J Incl Phenom Macrocycl Chem
DOI 10.1007/s10847-014-0432-4

ORIGINAL ARTICLE

Design, synthesis and evaluation of a new calix[4]arene based molecular receptor for multiple ion selectivity

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Received: 15 January 2014 / Accepted: 26 June 2014

Abstract The hydrophobic and conformational motifs of calix[4]arene stereostructure and plausible binding characteristics of heterocyclic 2-oxo-1,2-dihydroquinoline-4-carbohydrazide have been deployed for the design and synthesis of a new molecular receptor, **4** for multi-ion recognition. The target molecule was synthesized through the condensation of **3** with 2-oxo-1,2-dihydroquinoline-4-carbohydrazide (**6**) in refluxing ethanol. It has been determined that **4** exhibits an exclusive color change from colorless to yellow as well as a 5.5 fold increase in the fluorescence intensity upon interaction with fluoride due to formation of multiple hydrogen bonds. Consequent to fluoride induced deprotonation, **4** displays a dual selectivity for Cu^{2+} and Ni^{2+} ions from amongst plethora of investigated cations.

Keywords Calix[4]arenes · Quinoline carbohydrazide · Multi ion selectivity · Schiff base · Sensors

Introduction

The development of new multifunctional sensor systems with improved sensing properties and recognition mechanisms is an important academic and application challenge [1–3]. Molecular receptors with differential response towards multiple analytes are potentially cost effective and are highly desirable from the viewpoint of practical applications. However, it has been observed that only a few sensors show a multiple ion (or dual) response to both cations and anions. Most of these receptors lack the selectivity desired from the molecular probe. It has been observed that pre-organized molecular receptors capable of multipoint hydrogen bonding show a very good selectivity with ionic guests [4–6]. Literature survey indicates that from amongst anions, development of sensor materials for fluoride analysis is pivotal as fluoride is essential for prevention of dental caries [7], treatment of osteoporosis [8] and in the refinement of uranium but its excess in the living system can usher crippling skeletal fluorosis [9] and kidney failure. Likewise, from amongst cations, sensor materials for those ions are of special significance which are highly toxic but at the same time are essential in smaller quantities for smooth functioning of the biological systems [10]. Thus analysis of both cations and anions through a common molecular probe constitutes extremely important scientific target [11, 12]. One approach that can help to achieve such molecular receptors involves the utilization of supramolecular anionic systems that can reorient the receptor subunits to generate binding sites for cation selectivity. Although, fluoride complexes present a high possibility of spectroscopic metal ion sensing, there are only a limited number of publications describing the influence of fluoride ion on luminescence characteristics of receptors towards metal ions [13].

Utilizing this strategy, we report herein a new 2-oxo-1,2-dihydroquinoline-4-carbohydrazide bearing calix[4]arene Schiff base as a selective molecular receptor for fluoride ion and its deprotonated form for selective sensing of metal ions. To the best of our knowledge this the first calixarene based molecular receptor utilizing 2-oxo-1,2-dihydroquinoline-4-carbohydrazide units. Fluoride interaction with **4** exhibits a recognition mechanism based on the synergism of OHs and NHs, since both OH (phenolic)

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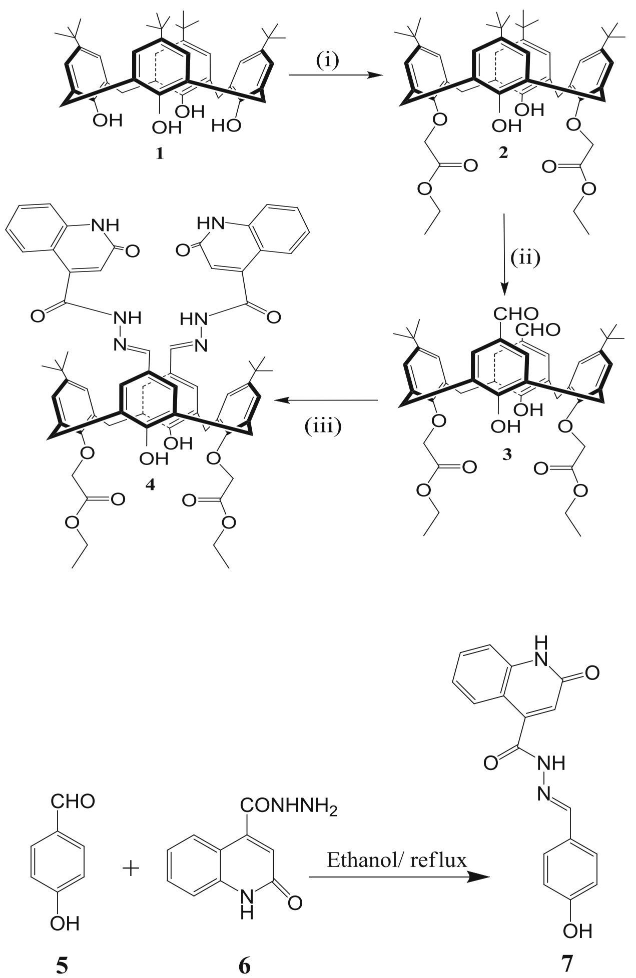
and CONH (amide and carbohydrazide) groups facilitate guest binding. Although many chromogenic/fluorescent sensors have been designed for F^- sensing, they are often inefficient in presence of other anions like $H_2PO_4^-$ and CH_3COO^-, hence it is useful to explore newer chromogenic sensors for selective recognition of F^-. For example, Chauhan and coworkers have recently reported four new urea based anion sensors which showed poor discrimination between different anions [14]. Another report published by Li and coworkers has described a new ferrocene based sensor [15] for F^-, which shows cross affinity for $H_2PO_4^-$. Additionally, fluorescence enhancement with anionic guests is a rather challenging task [16, 17] and it is encouraging that **4** can selectively recognize fluoride through visible color change and fluorescence turn on response. The deprotonated form of receptor **4**, obtained following fluoride interaction surprisingly exhibits increased affinity for Cu^{2+} and Ni^{2+} recognition.

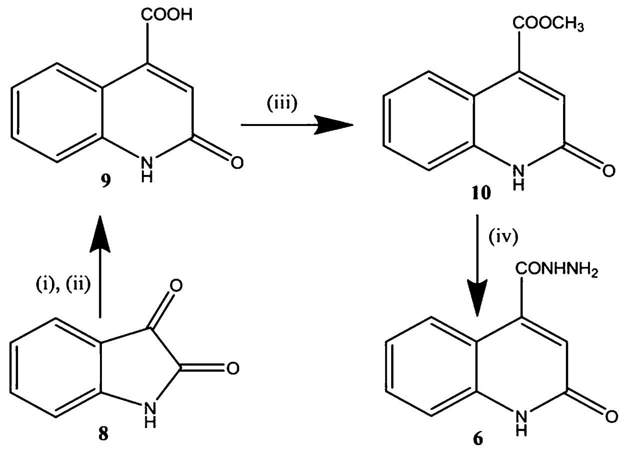


Scheme 1 Synthesis of **4** and **7**. Reagents and conditions: *i* Ethyl bromoacetate, K_2CO_3, CH_3CN, reflux; *ii* HMTA, TFA, reflux; *iii* 2-Oxo-1,2-dihydroquinoline-4-carbohydrazide, ethanol, reflux

Results and discussion

The synthesis of the target sensor molecule **4** (Scheme 1) commenced with the synthesis of the calixarene based aldehyde derivative **3,** which was achieved in one step from **2** with hexamethylenetetramine and trifluoroacetic acid. The synthesis of sensor **4** was accomplished in good yield by the condensation of **3** with two equiv of 2-oxo-1,2-dihydroquinoline-4-carbohydrazide (**6**) in refluxing ethanol. The reference compound **7**, on the other hand was synthesized by condensation of p-hydroxybenzaldehyde with **6**, which in turn was obtained by adopting the procedures reported in the literature [18] (Scheme 2).

The structures of compounds **4** and **7** were confirmed by recording their spectroscopic and analytical data. The ^{1}H NMR spectrum of **4** showed two doublets (4H each) for methylene bridge protons of calix[4]arene, two singlets (4H each) corresponding to calixarene aryl ring protons, two doublets (2H each) and two double doublets (2H each) corresponding to quinoline aryl ring protons and three singlets (2H each) corresponding to quinoline and carbohydrazone NH and calixarene OH (Fig. 1). The existence of compound **4** in cone conformation has been confirmed by means of ^{1}H NMR and ^{13}C NMR spectroscopy. ^{1}H NMR spectrum of **4** exhibits distinct doublets for the calixarene methylene bridge protons at 4.31 ppm (merged with OCH_2 protons) and 3.59 ppm, which are clear indication of existence of **4** in cone conformation. In addition to this, ^{13}C NMR spectrum of **4** also showed a signal for *syn* $Ar_2\mathbf{CH_2}$ at 31.46 ppm, thereby confirming the existence of **4** in cone conformation. Further confirmation of the structure was done by recording its HRMS which revealed prominent peaks at m/z 1,135.4810 (Intensity: 2.4×10^4) and 308.1017 (Intensity: 1700) corresponding to structures **4** and **7** respectively.



Scheme 2 Synthesis of **6**. Reagents and conditions: *i* $(CH_3CO)_2O$, reflux; *ii* NaOH, H_2O, 100 °C; *iii* $SOCl_2$, MeOH, reflux; *iv* $NH_2NH_2.2H_2O$, EtOH

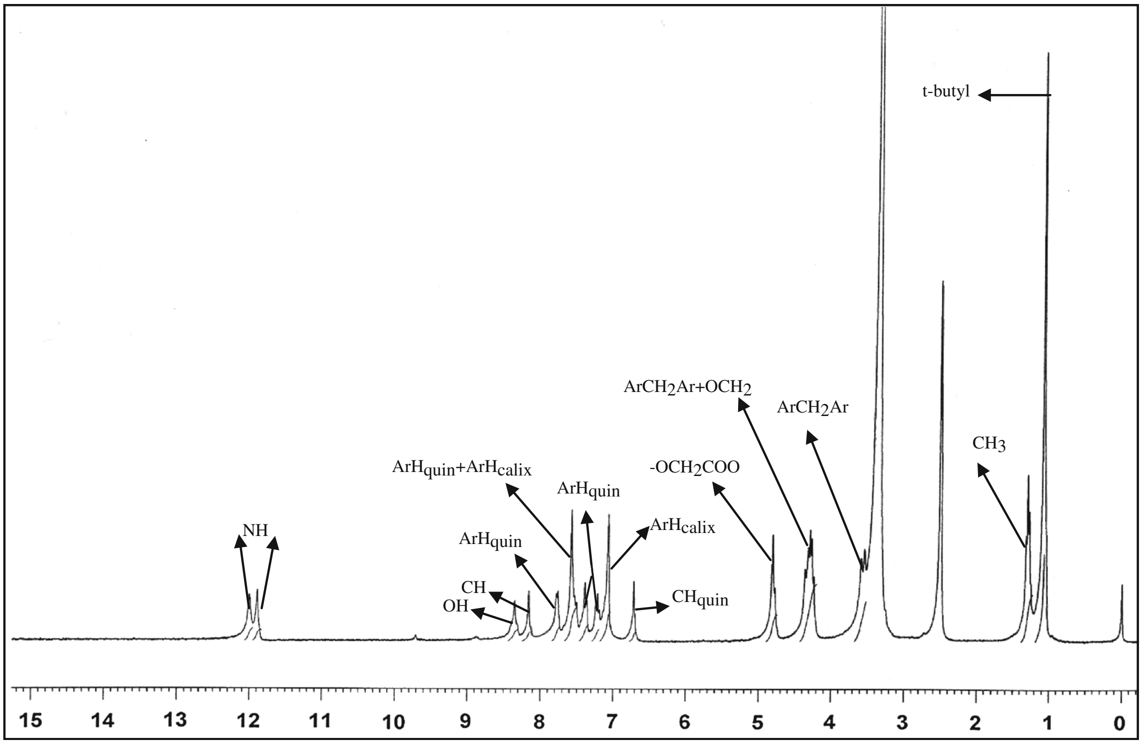


Fig. 1 ^{1}H NMR spectrum of **4**

UV–Vis spectroscopic studies

The ability of designed receptor **4** to complex with various anions was studied by spectrophotometric titrations in DMSO by adding standard solution of corresponding anions to a solution of the receptor. In the absence of external analytes, the UV–Vis spectrum of **4** in DMSO could be characterized by an absorption maxima at 327 nm, and a shoulder band around 285 nm. The former band could be attributed to the Ar–CH=N–NH conjugation. The critical anions of present interest included F^-, Cl^-, Br^-, I^-, HSO_4^-, $H_2PO_4^-$ and ClO_4^-. The absorption properties of **4** in the presence of TBA $(n\text{-}Bu_4N)^+$ salts of different anions were studied in detail. No change was observed in the absorption spectrum of **4** (30 µM) even upon the addition of 10 molar equivalents of Cl^-, Br^-, I^-, HSO_4^-, $H_2PO_4^-$ and ClO_4^- (Fig. 2). However, with the stepwise addition of tetrabutylammonium (TBA) fluoride (0–6.5 equiv.) to the DMSO solution of **4** (30 µM), the original absorption maximum weakened and an enhancement in the absorption was noticed in the wavelength range of 355 nm to 450 nm along with a distinct color change of the solution from colorless to yellow (Fig. 3). These changes occur presumably due to the charge transfer evoked after the interaction between the acidic receptor protons and fluoride.

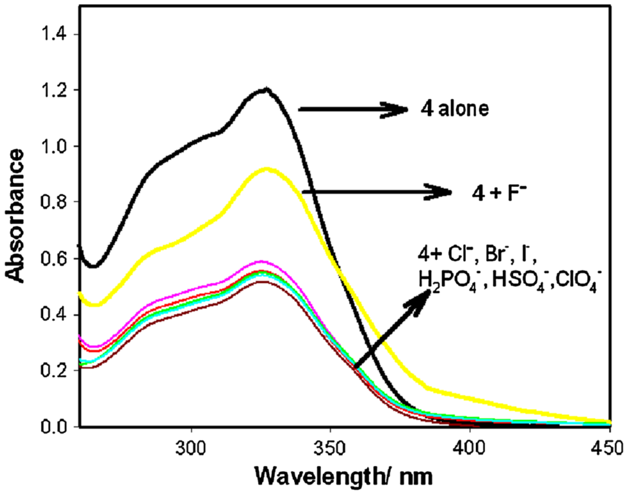


Fig. 2 UV–Visible absorption changes of **4** upon addition of 10 equiv of anions

Figure 4 displays the absorption spectral changes of receptor **4** (30 µM) upon gradual addition of 0 to 6.5 mol equivalent of TBAF. The reversibility of receptor response was checked by adding protic solvents (methanol, water) to the soution of receptor–fluoride complex. Interestingly, the color of the solution turned back to colorless, thereby suggesting that the protic solvents destroy the hydrogen bonding network between the receptor and the fluoride.

A major difficulty encountered in anion sensing endeavors concerns with the interference of other anions

Fig. 3 Color change of a DMSO solution of **4** upon F^- addition

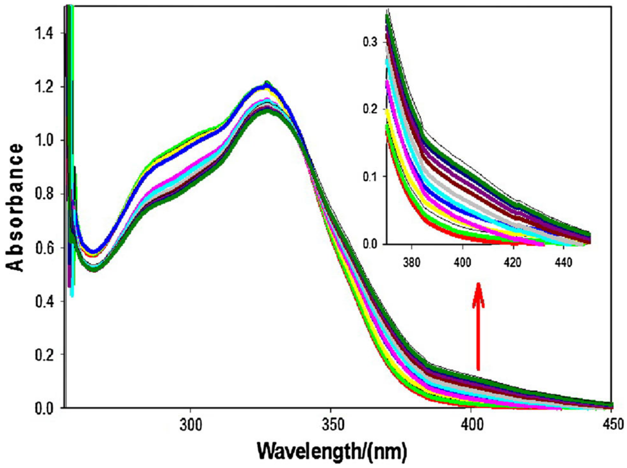


Fig. 4 Variation in absorption spectrum of **4** (30 μM) upon titration with TBAF (0–6.5 equiv)

present in the typical analyte solutions. Therefore, to further challenge the reliability of our fluoride detection system, we conducted competitive anion titrations, wherein absorption spectrum of other anions/fluoride ion co-existing systems was examined. The experiments revealed (Fig. 5) that highly selective detection of fluoride by **4** could be demonstrated, without much perturbation, even in the presence of equimolar amounts of other anions. It is noteworthy that **4** shows a selective color change with fluoride from colorless to yellow even in the presence of other anions. In essence, the high selectivity of host for fluoride could be attributed to several factors, which include appropriate acidity of the receptor donor groups, complementarity of shape between host and guest and multiple hydrogen bonding interactions.

The binding stoichiometry between **4** and fluoride determined by Job's method of continuous variation was 1:2 (**4**:F^-) (Fig. 6a).The binding constant for a 1:2 complex between **4** and fluoride in DMSO was determined from the increase in absorption intensity at 373 nm by using Benesi–Hildebrand equation [19], providing $K = 1.2 \times 10^8$ M^{-2} (Fig. 6b). Based upon the UV–Vis measurements, the detection limit [20] of receptor **4** towards F^- was determined to be 3.1 μM.

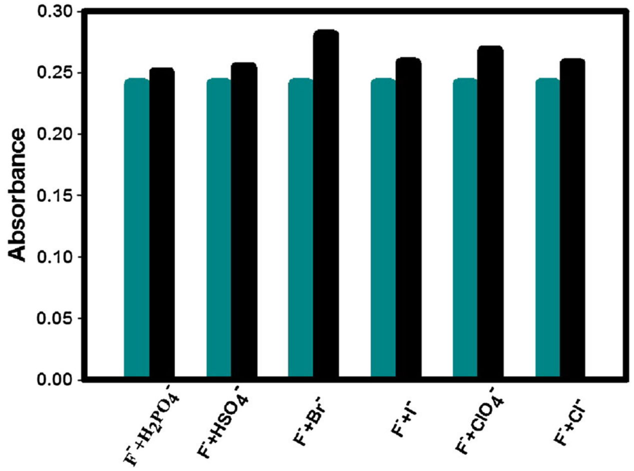


Fig. 5 Competitive selectivity of **4** for F^- in preference of other anions. *Green* bar represents the absorbance (at λ 373 nm) of **4** in presence of F^- alone and *black* bar denotes absorbance of F^-/X^- coexisting systems. (Color figure online)

The importance of calix[4]arene scaffold for the guest binding was evaluated by synthesis of an appropriate reference compound **7** (Scheme 1). **7** showed an absorption maximum at 317 nm in DMSO. It was observed that no apparent change was induced in the absorption spectrum of **7** even in the presence of excess TBAF (15equiv.). This observation affirmed the fact that presence of calix[4]arene scaffold is essential for guest binding probably because it provides the rigidity and accurate placement of binding sites required for interaction with the anionic guest.

Fluorescence spectroscopic analysis

Anion recognition through fluorescence measurements by **4** was also studied in DMSO. The fluorescence spectrum of **4** exhibited a very weak emission when excited at 325 nm. It was observed that upon addition of F^- (0–6.5 equiv) to DMSO solution of **4** (50 μM), a new emission band appeared around 505 nm along with a significant enhancement (5.5-fold) in fluorescence intensity at 505 nm. The fluorescence emission intensity of **4** increased linearly as a function of F^- concentration as shown in the inset of Fig. 7. Amongst various tested anions (F^-, Cl^-, Br^-, I^-, $H_2PO_4^-$, ClO_4^- and HSO_4^-), only F^- anion induced a sizable enhancement in the fluorescence intensity of **4**, while other anions exhibited a negligible response, indicating that **4** is a very selective receptor for F^-. Figure 7 describes fluoride induced changes in the fluorescence intensity of a DMSO solution of **4** (50 μM).

The association constant for **4**.F^- complex calculated from the fluorescence titration measurements by employing Benesi–Hildebrand equation (1.6×10^8 M^{-2}) (Fig. 8) was

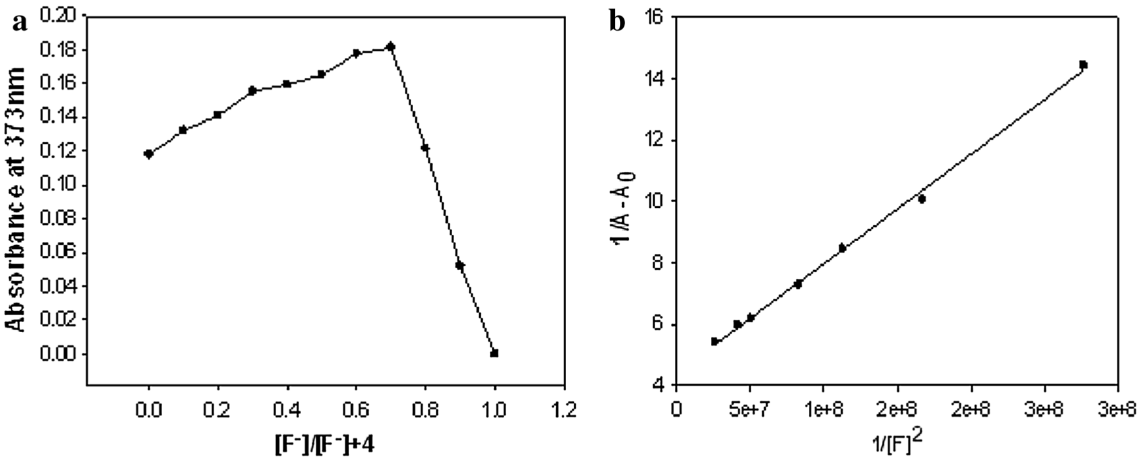


Fig. 6 **a** Job's plot for determining stoichiometry of receptor **4** with fluoride ions in DMSO. **b** Benesi–Hildebrand plot of **4** with F^- based on UV–Vis titration data

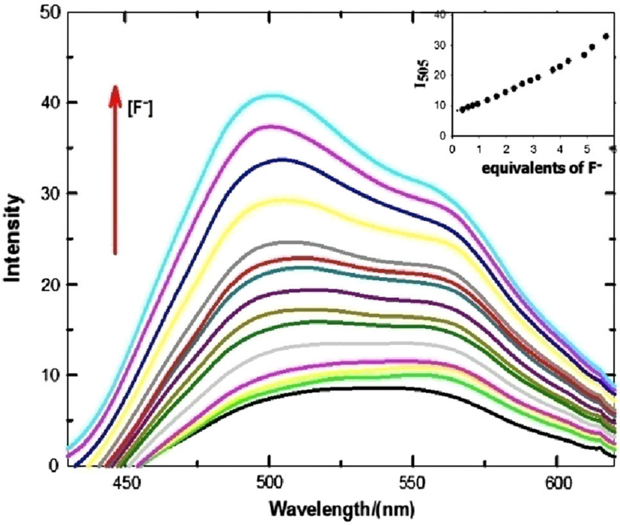


Fig. 7 Changes in the emission spectrum of **4** (50 μM) upon addition of TBAF (0–6.5 equiv.) in DMSO. Inset shows the change in fluorescence intensity at 505 nm with increasing equivalents of fluoride

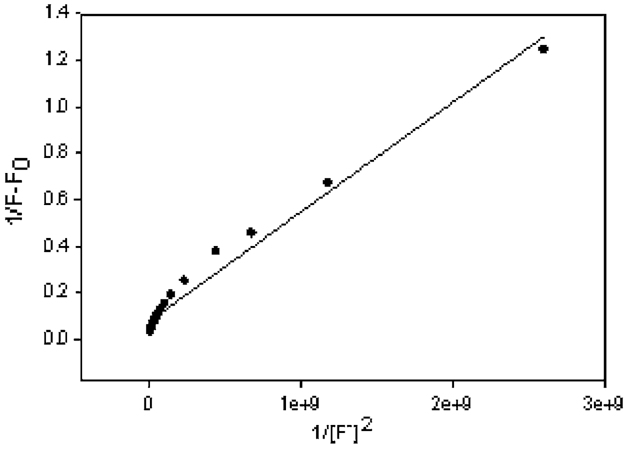


Fig. 8 Benesi–Hildebrand plot of **4** with F^- based on fluorescence data

consistent with the value derived from the UV–Vis titration studies, indicating a strong tendency for the formation of F^- ligand complexation species.

^{1}H NMR spectroscopic studies

The results obtained from the UV–Vis and fluorescence emission spectroscopy were further supported by ^{1}H NMR titrations carried out in DMSO-d_6 (Fig. 9). **4** exhibited three singlets in its ^{1}H NMR spectrum corresponding to quinoline NH protons, carbohydrazide NH protons and calixarene phenolic protons at δ 12.00, 11.89 and 8.41 ppm respectively. It was observed that after the addition of 0.1 equivalent of fluoride ions to the receptor solution (0.01 M), the characteristic NH and OH signals became broad to reveal that the commencement of interaction between **4** and fluoride ions occurs through H-bonding. The peaks broadened further as more TBAF was added and finally disappeared completely upon addition of 0.35 equivalents of F^-. These observations confirmed the assumption that quinoline NH, carbohydrazide NH and calixarene phenolic OH are involved in the interaction with fluoride through hydrogen bonding followed by deprotonation. Moreover, since deprotonation has been shown to occur at both the upper as well as lower rim of the calixarene receptor, these observations substantiate the fact that **4**.F^- interaction proceeds with a stoichiometric ratio of 1:2. Figure 10 shows the interaction mode between **4** and F^- proposed on the basis of these observations, wherein F^- first interacts with NH and OH through H-bond and eventually abstracts them.

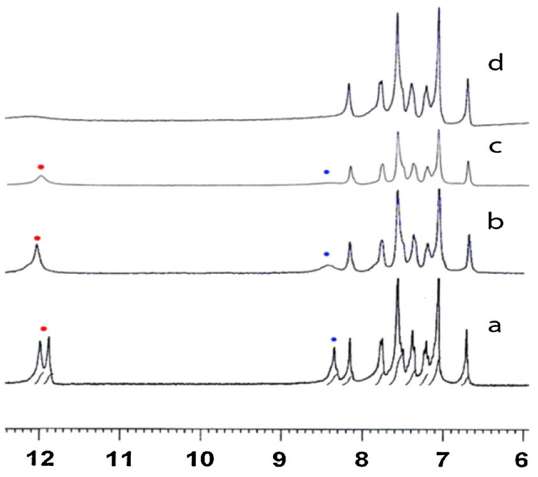


Fig. 9 Partial ^{1}H NMR (300 MHz) spectra of *a* **4** in DMSO-d$_6$; *b* **4** + 0.1 equiv. F$^-$; *c* **4** + 0.2 equiv. F$^-$; *d* **4** + 0.35 equiv. F$^-$

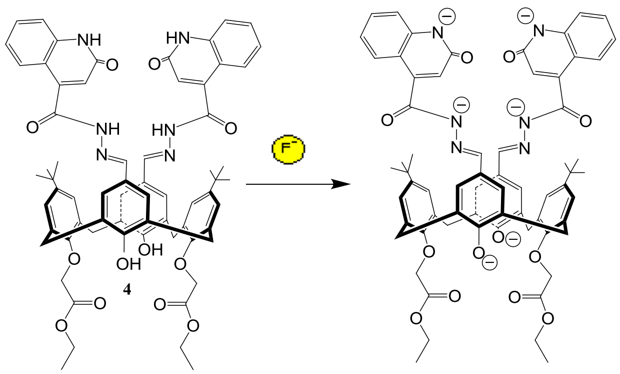


Fig. 10 Binding model for interaction between **4** and F$^-$

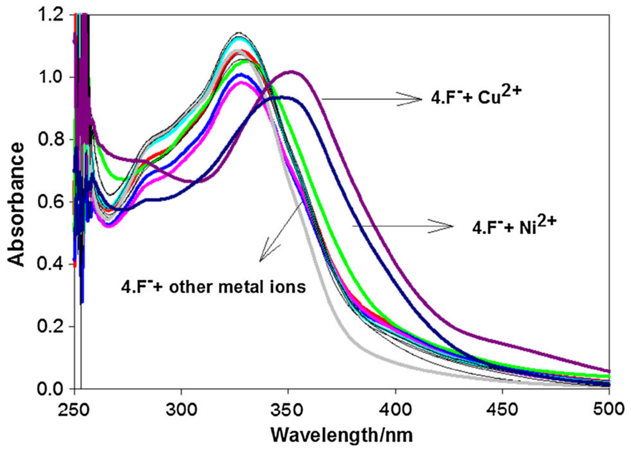


Fig. 11 UV–Vis absorption spectrum of **4**.F$^-$ upon addition of different metal ions (1.5 equiv) in DMSO

Recognition of metal ions through secondary interactions

Since ligands possessing free electron pairs can coordinate with metal ions to form metal ion complexes, we also investigated the behavior of compound **4** in the presence of perchlorate salts of various metal ions after fluoride addition. To ensure complete deprotonation of **4**, the behavior of compound **4** towards several alkali (Na$^+$, Cs$^+$, Li$^+$) and transition metal ions (Mn^{2+}, Co^{2+}, Cu^{2+}, Fe^{2+}, Ni^{2+}, Hg^{2+}, Ag$^+$, Cd^{2+}, Zn^2, Cr^{3+}) was studied after addition of fluoride ions (6 equivalents). It was observed that the system exhibited excellent selectivity towards Ni^{2+} and Cu^{2+} only (Fig. 11).

Upon addition of Cu^{2+} (Fig. 12a), the maximum corresponding to the deprotonated compound at 327 nm got shifted to 351 nm along with the appearance of a new absorption peak around 450 nm. While, in the presence of Ni^{2+} (Fig. 12b), the absorption maximum got shifted to 346 nm. The developed supramolecular system is thus further deployable for recognition of Cu^{2+} and Ni^{2+} which are otherwise not detected by **4** alone. The synthesized receptor also shows different absorption characteristics for them to allow their distinction from each other. The detection limit of Cu^{2+} and Ni^{2+} was determined to be 7.9 µM and 23 µM respectively. The selectivity towards Cu^{2+} and Ni^{2+} could be explained on the basis of the compatibility of the receptor with these ions in respect of cavity size, ionic radii, number and nature of binding sites probably collectively help in the selective complexation.

Conclusion

In summary, a novel calix[4]arene based molecular probe has been synthesized and evaluated as a multiple ion sensor. Fluoride recognition by **4** involves participation from multitude of hydrogen bond donor groups like phenolic OH, amide NH and carbohydrazide NH working synergistically. Since **4** shows selective coloration only with fluoride ion, it can be used as a naked eye sensor for F$^-$. The deprotonated system obtained after fluoride addition to **4** has been observed to function as an efficient sensor system for Cu^{2+} and Ni^{2+} ions as well.

Experimental

Materials and methods

All the reagents used in the study were purchased from Sigma Aldrich or Merck and were chemically pure. The solvents were dried and distilled prior to use. HPLC grade solvents were used for UV and fluorescence experiments. In the titration experiments, all the anions and metal ions were added in the form of TBA salts and perchlorate salts

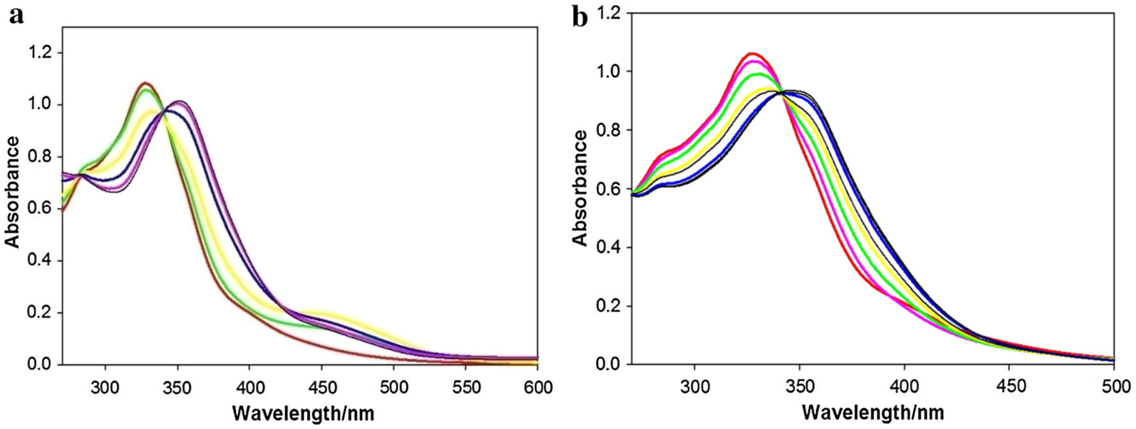


Fig. 12 Changes in the UV–Vis spectra of **4** in DMSO after addition of F^- (6.5 equiv) with increasing amount of **a** 1.5 equiv of Cu^{2+} and **b** 1.7 equiv of Ni^{2+}

respectively. ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 on a 300 MHz Bruker DPX 300 instrument using tetramethylsilane (TMS) at 0.00 as an internal standard. Mass spectrum was recorded on a Bruker Compass Data Analysis 4.0 Mass spectrometer. A Perkin Elmer Lambda 35 double beam spectrophotometer with variable bandwidth was used for the acquisition of the UV–Vis molecular absorbance. Melting points were determined on an electrothermal melting point apparatus obtained from M/S Toshniwal and were uncorrected.

General procedure for the synthesis of receptor **4** and reference compound **7**

5,17-diformyl-11,23-bis(p-tert-butyl)-26,28-bis(ethoxycarbonyl methoxy)-25,27-dihydroxy calix[4]arene was refluxed with 2-oxo-1,2-dihydroquinoline-4-carbohydrazide (2 mol equivalent) in dry ethanol for 12 h. The solid product thus separated out was filtered and recrystallised from ethanol to yield pure product **4** as a light green solid.

2-Oxo-1,2-dihydroquinoline-4-carbohydrazide(1 equiv) was refluxed for 8 h with p-hydroxybenzaldehyde in ethanol. Solid thus obtained was fitered and recrystallised from ethanol to afford the reference compound **7** in its pure form.

Analytical data for **4**

Light green solid; Yield: 75 %; Mp: 288 °C; UV (λ_{max}, DMSO): 327 nm; HRMS (ESI–MS) m/z:calcd 1,135.4811, found 1,135.4810; IR (KBr pellet, cm^{-1}): 3,384.61, 2,956.04, 1,728.40, 1,610.44, 1,196.19; ^1H NMR (300 MHz, DMSO-d_6, δ in ppm): 12.004 (s, 2H, N*H*, D_2O exchangeable), 11.891 (s, 2H, N*H*, D_2O exchangeable), 8.418 (s, 2H, O*H*, D_2O exchangeable), 8.352 (s, 2H), 7.786 (d, 2H), 7.578 (m, 6H), 7.39 (d, 2H), 7.22 (dd, 2H), 7.0 (s, 4H), 6.715 (s, 2H), 4.78 (s, 4H), 4.31 (m, 8H), 3.59 (d, 4H), 1.30 (t, 6H), 1.07(s, 18H); ^{13}C NMR (75 MHz, DMSO-d_6, δ in ppm) 14.43, 18.98, 31.46, 34.37, 56.50, 61.36, 72.48, 116.17, 116.68, 121.01, 122.63, 125.36, 126.40, 128.49, 129.22, 131.37, 132.48, 139.72, 145.09, 146.96, 147.53, 150.87, 151.05, 155.55, 161.64, 161.97, 169.36.

Analytical data for reference compound **7**

Light green solid; Yield: 73 %; Mp: 271 °C; UV (λ_{max}, DMSO): 317 nm; HRMS (ESI–MS) m/z:calcd 308.1030, found 308.1017; IR (KBr pellet, cm^{-1}): 3,350.68, 2,925.0835, 1,579.01, 1,101.72; ^1H NMR (300 MHz, DMSO-d_6, δ in ppm): 11.98 (s, 1H, N*H*, D_2O exchangeable),11.95 (s, 1H, N*H*, D_2O exchangeable), 10.03 (s, 1H, O*H*, D_2O exchangeable), 8.20 (s, 1H), 7.75 (d, 1H), 7.57 (d, 2H), 7.38 (dd, 1H), 7.22 (dd, 1H), 7.15 (d, 1H), 6.83 (d, 2H), 6.67 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, δ in ppm) 116.23, 116.64, 119.9, 120.99, 122.66, 125.33, 125.9, 129.59, 131.44, 139.73, 145.07, 149.71, 160.2, 161.61, 162.01.

Acknowledgement Tanu Gupta thanks the CSIR, India for research fellowship. Financial assistance from DST (FIST grant for HRMS to Department of Chemistry, IIT Delhi) and MoRD is gratefully acknowledged.

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