Tetrahedron Letters 49 (2008) 6257–6261

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Lower rim 1,3-di-amide-derivative of calix[4]arene possessing bis-{*N*-(2,2′-dipyridylamide)} pendants: a dual fluorescence sensor for Zn^{2+} and Ni^{2+}

Roymon Joseph[a], Balaji Ramanujam[a], Haridas Pal[b], Chebrolu P. Rao[a,*]

[a] *Bioinorganic Laboratory, Department of Chemistry, Indian Institute of Technology Bombay, Mumbai 400 076, India*
[b] *Radiation and Photochemistry Division, Bhabha Atomic Research Centre, Trombay, Mumbai 400 085, India*

ARTICLE INFO

Article history:
Received 23 June 2008
Revised 8 August 2008
Accepted 13 August 2008
Available online 19 August 2008

Keywords:
Dual fluorescence sensor
Ab initio calculations
N_4-coordination core
Fluorescence switch-on by Zn^{2+}
Fluorescence switch-off by Ni^{2+}
Lower rim 1,3-di-amide-derivative of calix[4]arene

ABSTRACT

Single crystal XRD structure of the lower rim 1,3-di-amide-derivative of calix[4]arene possessing bis-{*N*-(2,2′-dipyridylamide)} pendants (L) exhibit two distinct binding cores, viz., N_4 and O_6. L was found to be selective for Zn^{2+} by *switch-on* and for Ni^{2+} by *switch-off* fluorescence by forming 1:1 complexes. The binding and the composition of the complex formed have been addressed based on steady state and time-resolved fluorescence spectroscopy in addition to the absorption and ESI MS. As L can detect Zn^{2+} and Ni^{2+} to a concentration as low as 142 and 203 ppb, respectively, L can be a very sensitive molecular probe for these ions. The coordination details of the metal ion-bound complexes have been addressed based on ab initio calculations showing that the stabilization energies are commensurate with the coordination formed.

Design and synthesis of receptors for selective detection of ions is a challenging area of current research. Supramolecular systems like calix[4]arenes possess a framework which allows introduction of appropriate binding cores suitable for metal ion recognition. This can be done either at the lower rim or at the upper rim, especially by introducing organic moieties containing nitrogen, oxygen or sulfur or a combination of these as donor centres. Several calixarene-based systems have been shown to be receptors for cations,[1] anions[2] and neutral species[3] depending upon the coordination units present on the calixarene. There are a number of reports of selective binding of Zn^{2+} and Ni^{2+} by other synthetic systems, but calixarene-based examples are rather limited.[4] Moreover, receptors that can detect two different metal ions are much more rarer.[4,5] Recently, we reported[6] calix[4]arene derivatives which are selective for Zn^{2+} and I^-, and also one that can differentiate the binding of Pb^{2+}, Cd^{2+} or Hg^{2+}. Herein, we report the results of the experimental and computational studies of a lower rim 1,3-di-derivative of calix[4]arene possessing bis-{*N*-(2,2′-dipyridylamide)} moiety, as a dual sensor for Zn^{2+} in a *switch-on* and for Ni^{2+} in a *switch-off* mode of fluorescence.

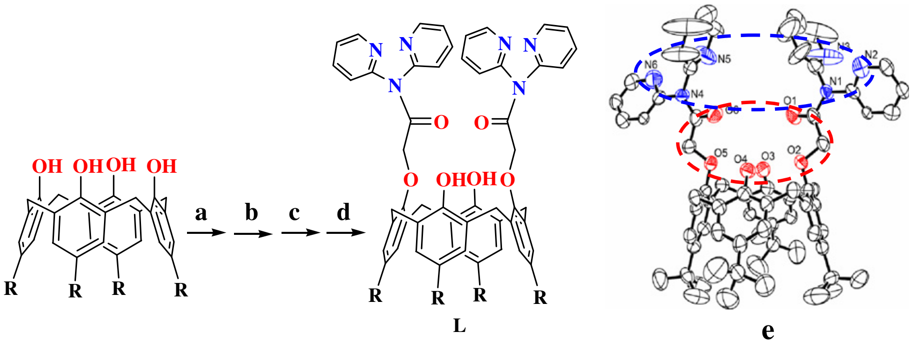
The dual fluorescence receptor molecule, L, was synthesized in four consecutive steps starting from *p*-*tert*-butyl calix[4]arene via the known intermediates[7] as given in Scheme 1. The products yielded satisfactory analytical and spectral results (SI 01).[8] Single crystals of L obtained from slow evaporation of an acetonitrile solution yielded only low resolution diffraction data owing to the decay of the crystal during the data collection, and hence the structure obtained was only sufficient to exhibit some structural features (SI 02, Scheme 1e). The crystal structure thus obtained clearly shows the presence of a cone conformation of L and is in conformity with the result obtained based on NMR analysis. Based on the crystal structure, L, can be visualized as having at least two binding cores: one with the pyridyl environment having four nitrogens (N_4) and the other with the lower rim plus amide oxygens (O_4 or O_6) (Scheme 1). Such binding cores were formed owing to the extended conformation exhibited by both the arms. Bent arms were generally found for pendants possessing CO–NH groups by forming a hydrogen bond between NH and the phenolic OH.[7a]

The metal ion binding properties of L were studied in methanol by fluorescence, absorption[9] and ESI MS. During the titration of L by M^{2+} using fluorescence spectroscopy (SI 03), L showed progressive enhancement in the intensity upon addition of Zn^{2+} (Fig. 1a) that saturates at ~10–20 equiv. This indicates an equilibrium-driven reaction wherein the overall enhancement was found to be 16–18-fold at saturation (Fig. 1b) though it is at least eightfold at 2 mol equiv of Zn^{2+}. This is attributable to the reversal of the photoelectron transfer of the pyridyl-N lone pair upon Zn^{2+}

---

* Corresponding author. Tel.: +91 22 2576 7162; fax: +91 22 2572 3480.
E-mail addresses: cprao@iitb.ac.in, cprao@chem.iitb.ac.in (C. P. Rao).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.08.049



Scheme 1. Schematic representation of the synthesis of the dual receptor molecule, L starting from *p-tert*-butylcalix[4]arene (R = *t*-butyl) and its structure from single crystal XRD, where (a) bromoethylacetate/K_2CO_3/acetone; (b) NaOH/C_2H_5OH, reflux; (c) $SOCl_2$/benzene, reflux; (d) 2,2′-dipyridyl amine/Et_3N/THF and (e) ORTEP diagram of L. (Hydrogens and solvent molecule are not shown for clarity.) Enclosures in blue and red indicate N_4- and O_6-binding cores, respectively.

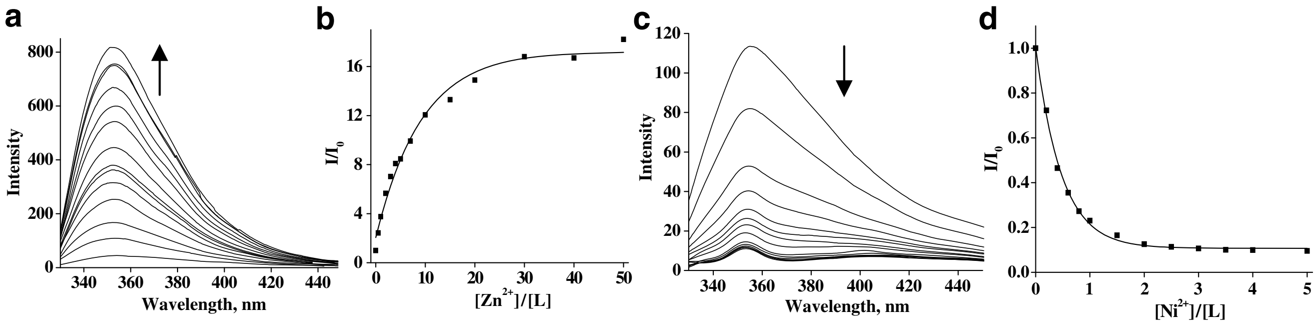


Figure 1. Fluorescence titration of L by Zn^{2+} or Ni^{2+}: (a) spectral traces during the titration by Zn^{2+}; (b) plot of relative intensity (I/I_0) versus $[Zn^{2+}]/[L]$ mol ratio; (c) spectral traces during the titration by Ni^{2+} and (d) plot of relative intensity (I/I_0) versus $[Ni^{2+}]/[L]$ mol ratio.

binding. Similar titrations carried out with Ni^{2+} exhibited fluorescence quenching (Fig. 1c and d) owing to the paramagnetic nature of this ion.

The complexed species formed were found to be 1:1 in both the cases. Based on the Benesi–Hildebrand equation, the association constants (K_{ass}) were found to be 18,173 ± 1726 and 238,930 ± 13,060 M^{-1}, respectively, for Zn^{2+} and Ni^{2+} complexes. With respect to naphthalene, L was found to have a quantum yield of 0.0356. While this is increased by about three times in the presence of Zn^{2+}, it is decreased by three times in the presence of Ni^{2+}.

Similar titrations carried out with other divalent ions, viz., Mn^{2+}, Fe^{2+}, Co^{2+}, Cu^{2+} and Hg^{2+}, exhibited almost no fluorescence quenching, while those carried out with Cd^{2+} exhibited marginal enhancement (Fig. 2a). Thus, the steady-state fluorescence data obtained from the titration of L with M^{2+} clearly suggests that L can detect Zn^{2+} by *switch-on* and Ni^{2+} by *switch-off* modes wherein the bipyridyl arms undergo appropriate conformational changes to accommodate either the Zn^{2+} or the Ni^{2+}. The minimum concentrations at which L can detect Zn^{2+} and Ni^{2+} are 142 and 203 ppb, respectively (Fig. 2b, SI 03).

In order to confirm the binding and stoichiometry of Zn^{2+} or Ni^{2+} with L, ESI MS spectra were measured in both the cases and the formation of 1:1 species was found at *m/z* 1160.8 and 1130 for Zn^{2+} and Ni^{2+} (SI 04), respectively. The isotopic peak pattern confirmed the presence of these metal ions. The results were further supported by measuring the absorption spectra wherein

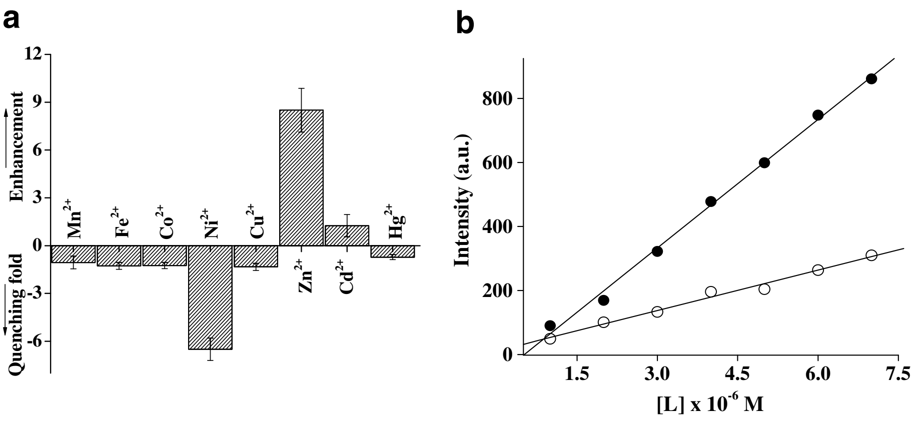


Figure 2. (a) Histogram showing the number of times of quenching or enhancement in the relative fluorescence intensity (I/I_0) in case of titration of L with M^{2+} at 2 mol equiv of M^{2+}. The error bars were placed based on four different measurements. (b) Titration of L with Zn^{2+} (●) along with the L (○) by keeping $[Zn^{2+}]/[L]$ ratio as 1:1.

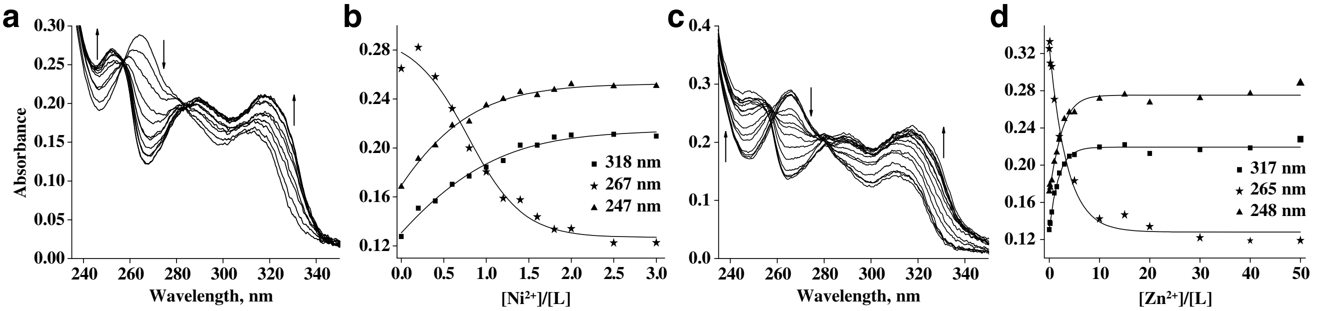


Figure 3. Absorption spectral data during the titration of L with Ni^{2+} or Zn^{2+}: (a) Spectral traces in case of Ni^{2+}; (b) absorbance versus $[Ni^{2+}]/[L]$ mol ratio; (c) spectral traces in case of Zn^{2+} and (d) absorbance versus $[Zn^{2+}]/[L]$ mol ratio.

isosbestic points were observed at 257 and 283 nm in case of Ni^{2+}, and 257 nm in the case of Zn^{2+}, indicating a transition between the complexed species and the free species (Fig. 3). Increase in the absorbance of 317–318 nm band is indicative of the interaction of Ni^{2+} or Zn^{2+} with nitrogens of pyridyl moieties present on both the arms. Binding of Ni^{2+} or Zn^{2+} with pyridyl nitrogens has also been shown based on computational calculations as given in this Letter. While the titration of Zn^{2+} is equilibrium driven, that of the Ni^{2+} is stoichiometric as already observed based on fluorescence studies, and the complexes formed were found to be 1:1 based on Job plots made using the absorption data (Fig. 4).

In order to establish the formation of the complex, reaction mixtures were titrated with perchloric acid followed by re-titration with $(n\text{-}C_4H_9)_4NOH$. These studies revealed switch *on–off–on* fluorescence behaviour in the case of Zn^{2+}. The behaviour was exactly the reverse in the case of the titration of L with Ni^{2+}(SI 05).

The formation of the complexed species by L has been further addressed by measuring the fluorescence life times of the species during the titration (Fig. 5, SI 06). The data of L alone fit with bi-exponential decay that is associated with two species having 0.33 ns (42%) and 2.12 ns (58%). When L is titrated against Zn^{2+}, the decay curve fits with a single species exclusively having 0.8 ns (100%), and when titrated with Ni^{2+} it fits well with one major, viz., 1.76 ns (85%) and one minor, viz., 7.85 ns (15%) species. Thus the results of the life time measurements are in accordance with those of the steady state. The fluorescence behaviour of L in the presence of Zn^{2+} or Ni^{2+} is shown in Scheme 2.

Though the composition of these complexes has been established to be 1:1 based on fluorescence, absorption and ESI MS, no structural features could be deduced in the absence of the single crystals of these complexes. Hence, the metal ion binding has been addressed through computational calculations. The starting point

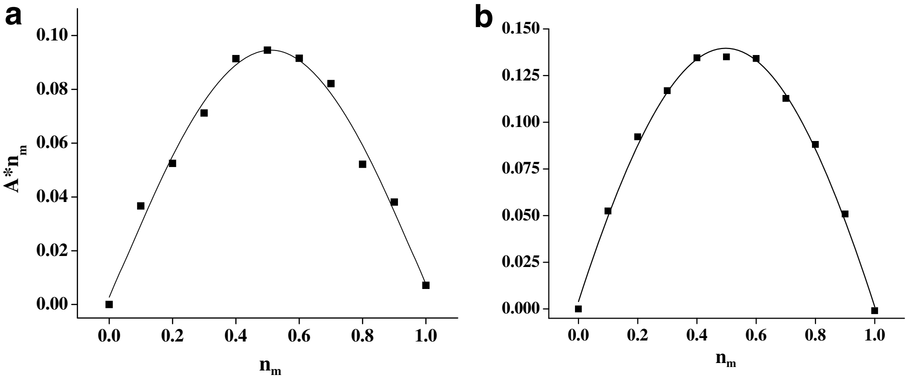


Figure 4. Job plot of n_m versus $A * n_m$, where n_m is mol fraction of the metal ion added and A is absorbance: (a) Ni^{2+} and (b) Zn^{2+}.

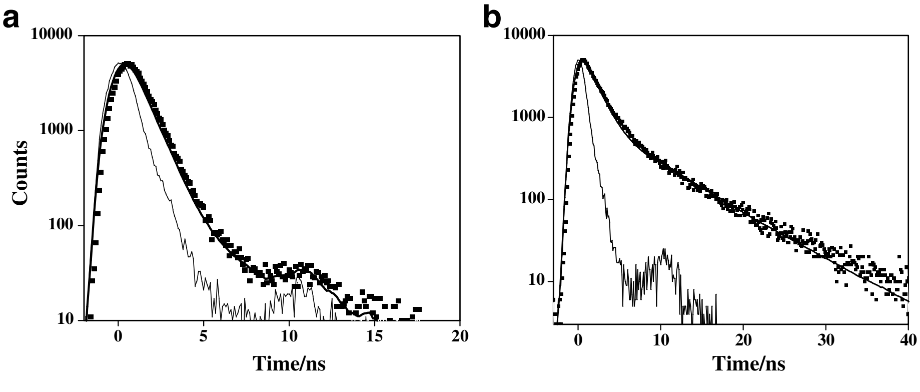
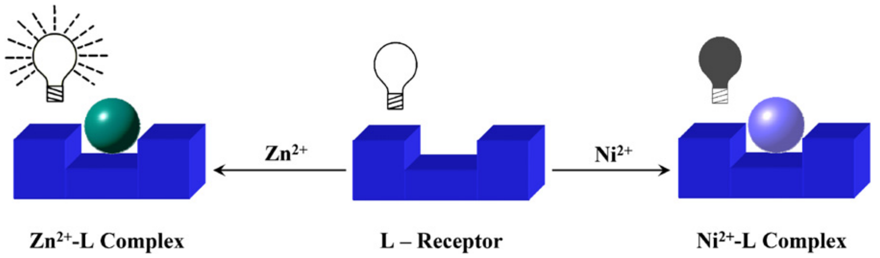


Figure 5. Fluorescence decay plots as a function of time during the titration of L: (a) with Zn^{2+} and (b) with Ni^{2+}. The trace with '-.-.-.' represent prompt for the lamp. The filled points represent the data. The line that passes through the points is the fit.



Scheme 2. *Switch-on* and *switch-off* fluorescence behaviour of L upon complexation with Zn^{2+} and Ni^{2+}, respectively.

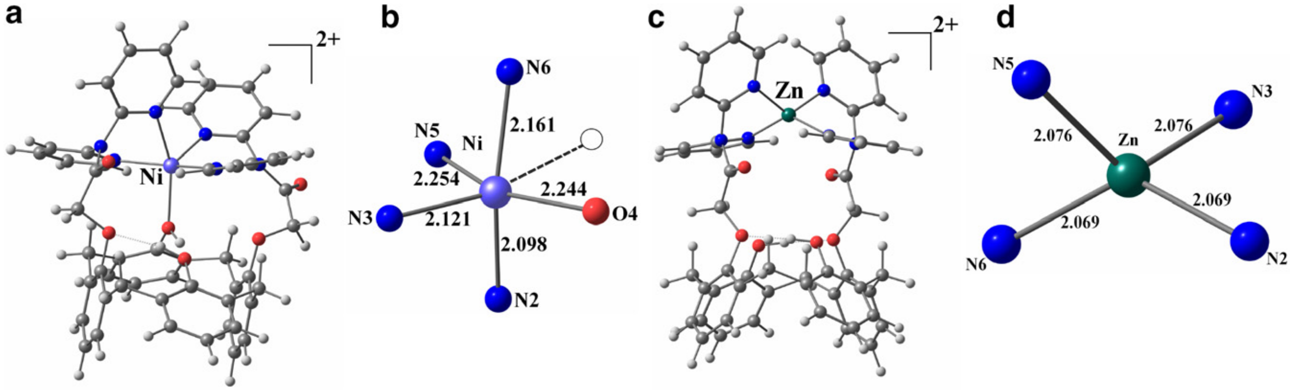


Figure 6. UHF/6-31G optimized structures of (a) Ni^{2+}–L′ complex; (b) coordination sphere of Ni^{2+} in (a), the open circle shown in the coordination sphere refers to the vacant site; (c) Zn^{2+}–L′ complex and (d) coordination sphere of Zn^{2+} in (c). Metal to ligand distances in Å are shown on the bonds. The bond angles at the Ni^{2+} coordination site were found to be: N2···Ni···N3 = 82.7; N2···Ni···N5 = 105.1; N2···Ni···N6 = 160.2; N2···Ni···O4 = 88.6; N3···Ni···N5 = 90.9; N3···Ni···N6 = 85.0; N3···Ni···O4 = 114.5; N5···Ni···N6 = 90.4; N5···Ni···O4 = 154.6 and N6···Ni···O4 = 96.1 Å. The bond angles at the Zn^{2+} coordination site were found to be: N2···Zn···N3 = 95.3; N2···Zn···N5 = 106.3; N2···Zn···N6 = 133.7; N3···Zn···N5 = 123.3; N3···Zn···N6 = 106.3 and N5···Zn···N6 = 95.3 Å.

for the calculations of L was its crystal structure. Since the number of atoms involved in the computations was too large, a model (L′) was built by replacing the upper rim *t*-butyl groups with hydrogens. Thus, the L′ has the same binding features as those of L. The L′ was optimized in HF/3-21G followed by HF/6-31G before using for metal ion binding (SI 07, GAUSSIAN 03).[10] The initial geometry for the computations of the metal-bound species was obtained by placing Ni^{2+} or Zn^{2+} at a non-interacting position well above the pyridyl core of the optimized L′. The computational calculations carried out in the case of the [Ni–L′]$^{2+}$ complex exhibited Ni^{2+} a distorted octahedral geometry (Fig. 6a) with one of the ligating sites being vacant and bound through all four pyridyl nitrogens plus one lower rim phenolic-OH (Fig. 6b). Similar optimization yielded Zn^{2+} in a distorted tetrahedral geometry (Fig. 6c) wherein the metal ion is bound through all four pyridyl nitrogens in the [Zn–L′]$^{2+}$ complex (Fig. 6d) (SI 08). The complexation is a result of metal ion-induced conformational changes brought in the pendant arms of L so that the core possessing the ligating atoms is well poised for binding. The single point energy analysis of the optimized complexes yielded stabilization energies (ΔE) of -453.0 and -408.4 kcal/mol for Ni^{2+} and Zn^{2+} complexes, respectively, with the calculations performed at HF/3-21G. These were found to be -450.1 and -408.4 kcal/mol, respectively, at HF/6-31G level (SI 09). The stabilization energies were found to be well within the formation of 5- or 4-coordination bonds with Ni^{2+} or Zn^{2+}.

Though some calix[4]arene-based derivatives for sensing different metal ions have been described, the receptor, L, reported in this Letter is unique by providing a dual response to sense Zn^{2+} as *switch-on* and Ni^{2+} as *switch-off* based on fluorescence. All the studies reported in this Letter conclusively demonstrated complex formation between L and Zn^{2+} or Ni^{2+} with compositions of 1:1. Using L, the Zn^{2+} concentration can be detected to be as low as 142 ppb and the Ni^{2+} to be 203 ppb and hence L is a very sensitive molecular probe for these ions. The coordination details of binding were deduced from computational calculations. Thus the present study not only provides impetus for designing receptors suitable for multi metal ion recognition, but also provides clues in rationalizing the metal ion placements in metalloproteins.

Acknowledgements

C.P.R. acknowledges the financial support from DST, CSIR and DAE-BRNS. R.J. gratefully acknowledges UGC for SRF. We thank Dr. Amjad Ali for an initial sample of L. We also thank SAIF, IIT Bombay, for ESI MS data.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.08.049.

References and notes

1. (a) Quang, D. T.; Jung, H. S.; Yoon, J. H.; Lee, S. Y.; Kim, J. S. *Bull. Korean Chem. Soc.* **2007**, *28*, 682; (b) Bodenant, B.; Weil, T.; Businelli-Pourcel, M.; Fages, F.; Barbe, B.; Pianet, I.; Laguerre, M. *J. Org. Chem.* **1999**, *64*, 7034; (c) Chang, K.-C.; Su, I.-H.; Senthilvelan, A.; Chung, W.-S. *Org. Lett.* **2007**, *9*, 3363; (d) Ho, I.-T.; Lee, G.-H.; Chung, W.-S. *J. Org. Chem.* **2007**, *72*, 2434; (e) Kim, J. S.; Kim, H. J.; Kim, H. M.; Kim, S. H.; Lee, J. W.; Kim, S. K.; Cho, B. R. *J. Org. Chem.* **2006**, *71*, 8016; (f) Talanov, V. S.; Roper, E. D.; Buie, N. M.; Talanova, G. G. *Tetrahedron Lett.* **2007**, *48*, 8022; (g) Lee, J. Y.; Kim, S. K.; Jung, J. H.; Kim, J. S. *J. Org. Chem.* **2005**, *70*, 1463; (h) Kim, J. S.; Quang, D. T. *Chem. Rev.* **2007**, *107*, 3780; (i) Valeur, B.; Leray, I. *Coord. Chem. Rev.* **2000**, *205*, 3; (j) Yam, V. W.-W.; Lo, K. K.-W. *Coord. Chem. Rev* **1998**, *184*, 157.

2. (a) Evans, A. J.; Matthews, S. E.; Cowley, A. R.; Beer, P. D. *Dalton Trans.* **2003**, 4644; (b) Schazmann, B.; Alhashimy, N.; Diamond, D. *J. Am. Chem. Soc.* **2006**, *128*, 8607; (c) Kim, H. J.; Kim, S. K.; Lee, J. Y.; Kim, J. S. *J. Org. Chem.* **2006**, *71*, 6611.
3. *Calixarenes in Action*; Mandolini, L., Ungaro, R., Eds.; Imperial College Press: London, 2000.
4. (a) Bodenant, B.; Weil, T.; Businelli-Pourcel, M.; Fages, F.; Barbe, B.; Pianet, I.; Laguerre, M. *J. Org. Chem.* **1999**, *64*, 7034; (b) Unob, F.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* **1998**, *39*, 2951; (c) Cao, Y.-D.; Zheng, Q.-Yu.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron Lett.* **2003**, *44*, 4751; (d) Bagatin, I. A.; de Souza, E. S.; Ito, A. S.; Toma, H. E. *Inorg. Chem. Commun.* **2003**, *6*, 288.
5. (a) Kim, S. K.; Lee, S. H.; Lee, J. Y.; Lee, J. Y.; Bartsch, R. A.; Kim, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 16499; (b) Kim, J. S.; Kim, H. J.; Kim, H. M.; Kim, S. H.; Lee, J. W.; Kim, S. K.; Cho, B. R. *J. Org. Chem.* **2006**, *71*, 8016.
6. (a) Dessingou, J.; Joseph, R.; Rao, C. P. *Tetrahedron Lett.* **2005**, *46*, 7967; (b) Kumar, A.; Ali, A.; Rao, C. P. *J. Photochem. Photobiol. A* **2006**, *177*, 164; (c) Joseph, R.; Gupta, A.; Rao, C. P. *J. Photochem. Photobiol. A* **2007**, *188*, 325; (d) Joseph, R.; Gupta, A.; Rao, C. P. *Indian J. Chem. A* **2007**, *46*, 1095.
7. (a) Rao, P. V.; Rao, C. P.; Kolehmainen, E.; Wegelius, E. K.; Rissanen, K. *Chem. Lett.* **2001**, 1176; (b) Ali, A.; Salunke-Gawali, S.; Rao, C. P.; Linares, J. *Inorg. Chem. Commun.* **2004**, *7*, 1298; (c) Kraf, D.; Loon, J.-D.; Owens, M.; Verboom, W.; Vogt, W.; McKervey, M. A.; Boihmer, V.; Reinhoudt, D. N. *Tetrahedron Lett.* **1990**, *31*, 4941; (d) Collins, E. M.; McKervey, M. A.; Madigan, E.; Moran, M. B.; Owens, M.; Ferguson, G.; Harris, S. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3137; (e) Bohmer, V.; Ferguson, G.; Gallagher, J. F.; Lough, A. J.; McKervey, M. A.; Madigan, E.; Moran, M. B.; Phillips, J.; Williams, G. *J. Chem. Soc., Perkin Trans. 1.* **1993**, 1521.
8. The purity of L was checked by TLC using $CHCl_3/CH_3OH$ in 9.3:0.7 v/v ratio to result in one single spot with $R_f = 0.37$. Mp 165–170 °C (decomposes). Yield (40%, 0.58 g). Anal. Calcd for $C_{68}H_{74}N_6O_6$ (1071.63): C, 76.22; H, 6.96; N, 7.84. Found: C, 76.32; H, 7.43; N, 7.57. FTIR: (KBr, cm^{-1}): 1653 ($\nu_{C=O}$), 3343 (ν_{OH}). ^1H NMR: ($CDCl_3$, 400 MHz δ ppm): 0.95 (s, 18H, ($C(CH_3)_3$), 1.23 (s, 18H, ($C(CH_3)_3$), 3.21 (d, 4H, Ar-CH_2-Ar, J = 13.14 Hz), 4.37 (d, 4H, Ar-CH_2-Ar, J = 13.14 Hz), 4.79 (s, 4H, –OCH_2CO–), 6.76 (s, 4H, Ar-*H*), 6.96 (s, 4H, Ar-*H*), 7.13 (t, 4*H*, Py-H, J = 4.88 Hz), 7.33 (s, 2*H*, –OH), 7.61 (d, 4H, Py-*H*, J = 7.94 Hz), 7.74 (t, 4H, Py-*H*, J = 6.10 Hz), 8.42 (d, 4H, Py-*H*, J = 5.81 Hz). ^{13}C NMR: ($CDCl_3$, ~100 MHz δ ppm): 31.16, 31.79 ($C(CH_3)_3$), 31.88 (Ar-CH_2-Ar), 33.88, 34.98 ($C(CH_3)_3$), 74.81 (OCH_2CO), 122.29, 125.05, 125.66, 128.07, 132.87, 138.52, 141.24, 146.93, 148.95, 150.54, 151.17, 153.77 (py and calix-Ar-*C*), 169.23 (*C*=O). *m/z* (ES-MS) 1071.72 ($[M]^+$ 100%), 1072.72 ($[M+H]^+$ 45%).
9. All the metal salts used for the titrations were perchlorates (caution: since perchlorates are known explode under certain conditions, these are to be handled carefully!) with formula, $M(ClO_4)_2 \cdot xH_2O$. All the solvents used were of analytical grade and were purified and dried by routine procedures immediately before use. Steady state fluorescence emission spectra were measured on Perkin–Elmer LS55 by exciting the solutions at 320 nm and measuring the emission spectra in 330–480 nm range. In the fluorescence studies performed in CH_3OH solution, a 50 µl of $CHCl_3$ solution of L (i.e., the 3 ml solution contains 2.950 ml of CH_3OH and 0.050 ml of $CHCl_3$) was always used. All the measurements were made using 1 cm quartz cell and a final L concentration of 10 µM was maintained. During the titration, the concentration of metal perchlorate was varied accordingly in order to result in the requisite mol ratios of metal ion to L, and the total volume of the solution was maintained constant at 3 ml in each case by adding appropriate solvent or solvent mixtures. The same solutions were used for absorption studies.
10. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S. Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B. W.; Wong, W.; Gonzalez, C.; Pople, J.A. GAUSSIAN 03, Revision B.05. Gaussian: Pittsburgh, PA, 2003.