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Triazole Linked Picolylimine Conjugate of Calix[6]arene as a Sequential Sensor for La^{3+} Followed by F^-

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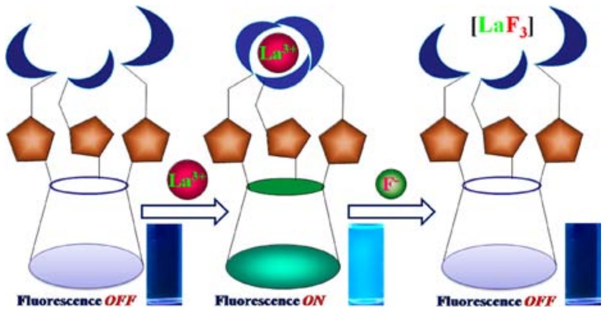
ABSTRACT



A new 1,3,5-tris-triazole linked picolylimine conjugate of calix[6]arene (L) has been shown to be selective toward La^{3+} by *turn on* fluorescence with ~70-fold enhancement and emits blue, with a minimal detection limit of 65 ± 5 ppb (490 nM). The species of recognition has been modeled computationally to have a monocapped twisted square antiprism with a N_6O_3 binding core about La^{3+}. The *in situ* complex of L with La^{3+} recognizes F^- via fluorescence quenching. The reversible response of sensing La^{3+} and F^- sequentially by L has been demonstrated.

Both cations and anions play important roles in biology and the environment, wherein the lanthanides and halides are not exceptions.[1] Lanthanum compounds are involved in lipid peroxidation, ATPase activity,[2] phosphodiester hydrolysis,[3] as antitumor agents,[4] and in the diagnosis of hyperphosphatemia.[3] However, the increased utility of the compounds of lanthanum in the industry, its discharge into the environment, poses a greater threat to life, and hence the development of methods to detect such ions is of importance to chemists.[5] Fluoride is one of the most significant anions in the biological systems due to its role in dental care[6] and in the treatment of osteoporosis.[6b] Excess fluoride exposure may cause collagen breakdown, bone disorders, and immune system disruption.[7] Thus the development of synthetic receptors for the selective recognition of lanthanum and fluoride continues to intrigue researchers. In the literature, calix[6]arene-picolinamide derivatives have been used as extractants in the separation

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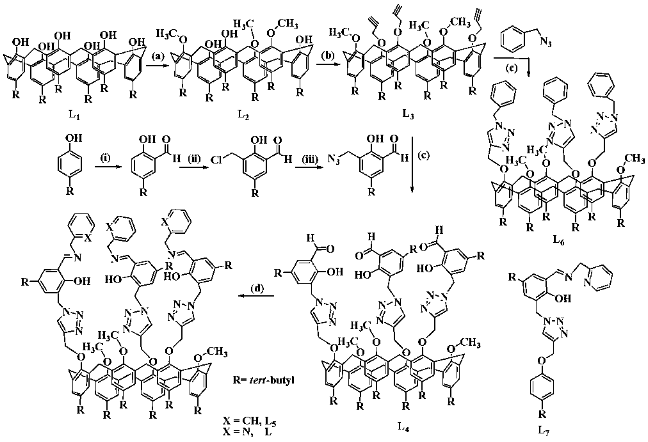
of actinides vs lanthanides; however, no selectivity was shown toward any particular lanthanide.[8a] In contrast, a calix[6]arene–napthoic acid derivative shows fluorescence enhancement toward La^{3+} and Y^{3+} by ~2- and ~3-fold respectively, without much selectivity.[8b] The binding of fluoride is expedited in the presence of Cs^+ due to ion pair formation by a crown-calix-pyrrole conjugate.[9] To our knowledge, we have not found any calix[6]arene conjugate that is suitable for sensing La^{3+} followed by $\bar{F}$. Therefore, the present communication deals with the selective sensing property by a triazole linked picolylimine appended 1,3,5-tris-conjugate of calix[6]arene (**L**) toward La^{3+} and the $\{\mathbf{L}\cdot La^{3+}\}$ complex toward F^-.

The precursors, **L**, and the control ($\mathbf{L_4}$, $\mathbf{L_5}$, $\mathbf{L_6}$, and $\mathbf{L_7}$) molecules were synthesized (Scheme 1) and characterized (S01–S09 in the Supporting Information (SI)).[10,11] The bridged diastereotopic protons were observed as two doublets at 3.23 and 4.23 ppm suggesting that **L** is in a flattened cone conformation.[12a]

Scheme 1. Synthesis of **L**, $\mathbf{L_4}$, $\mathbf{L_5}$, and $\mathbf{L_6}$[a]



[a] (a) CH_3I, K_2CO_3, Dry Acetone, 70 °C, 5.5 bar, 24 h. (b) Propargyl bromide, Cs_2CO_3, dry dimethylformamide, 90 °C, 4 h. (c) 5-*tert*-Butyl-3-(azidomethyl)-2-hydroxybenzaldehyde, $CuSO_4\cdot 5H_2O$, sodium ascorbate, (*tert*-BuOH+dichloromethane (9:1))/Water as 1:1 ratio, rt, 12 h. (d) Picolyl amine (**L**), and benzyl amine ($\mathbf{L_5}$), CH_3OH, rt, 12 h. (i) $SnCl_4$, Bu_3N, $(CH_2O)_n$, toluene, reflux, 8 h, N_2 atm. (ii) HCHO, HCl, rt, 48 h. (iii) NaN_3, dimethylformamide, rt, 12 h.

The ion recognition of **L** has been studied by fluorescence spectroscopy in ethanol by exciting the solutions at 330 nm and by varying the mole ratio of the added metal ion, viz., La^{3+}, Pr^{3+}, Nd^{3+}, Sm^{3+}, Eu^{3+}, Gd^{3+}, Dy^{3+}, and Ho^{3+} (S10–S11 in SI). **L** is a weak emitter, and its fluorescence intensity increases as a function of added La^{3+} concentration until 8 equiv, beyond which it saturates. Thus it exhibits an overall enhancement of ~70 ± 10-fold due to the binding of La^{3+} to **L** yielding a K_a of 36 694 ± 760 M^{-1} based on the Benesi–Hildebrand equation (Figure 1) (S12 in SI). Indeed a value of ~33 800 M^{-1} is obtained based on isothermal titration calorimetry (S13 in SI). The quantum yields of **L** and its La^{3+} complex were 0.001 and 0.075 respectively with reference to anthracene (S14 in SI).

The minimum detectable concentration of La^{3+} by **L** is 65 ± 5 ppb (490 nM) (S15 in SI). Similar titrations were carried out with the control molecules, viz., $\mathbf{L_4}$, $\mathbf{L_5}$, and $\mathbf{L_6}$, and found that these do not exhibit any considerable change in the fluorescence intensity upon addition of La^{3+}. $\mathbf{L_7}$ shows selectivity toward La^{3+} with an ~16-fold increase in fluorescence intensity, but its sensitivity is much less than **L**.

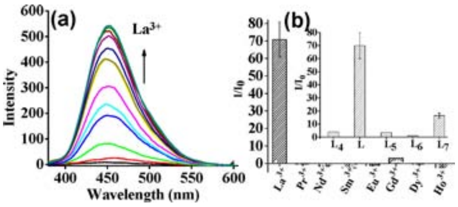


Figure 1. Fluorescence titration of **L** {25 μL of 5 μM solution} with M^{3+} {5 μM, variable volume} ethanol: (a) Fluorescence spectra obtained during the titration of **L** with La^{3+} (λ_{ex} = 330 nm). (b) Histogram showing the number of folds of fluorescence enhancement (I/I_0) in the titration of **L** with M^{3+} (450 nm band) (**Inset:** Histogram of relative intensity plot for control molecules).

This result suggests that the imino-phenolic-binding core is required, while additional binding through a pyridyl moiety results in further enhancement in the emission. Fluorescence titrations carried out with the other seven lanthanides showed no appreciable change in the intensity of **L**, suggesting that **L** is selective toward La^{3+} among these eight ions. When **L** binds to La^{3+}, the C=N bond isomerization and excited-state proton transfer (ESPT) are inhibited, leading to a fluorescence increase.[13]

These results were further supported by spectrophotometric titrations. The absorption spectra exhibited isosbestic points at 270, 290, and 340 nm upon the titration, indicating the transition between the unbound and the La^{3+} bound species. At higher concentrations of La^{3+}, the spectra exhibited an increase in the absorbance at 370 and

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250 nm but a decrease in the 325 nm band (S16 in SI) and the stoichiometry of the complex formed was 1:1 as derived from Job's plot (S17 in SI).

The La^{3+} sensing property of **L** has been further demonstrated by observing the visual fluorescent colors under a 365 nm lamp. A distinct color change was observed only in the case of La^{3+}, while no other lanthanide ion exhibits such a change (Figure 2a). Even the ESI-MS confirms the 1:1 complex formation, where the spectrum shows a molecular ion peak at m/z = 2238.1 and the observed isotopic peak pattern supports the presence of the La^{3+} and agrees well with the calculated one (Figure 2b).

Since the *in situ* generated $\{\mathbf{L}\cdot La^{3+}\}$ complex exhibits fluorescence enhancement, this is further subjected to the interaction by halides. The titration of $\{\mathbf{L}\cdot La^{3+}\}$ with halides results in fluorescence quenching in the order $F^- \gg Cl^- > Br^-, I^-$, suggesting a major change in the fluorescence intensity only in the case of F^- and not in the presence of Cl^-, Br^-, and I^- (Figure 3a). A similar trend was observed in the case of 2-aminopyridyl-bridged calix[6]arene.[14a]

During the titration, the initial fluorescence intensity of $\{\mathbf{L}\cdot La^{3+}\}$ decreases gradually with the increase in the concentration of the added F^- (Figure 3b) (S18 in SI).

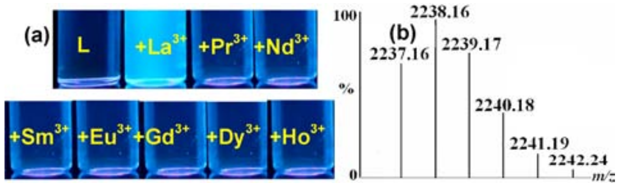

Figure 2. (a) Colorimetric titration of **L** (5 μM) with different lanthanide ions (20 μM) in ethanol. (b) ESI mass spectrum showing the isotopic peak pattern of the molecular ion peak for the 1:1 complex formed between **L** and La^{3+}.

Similar studies carried out with other fluoride salts, viz., NaF and KF, also exhibited quenching of fluorescence. In the literature, tetraamide derivatives of calix[6]arene were shown to sense both F^- and $CH_3CO_2^-$ but without much selectivity, though the sensitivity is better than that observed for the other anions.[14b] In the titration with F^-, the absorbance of the band at ~370 nm decreases and that at ~325 nm increases (Figure 3c).

Titration of $\{\mathbf{L}\cdot La^{3+}\}$ with F^- shows a decrease in the intensity of m/z = 2237.09 with a concomitant increase of m/z = 2100 in ESI-MS spectra (S19 in SI).

The F^- sensing property of $\{\mathbf{L}\cdot La^{3+}\}$ has been further supported by observing the fluorescent color change visually and found that the color is bleached only in the presence of F^- and no other halide, indicating the selective sensing of F^- ion by the complex $\{\mathbf{L}\cdot La^{3+}\}$ (Figure 4).

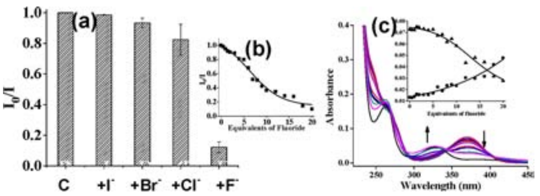

Figure 3. (a) Histogram showing the fluorescence quenching of {**L** + 6 equiv of La^{3+}} when titrated with different halides, where [C = $\{\mathbf{L}\cdot La^{3+}\}$]. (b) Plot of fluorescence quenching of {**L** + 6 equiv of La^{3+}} as a function of the addition of different equivalents of fluoride. (c) Absorption spectra of {**L** + 6 equiv of La^{3+}} with F^- (**Inset**: Plots of absorbance vs mole ratio of $[F^-]$/{**L** + 6 equiv of La^{3+}} for different bands).

The reusability and reversible response of the fluorescent chemosensing ensemble, viz., $\{\mathbf{L}\cdot La^{3+}\}$, has been demonstrated by four alternate cycles carried out by titrating **L** with La^{3+}, followed by F^-, and repeating this in a cyclic fashion.

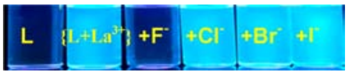

Figure 4. Visual colors observed when $\{\mathbf{L}\cdot La^{3+}\}$ is titrated against different halides under UV light (365 nm).

La^{3+} shows a remarkable change by showing fluorescence *ON* behavior through forming the $\{\mathbf{L}\cdot La^{3+}\}$ complex. Further titration of this with F^- results in quenching of fluorescence and hence acts as an *OFF* switch. The repeated demonstration of the *ON*/*OFF* behavior of fluorescence as well as visual color changes clearly suggest that **L** is a reversible and reusable sensor for La^{3+} followed by F^- in a sequential manner (Figure 5a).

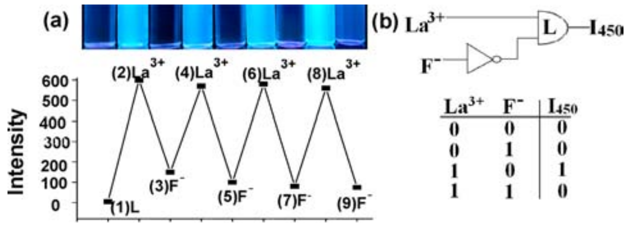

Figure 5. (a) Fluorescence experiment showing the reversibility of the receptor for sensing La^{3+} and F^- sequentially. Fluorescence intensity obtained during the titration of **L** with La^{3+} and F^- in ethanol. Above are the vials showing visual fluorescent color change at every cycle, where (1) = **L**; (2) = **L** + La^{3+}; (3) = (2) + F^-; (4) = (3) + La^{3+}; (5) = (4) + F^-; (6) = (5) + La^{3+}; (7) = (6) + F^-; (8) = 7 + La^{3+}; (9) = (8) + F^- (La^{3+} = 10 equiv, F^- = 20 equiv). (b) INHIBIT (INH) logic gate.

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In considering the INHIBIT logic gate properties of **L**, La^{3+} and F^- act as inputs while the emission intensity at 450 nm (I_{450}) acts as output (Figure 5b). The output is *zero* when (a) both the La^{3+} and F^- are absent; (b) F^- alone is present; or (c) both La^{3+} and F^- are present, and the gate is *OFF*. The output is *one* when La^{3+} alone is present and the gate is *ON*. Thus **L** can act as an INHIBIT logic gate.[15a,b]

In order to understand the binding behavior of **L** with La^{3+}, the complex $\{\mathbf{L}\cdot La^{3+}\}$ has been optimized by using the Gaussian G03 package.[16] In the optimized structure of $\{\mathbf{L}\cdot La^{3+}\}$, the La^{3+} is bonded to three salicylaldimine oxygens, three imine nitrogens, and three pyridyl nitrogens (Figure 6a) resulting in a nine-coordinated La^{3+} with a monocapped twisted square antiprismatic geometry[12b,17] (Figure 6b) (S23−S25 in SI).

Molecular Orbitals (MOs) were calculated using the HF/LANL2DZ level. Some of the MOs are shown in Figure 6. The percentages of the orbitals present on different fragments were calculated (S26 in SI). The HOMOs were majorly localized on Schiff's base, a phenolic residue, though these were extended with the imino-, phenolic-O orbitals. The LUMOs are present on pyridyl residues. Therefore, the computational studies further support the involvement of the pyridyl-imino-phenolic core in La^{3+} binding.

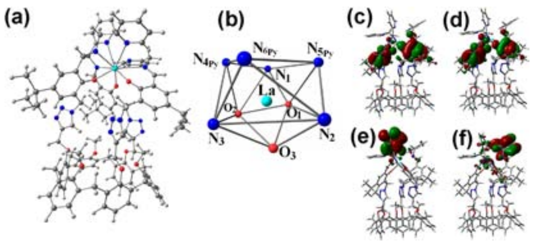

Figure 6. HF/LANL2DZ optimized structure of (a) $\{\mathbf{L}\cdot La^{3+}\}$. (b) Coordination sphere about the lanthanum ion. Bond lengths (Å) in the coordination sphere are $La-O_1 = 2.394$, $La-O_2 = 2.369$, $La-O_3 = 2.369$, $La-N_1 = 2.979$, $La-N_2 = 2.954$, $La-N_3 = 2.811$, $La-N_4py = 3.144$, $La-N_5py = 3.105$, $La-N_6py = 2.935$. (c) HOMO − 1, (d) HOMO, (e) LUMO, (f) LUMO + 1.

A new triazole linked picolylimine conjugate of calix[6]arene (**L**) has been synthesized and characterized. The receptor **L** exists in a flattened cone conformation in the solution state as evident from ^1H NMR. **L** showed selectivity toward La^{3+} among the eight lanthanide ions studied by *switch on* fluorescence. Binding of La^{3+} to **L** has been further supported by absorption titration. While the Job's plot suggests the formation of a 1:1 complex, the ESI-MS confirms the same by yielding an $m/z = 2238.1$ peak with the expected isotope peak pattern for the presence of La^{3+}. **L** exhibits a colorimetric response for La^{3+} under 365 nm. Therefore, **L** can detect La^{3+} up to (65 ± 5) ppb (490 nM) by *switch on* fluorescence. The *in situ* generated $\{\mathbf{L}\cdot La^{3+}\}$ complex showed selectivity toward F^- among all the halides as studied by fluorescence and absorption spectroscopy. Among the transition metal ions, *viz*., Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+}, only Zn^{2+} shows fluorescence enhancement. But in the titration of F^-, the fluorescence is quenched only in the case of $\{\mathbf{L}\cdot La^{3+}\}$ but not $\{\mathbf{L}\cdot Zn^{2+}\}$, suggesting that both **L** and La^{3+} are required for fluoride sensing and the sensing is not possible with **L** and Zn^{2+} (S20−22 in SI). The reversibility of **L** to sense La^{3+} and F^- has been demonstrated by repeatedly adding these ions one after the other to complete four cycles. Thus **L** is a potential sensor for La^{3+} followed by F^- in a sequential manner and perhaps finds application in biological and ecological systems.

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Supporting Information Available. Experimental methods and spectral data. Fluorescence and absorption spectral traces, ITC data, and molecular modeling. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.