Tetrahedron Letters 53 (2012) 2996–2999

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Preferential recognition of zinc ions through a new anthraquinonoidal calix[4]arene

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ARTICLE INFO

Article history:
Received 2 January 2012
Revised 22 March 2012
Accepted 23 March 2012
Available online 30 March 2012

Keywords:
Calix[4]arene
Anthraquinonoidal
Preferential recognition
Zinc ions

ABSTRACT

A novel anthraquinonoidal calix[4]arene derivative was designed and synthesized for the preferential recognition of biologically important zinc in preference to prominently similar cadmium ions and other metal ions via quenching of fluorescence intensity. The stoichiometry of host guest complexation has been determined to be 1:1. The fluorescence changes associated with the recognition event may be attributed to the interaction of zinc ions with the nitrogenous functionality attached at the lower rim of calix[4]arene cavity which allows spatial disposition of the anthraquinonoid segments.

Calix[*n*]arenes are known to provide useful sigma framework for the design of molecular receptors for recognition of ionic and molecular species.[1] Their versatility is usually attributed to the presence of a preorganized cavity and many potentially useful functionalization sites.[2] Macromolecules appended with fluorescent probes have also received considerable attention due to sensitivity and high specificity associated with the fluorescence based technique.[3,4] The selection of a suitable fluorophore appended calixarenes is thus extremely important to translate the recognition event into a measurable optical signal.[5,6]

Our interest in the development of suitable receptors for recognition of zinc ions through non covalent interactions originates both from academic and application challenges involved in such a design. Zinc is the second most abundant transition metal ion in the living organisms located mainly in brain, muscle, prostate, bone, liver, and parts of the eye. It is believed to play a significant role in the regulation of many cellular and enzymatic processes as well. To expatiate the biological role of Zn^{2+}, there is an urgent need to develop a direct recognition method which could efficiently differentiate it from closely resembling but toxic cadmium ions.[7,8] It has been observed that though several fluorescent chemosensors for Zn^{2+} have been reported in the literature, examples of preferential recognition of Zn^{2+} over Cd^{2+} are rare.[9] Amongst known zinc probes are included zinc chelators like picolyamine, iminodiacid, or cyclin based molecular probes which not only usher covalent bonds and strict analytical protocols but unfortunately also interact with other biologically significant ions such as calcium, magnesium, copper, nickel lead, mercury, manganese, iron, and cobalt ions. The latter ions frequently quench fluorescence and cause predominant analytical interference leading to low signal to noise ratios. Paucity of suitable sensor materials which do not require elaborate analytical sample preparation protocols but promise selective recognition of zinc ions without interference from toxic cadmium and other ions present in the biological broth is thus pivotal to further our knowledge on exploring the role of zinc in biological systems.[10]

Previous work on zinc ion complexation[10b–d] helped us to design a new molecular receptor based upon calix[4]arene scaffold in the cone conformation with imidazole as the binding unit and anthraquinone as the signaling unit. The designed receptor was synthesized through a series of steps as shown in Scheme 1.[11] Its molecular structure was confirmed by ^{1}H NMR and ^{13}C spectra as well as ESI-MS analysis (Supplementary data, Fig. S1). The advantage of designed and synthesized probe is that it emits and excites in the visible region of the spectrum and thus promises reduced scattering and low background emissions.[12] In this Letter we describe our results on the evaluation of recognition capability of the synthesized molecular receptor toward different metal ions using UV–vis absorbance, fluorescence, and ^{1}H NMR spectroscopic techniques.

A reference compound (**5**) having similar binding motifs as well as the signaling unit was also synthesized for comparison purposes.

The Zn^{2+} recognition ability of **4** was first examined in $CHCl_3$:CH_3CN (1:4, v/v) by determining the changes, if any, in its UV–vis spectra in the presence of different metal ions (0.13 mM). It is interesting to note that a significant change in the absorption

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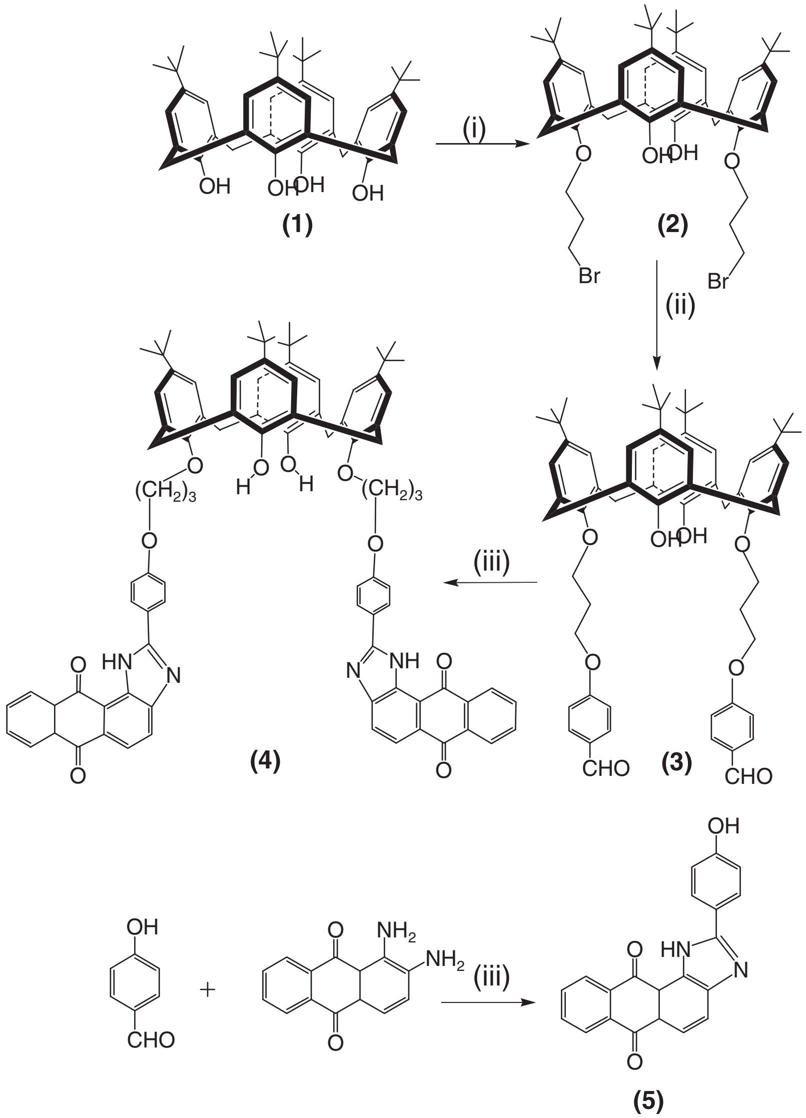
0040-4039/$ - see front matter © 2012 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.tetlet.2012.03.096



Scheme 1. Synthesis of anthraquinonoidal calix[4]arene. Reagents and conditions: (i) 1,3 dibromo propane, K_2CO_3, reflux, (ii) *p*-hydroxy benzaldehyde, K_2CO_3, reflux, (iii) 1,2 diamino anthraquinone, acetic acid, lead tetra acetate, reflux.

spectrum of **4** was observed upon addition of Zn^{2+}, while negligible changes were observed in the presence of other cations investigated (Fig. 1). The absorption maximum of **4** appeared at 422 nm which is a characteristic absorption of anthraquinone functionality. Upon addition of 3 equiv of Zn^{2+}, a hypsochromic shift of 15 nm from 422 nm to 404 nm in the UV–vis spectra of **4** was observed. This blue shift could be attributed to the interaction of Zn^{2+} with the nitrogen atoms of the imidazole rings.

The recognition of Zn^{2+} by **4** was further studied by fluorescence spectroscopy. A dilute solution of **4** (40 μM) in $CHCl_3$:CH_3CN (1:4, v/v) was prepared and the fluorescence emission spectrum of the compound was recorded by fixing the excitation wavelength at 420 nm which exhibited a characteristic emission band at 565 nm, whereas the maximum for anthraquinone unit alone was determined to appear at 555 nm (Supplementary data, Fig. S2).[13]

The fluorescence intensity of the compound **4** was measured in the presence of varying concentrations of different metal ions. Interestingly, the results obtained for Zn^{2+} were in contrast to its anticipated behavior as zinc is usually termed spectroscopically silent metal ion which does not alter the properties of fluorescence signal of many probes. Figure 2 clearly indicates a significant quenching of the fluorescence emission intensity observed in the presence of Zn^{2+}. Fluorescence intensity decreases by 75% in the presence of 0.13 mM Zn^{2+}.

In order to evaluate the role of calix[4]arene scaffold for recognition ability of **4**, fluorescent properties of the reference compound **5** in the presence of Zn^{2+} were investigated. Figure 3 presents a relative decrease in fluorescence intensity of **4** and reference compound **5**, respectively, in the presence of Zn^{2+}. It is quite evident that the fluorescence quenching, while prominent for compound **4**, is insignificant for reference compound **5**. This implies that calixarene framework is exercising an important control on Zn^{2+} recognition process by providing appropriate rigidity to the molecule.

Selectivity is extremely important for ion sensing; especially for zinc ion recognition (vide supra). To assess the selectivity of **4** toward Zn^{2+}, titration experiments were performed with other metal ions with perchlorate as the counter ion. Figure 4 depicts relative decrease in the fluorescence intensity of **4** upon interaction with various metal ions. It was found that Pb^{2+}, Co^{2+}, and Fe^{2+} partly quench the fluorescence intensity of **4**. This might be due to the collisional quenching of molecular fluorescence as are well-known

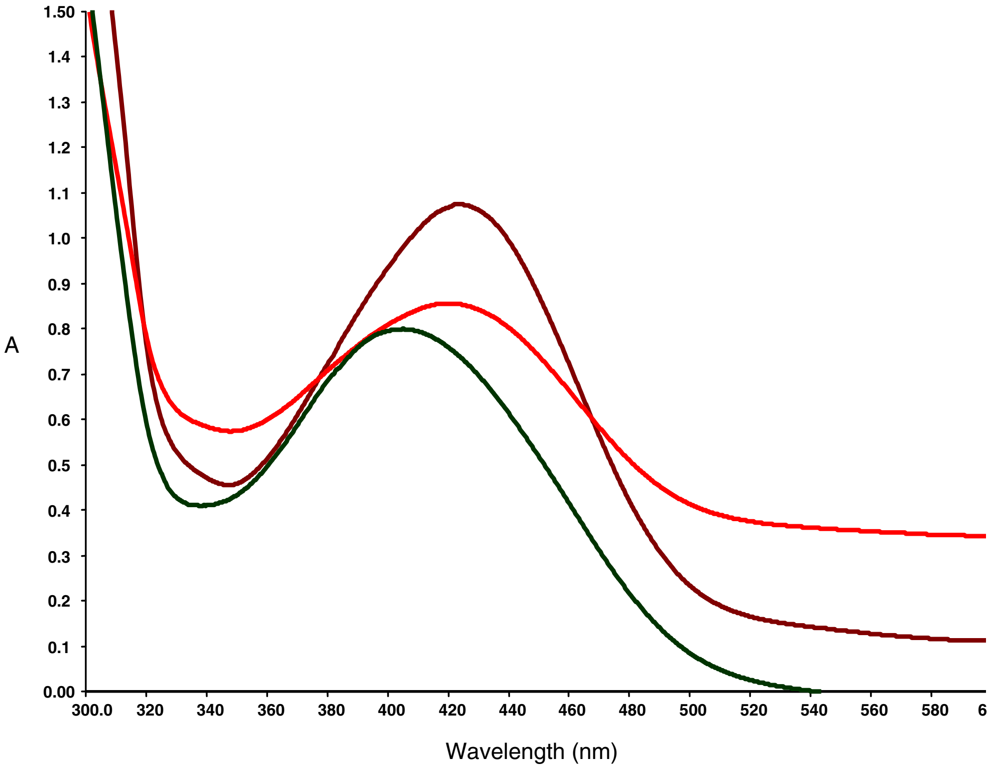


Figure 1. Change in UV–vis absorption spectra of ligand (**4**) [60 μM] upon addition of various metal ions —. Receptor alone. — Receptor + excess of different metal ions. — Receptor + 3 equiv of Zn^{2+}.

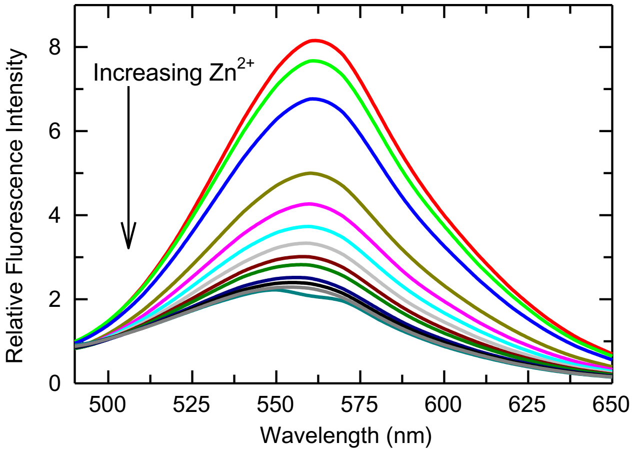


Figure 2. Quenching of fluorescence intensity of (**4**) in the presence of Zn^{2+} in $CHCl_3$:CH_3CN = (1:4, v/v) [(**4**) = 40 μM, $\lambda_{excitation}$ = 420 nm].

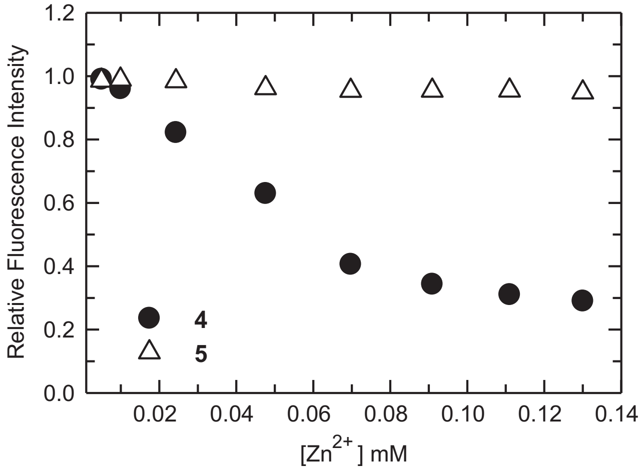


Figure 3. Relative decrease in the fluorescence intensity of **4** and reference compound **5** upon addition of Zn^{2+} in $CHCl_3$:CH_3CN (1:4, v/v) ($\lambda_{excitation}$ = 420 nm).

heavy metal ion quenchers which decrease the fluorescence intensity by promoting intersystem crossing. This was further substantiated by conducting similar experiments with the reference **5**. Fluorescence quenching was observed with Pb^{2+}, Co^{2+}, and Fe^{2+} upon titration with the reference compound **5**. No change in the emission spectra was observed upon addition of Cd^{2+} while Hg^{2+}, Ni^{2+}, Li^{+}, Mn^{2+}, and Na^{+} had marginal effect on the fluorescence emission signal of the compound (Fig. 4). Small enhancement in the fluorescence intensity of **4** was observed in the presence of Mn^{2+}, Ag^{+}, and Li^{+}. This might be due to the poor complexation of these ions with **4**.[14]

Fluorescence data of ligand [**4**] with increasing concentrations of Zn^{2+} were further studied to determine the mode of interaction between the host and the guest. A plot of Fo/F versus [Zn^{2+}] was found to be linear indicating that between ligand [**4**] and was of the 1:1 type (Supplementary data, Fig. S5).

Selectivity coefficients were computed for many metal ions using $K_{M^{n+},Zn^{2+}} = \Delta m_{M^{n+}}/\Delta m_{Zn^{2+}} = \Delta F_{M^{n+}}/\Delta F_{Zn^{2+}}$ where K is the selectivity coefficient, Δm is the calibration sensitivity and ΔF is the decrease in fluorescence intensity in the presence of constant concentration of metal ions. Selectivity coefficient for Cd^{2+} was found to be zero indicating the absence of any interference from it. Selectivity coefficients for all other metal ions were also found to be much lower to pose any significant hindrance in the recognition of Zn^{2+} (Supplementary data, Fig. S3).

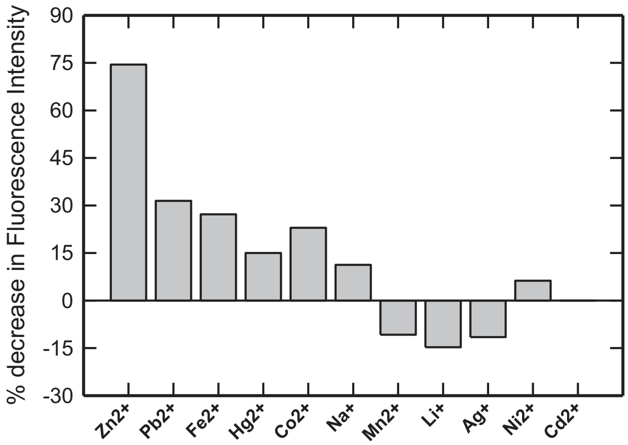


Figure 4. Percentage decrease in the fluorescence intensity of the compound (40 μM) upon addition of various metal ions in $CHCl_3$: CH_3CN (1:4, v/v) ($\lambda_{excitation}$ = 420 nm).

To further analyze the selectivity of the synthesized receptor to transition metal ions, competitive experiments with transition metals in conjunction with Zn^{2+} were performed (Supplementary data, Fig. S4). The data clearly showed that Ni^{2+}, Hg^{2+}, Pb^{2+}, and Fe^{2+} have marginal effect; the fluorescence quenching observed was slightly lower than that observed for the solution containing Zn^{2+} only. The presence of Mn^{2+} with Zn^{2+} resulted in reduction in fluorescence intensity to an appreciable amount. However, the extent of recognition through fluorescence quenching remains unaltered in the presence of Co^{2+} and Cd^{2+}. These results highlight the much better selectivity for Zn^{2+} over Cd^{2+} and Co^{2+} by **4**.

To elucidate the binding mode of Zn^{2+} with compound **4**, ^1H NMR titrations in $CDCl_3$ were performed. The NMR spectra of **4** in the presence of increasing equivalents of $Zn(ClO_4)_2$ resulted in desheilding and broadening of the signals of the protons of anthraquinone unit as compared to those of free receptor. The addition of 5 equiv of Zn^{2+} leads to the deshielding of anthraqunione protons by 0.05–0.15 ppm, respectively. The effect becomes much more prominent when excess of Zn^{2+} is present in solution. In the aromatic region, peaks corresponding to anthraquinone unit became broad but the positions of protons corresponding to the calixarene ring remained unaffected. A small shift in the UV–vis spectra upon addition of Zn^{2+} ruled out the involvement of NH proton of imidazole ring in binding Zn^{2+}. These results suggest that the interaction of the zinc ions takes place with the other donor nitrogen atoms of the imidazole ring as observed earlier.[15,16]

It has been known that Zn^{2+} can adopt various geometries with the coordination numbers ranging from two to six.[16] Thus it can be stipulated that it can adopt this geometry by interacting with the nitrogen atom of imidazole ring.

In conclusion, we have developed anthraquinonoidal calix[4]arene based compound (**4**[17,18]), which is capable of recognizing Zn^{2+} effectively with high selectivity without interference from Cd^{2+} and a host of other toxic metal ions studied.

Acknowledgement

R.S. and S.P. thank CSIR, India for fellowships.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.096.

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17. *Procedure for the synthesis of **4***: To a solution of calix[4]arene (3) (0.102 mmol) in CH_3CN:EtOH(7:3, v/v) was added 1,2 diaminoanthraquinone (0.22 mmol). The reaction mixture was refluxed for 24 h. The solvent was evaporated to dryness under reduced pressure and the residue was stirred with lead tetraacetate (0.11 mmol) in acetic acid (10 ml) for overnight. After completion of the reaction, product was filtered which was further purified by column chromatography and recrystallized from $CHCl_3$/MeOH.
18. *Analytical data for **4***: 68%; mp 286–288 °C (decomposed); UV (λ_{max}, $CHCl_3$): 423 nm. IR (KBr pellet, cm^{-1}): 3438, 2960, 1664, 1292, 1259.HRMS (ESI-MS) *m*/*z*: calcd 1409.6517, found 1409.6573; ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 10.62 (s, 2H, N*H*, D_2O exchangeable), 8.11 (m, 4H), 7.94 (m, 4H), 7.82 (m, 6H), 7.65 (m, 4H), 7.08 (s, 4H), 6.99 (d, 4H), 6.92 (s, 4H), 4.35 (m, 8H), 4.13 (t, 4H), 3.41 (d, 4H), 2.47 (m, 4H), 1.29 (s, 18H), 1.04 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm): 184.46, 161.24, 150.56, 141.68, 133.94, 128.3, 127.17, 114.88, 33.78, 31.62, 29.8.