating a change in the spectrophotometric properties attributed to the oxynionic form.46 The deprotonation trend is followed by 1, while tetrabutylammonium fluoride (TBAF) is added even in a Ni²⁺-saturated solution, where a decrease in absorbance can be observed, probably due to NiF₂ formation. As topaqunione, compound 1 must interact with the metallic ion by coordinating with the hydroxycarbonyl region but with low efficacy at this stage (Figure 5a).

Perezone 1 did not give any interaction with Ni²⁺, but in the presence of fluoride, the absorption at λₘₐₓ = 408 nm with a shoulder at λₘₐₓ = 562 nm is relevant due to the oxanyanion generated by the basicity of the medium already reported for perezone or topaqunione (Figure 5a). The behavior of compounds 2 and 3 is similar but different in comparison with 1; both suffered a blue-shifted absorption from λₘₐₓ = 530 nm to 385 nm in the presence of fluoride, instead of the bathochromic effect showed by 1, which can be attributed to the NH–F interaction and the consequent loss of conjugation. This effect has been tracked previously in anion sensing studies (Figures S10 and S11), but the main difference comes from cation sensing, where 2 and 3 show a slightly better interaction with Ni²⁺ than 1. This interaction increases in the presence of fluoride for both compounds (Figure 5b,c), inferring compounds 2 and 3 are heteroditopic-ion recognizers in comparison with 1, where the interaction with cations depends on basicity. These results indicated that the contribution of pyrrole is relevant for recognizing the fluoride and the metal ion in the second stage and that the carbonyl in the side chain is helpful, but not expendable, to cause the interaction, as demonstrated by compound 2 where a broad shoulder can be observed at λₘₐₓ = 530 nm. Under these conditions, from ¹H NMR titration (compound 3, Figure S18), we did not appreciate pyrrole deprotonation. It is important to mention that, as has been discussed in recent works,48 the deprotonation of pyrrole by the fluoride anion can be ruled out, considering that its pK₆ value is approximately 16; nevertheless, it is capable of doing so with hydroxyquinone which, as mentioned above, has a pK₆ value of approximately 6, that is considerably more acidic than the heterocycle; so, if such deprotonation would exist, then the equilibrium would shift toward the formation of the oxanyanion.

Focusing on compound 4, after the addition of TBAF to a solution of such derivative, a change in the color from purple (λₘₐₓ = 562 nm) to yellow (λₘₐₓ = 408 nm) was observed, which can be explained by the loss of conjugation between quinone and the pyrrole ring, which then interacts with fluoride in a different way than during only deprotonation (Figure 6a). As shown by the absorbance profile, the stoichiometric ratio for the complex 4–F⁻ is 1:1 (Figure S14). Kₐ = 1.6 × 10⁵ M⁻¹ was calculated by the adjusted nonlinear minimum square model (Figure S16). On the other hand, the addition of Ni²⁺ to 4 showed a smooth absorption band at λₘₐₓ = 459 nm (Figure 6b), indicating a change in the conjugation of the hydroxyquinone moiety; this is due to the competition with a strong intramolecular hydrogen bond. More interestingly, when Ni²⁺ is added to the TBAF saturated solution of compound 4, it is observed that the effect on the absorption at λₘₐₓ = 459 nm (Figure 6c) is still more remarkable than when TBAF is added to the Ni²⁺ saturated solution (Figure 6d), where the band at λₘₐₓ = 459 nm becomes predominant, inferring a cooperative effect on the ditopic recognition. Job’s plot of this last interaction shows a 2:1 stoichiometry (Figure S17).

To confirm the interaction of pyrrole with the fluoride anion, ¹H NMR titration was performed for compounds 3 and 4 in anhydrous deuterated acetonitrile with TBAF salt (Figures S18–S20). The ¹H NMR spectra showed that the –NH2-free proton of pyrrole suffered a downfield shift up to 10.5 ppm, that is, 3–4 ppm downfield from a typical dipyrrromethane 49,50 prima facie due to a hydrogen bonding involving quinone’s vicinal carbonyl; so, it is expected that fluoride must compete with this intramolecular reaction. A downfield shift of the –NH signal over 2 ppm was observed up to the saturation of the salt in the mixture (Figures 7 and S19 and S20).

Our proposal of interaction between compound 4 and the tested ions has a “kick-off” as soon as fluoride is added to the solution, generating oxanyonic species, which was observed via...
UV/vis and NMR spectroscopy methods. As the presence of fluoride increases, the interaction leads to a 1:1 complex formed by the dipyrromethane moiety; at this step, we can find the most intense colorimetric shift (hypsochromic, from $\lambda_{\text{max}} = 562$ nm to $\lambda_{\text{max}} = 408$ nm, which was monitored by UV/vis spectroscopy) suffered by 4. The species of the complex $[4 + F^-]$ in the solution can recognize the $\text{M}^{2+}$ ions, which can be observed as the new transition band that emerges during both crossed titrations (Scheme 3). This last phenomenon was also reported by Gupta and Mir to generate coordination complexes of hydroxynapthoquinones and metal ions.\textsuperscript{51,52}

The proposed stoichiometry of the last interaction stage is supported by Job’s plot, showing a 2:1 ratio of $\text{Ni}^{2+}$ ions per $[4 + F]$ complex.

A practical advantage of receptor 4 was evaluated toward a solution of commercial toothpaste where a change in coloration from purple to yellow was appreciated at a time when the paste and compound 4 were mixed without a solvent. Moreover, the titration of fluoride was then carried out with a solution of the commercial toothpaste corresponding to 1 mg F$^-$/L. 20 µL (0.007 mg F$^-$) of compound 4 ($5 \times 10^{-4}$ M in CH$_3$CN) was added to reach 200 µL (0.0625 mg F$^-$/L). As shown in Figure 8, 4 changes in the absorbance from 0.01 mg/L of the fluoride solution, demonstrating the potential use of this compound as a low-concentration fluoride sensor. This last topic is currently under examination.

**CONCLUSIONS**

Naturally occurring compounds have potential for application in the construction of complex molecules due to their unique properties and potential ability to generate stimuli-responsive materials and chemical receptors through the use of semisynthetic approaches. In this work, it was possible to modify specific properties of a naturally occurring chemical entities to create a “multitasking” molecule focused on metal recognition. Compounds 2–4 were synthesized from the naturally occurring compound perezone by clean, economical, and environmentally safe methods; as a case in point, all of these are part of the goals of modern synthetic organic chemistry.\textsuperscript{53}

Although ion sensing is an emerging and fast-evolving area,
only a few reports of ion pair receptor agents from pyrrole−quione entities have been described.\textsuperscript{30,33,40,54,55} The advantage of functionalizing hydroxyquinones with pyrrole or pyrrole derivatives, such as \textit{meso}-alkyldipyrromethanes, involves a synergistic effect; while pyrrole or dipyrromethane moieties interact with the anionic species, hydroxyquinone stabilizes the counterion, affording high sensitivity for this unique ion pair (\(\text{Ni}^{2+}\) and \(\text{F}^-\)), even in aqueous solutions and at low concentrations.

\section*{EXPERIMENTAL SECTION}

\subsection*{General Methods.} Nuclear magnetic resonance spectra were recorded on a Varian Mercury 400 spectrometer. \(^1\)H NMR spectra were recorded at 400 MHz and are reported as follows: the chemical shift in ppm is relative to tetramethylsilane (TMS) as an internal standard (for spectra obtained in CDCl\(_3\)); multiplicity: \(s =\) singlet, \(d =\) doublet, \(t =\) triplet, \(q =\) quartet, \(m =\) multiplet, or overlap of nonequivalent resonances. \(^{13}\)C NMR spectra were recorded at 100 MHz, and the chemical shift in ppm is relative to TMS from the solvent signal (CDCl\(_3\)).

Figure 6. UV/vis spectroscopic titration curves of (a) \(4 + \text{TBAF}\). (b) \(4 + \text{Ni (ClO}_4\text{)}\)\(_2\). (c) \([4 + \text{TBAF}] + \text{Ni (ClO}_4\text{)}\)\(_2\). (d) \([4 + \text{Ni (ClO}_4\text{)}\)\(_2\] + TBAF.

Figure 7. Graphics of the chemical shift observed during the \(^1\)H NMR titration of compound 4 with TBAF in CD\(_3\)CN at 22 °C.
δ 77.0 ppm). The NMR spectra were measured in CD$_3$CN. The UV/vis spectra were measured with a GENESYS 10S spectrophotometer using a quartz cell of 1 cm$. CH$_3$CN employed for UV/vis experiments was of high-performance liquid chromatography-grade. All employed reagents were purchased from commercial sources. Reagents and solvents were of the highest quality available and used as received. Thin layer chromatography was performed on silica gel plates visualized with a UV lamp at 254 nm. Flash chromatography was performed on Aldrich silica gel (70−230 mesh).

**Syntheses.** **Pyrrolyl Perezone Synthesis (2, 3).** To a solution of 1 (0.1 g, 0.3 mmol) dissolved in dichloromethane (DCM, 2.5 mL) was added pyrrole (0.1 mL, 1.45 mmol). The mixture was stirred for 10 min, then SiO$_2$ (1.0 g) was added, and the solvent was removed under vacuum. The reaction was kept at room temperature for 16 h. The residue was purified by flash column chromatography (Hex−EtOAc 4:1).

(R)-2-Hydroxy-6-methyl-3-(6-methyl-5-oxoheptan-2-yl)-5-(1H-pyrrol-2-yl)cyclohexa-2,5-diene-1,4-dione 2. $^1$H NMR (400 MHz, chloroform-$d$): δ 11.01 (s, 1H), 7.37 (s, 1H), 7.09 (s, 1H), 6.79 (s, 1H), 6.39 (s, 1H), 5.08 (m, 1H), 3.17−2.97 (m, 1H), 2.31 (s, 4H), 2.03−1.72 (m, 4H), 1.68−1.39 (m, 6H), 1.32−1.09 (m, 3H). $^{13}$C NMR (100 MHz, chloroform-$d$): δ 190.84, 183.19, 150.99, 133.45, 131.42, 128.97, 126.42, 124.55, 123.89, 123.11, 119.18, 110.51, 34.18, 29.60, 26.74, 25.65, 18.35, 17.61, 14.40. mp 73−75 °C. LRMS (ESI) $m/z$: 314.17 [M + 1]. HRMS: 314.1756 [M + 1] (314.175619 estimated), yield 0.09 g, 68%.

(R)-2-Hydroxy-6-methyl-3-(6-methyl-5-oxoheptan-2-yl)-5-(1H-pyrrol-2-yl)cyclohexa-2,5-diene-1,4-dione 3. $^1$H NMR (400 MHz, chloroform-$d$): δ 11.00 (s, 1H), 7.45 (s, 1H), 7.12 (td, $J = 2.8, 1.2$ Hz, 1H), 6.80 (ddd, $J = 4.0, 2.4, 1.3$ Hz, 1H), 6.39 (ddt, $J = 3.9, 2.6, 0.5$ Hz, 1H), 3.05 (ddt, $J = 13.9, 6.9$ Hz, 1H), 2.44−2.34 (m, 2H), 2.31 (s, 4H), 2.10−1.97 (m, 1H), 1.88 (ddt, $J = 13.6, 9.1, 6.3$ Hz, 1H), 1.25 (dd, $J = 7.1, 0.5$ Hz, 5H), 1.05 (ddd, $J = 6.9, 2.7, 0.5$ Hz, 8H). $^{13}$C NMR (100 MHz, chloroform-$d$): δ 214.61, 190.76, 182.99, 151.22, 133.48, 128.99, 126.35, 124.12, 119.37, 110.62, 40.73, 38.93, 29.42, 28.00, 18.34, 18.31, 18.26, 14.45. LRMS(EI) $m/z$ (rel. int.): 331 ([M + 2], 12), 330 ([M + 1], 35), 329 ([M+], 100), 311 (1S), 244 (58), 230 (47). HRMS (FAB+): 330.1708 (estimated, 330.1705) yield 0.06 g, 44%, corresponding to the literature.

(R)-6,6′-(5,5′-(Propane-2,2-diyl)bis(1H-pyrrole-5,2-diyl))bis(3-hydroxy-5-methyl-2-((R)-6-methyl-5-oxoheptan-2-yl)cyclohexa-2,5-diene-1,4-dione) 4. In a round-bottom flask was added a solution of pyrrolyl perezone 3 (44 mg, 0.14 mmol) and acetone (1 mL). The solution was diluted with water (5 mL) and, while stirring, HCl 35% (10 μL) was added to the formed mixture. The reaction mixture was stirred for 36 h at room temperature. The crude was neutralized with aqueous NaHCO$_3$ and extracted with DCM (3 × 5 mL). The organic layer was dried over anhydrous Na$_2$SO$_4$, filtrated, and concentrated under reduced pressure. The crude was purified via flash column chromatography (Hex−AcOEt 7:3) to give product 4 as a blue-violet solid; yield 25 mg, 53%, mp 150−152 °C. $^1$H NMR (400 MHz, chloroform-$d$): δ 10.94 (s, 2H), 6.78 (s, 2H), 6.26 (s, 2H), 5.60 (s, 2H), 3.02 (m, 2H), 2.55 (m, 2H), 2.45−2.32 (m, 4H), 2.27 (s, 6H), 1.80−1.63 (m, 10H), 1.24 (s, 6H), 1.02 (d, $J = 12.9$ Hz, 12H). $^{13}$C NMR

**Scheme 3. Interaction Proposal between 4, F$^−$, and M$^{2+}$ Species Based on NMR and UV/Vis Spectroscopic Titrations**
NMR Studies on Host and Guest. The NMR experiments were performed in CD$_3$CN. To a 0.01 M solution of TBAF (1×10$^{-2}$ M) until saturation and spectra were recorded.

UV/Vis Studies on Host and Guest. The UV/vis experiments were performed in CH$_3$CN (HPLC-grade). To a solution of 5×10$^{-4}$ M of 4 were added different equivalents of TBAF (1×10$^{-2}$ M) until saturation. To another solution of 4 at the same concentration were added different equivalents of Ni (ClO$_4$)$_2$ (1×10$^{-2}$ M) until saturation. To a solution of 5×10$^{-4}$ M of 4 previously saturated with Ni (ClO$_4$)$_2$ were added different equivalents of TBAF. To a solution of 5×10$^{-4}$ M of 4 previously saturated with TBAF were added different equivalents of Ni (ClO$_4$)$_2$. The same protocol was applied to evaluate compounds 1–3.

Method of Continuous Variations for Job’s Plot. The UV/vis experiments were performed in CH$_3$CN (HPLC-grade). Solutions of compounds 2–4 (hosts) and TBAF (guest) were prepared at the same concentration (5×10$^{-4}$ M). Solutions of host/guest (1 mL) were prepared for measurements as 100–0, 90–10, 80–20, 70–30, 60–40, 50–50, 40–60, 30–70, 20–80, 10–90, and 0–100 proportions.

**ASSOCIATED CONTENT**

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c01420.

NMR spectra, UV/vis spectra, and stoichiometry of complexes between compounds and ionic species (PDF)

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Notes
The authors declare no competing financial interest.

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