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A New Hg^{2+}-Selective Fluorescent Sensor Based on a 1,3-Alternate Thiacalix[4]arene Anchored with Four 8-Quinolinoloxy Groups

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A new thiacalix [4]arene derivative in a 1,3-alternate conformation bearing four quinolinoloxy groups through propyl chains has been synthesized, and its metal ion-binding and fluorescence-sensing properties were investigated in both THF and 10% H_2O–THF systems. The designed ligand exhibited pronounced Hg^{2+}-selective on–off type fluoroionophoric properties among the representative transition and heavy metal ions including Cu^{2+}. The detection limit for Hg^{2+} was found to be 2.0×10^{-6} M in the mixed H_2O–THF system. Detailed spectral studies including ^{1}H NMR and MALDI-TOF mass spectroscopy reveal the unusual formation of a tetramercury complex with the ligand, in which the four propyl arms containing the quinolinoloxy groups adopt a “tetrapodand” conformation enclosing one Hg^{2+} ion each in the four cavities thus formed.

Introduction

In recent years there has been an upsurge of interest in the development of fluorescent sensors for the detection of heavy metal ions that are of concern in toxicology and environmental science.[1] Mercury is a notorious heavy metal which causes severe neurotoxic, genotoxic, and immunotoxic effects and thus poses severe risk for human beings and other organisms.[2] Because of its toxicity, whether in the inorganic form as Hg^{2+} or in the organic form as methyl mercury compounds, development of highly efficient Hg^{2+} sensors with high selectivity and sensitivity is still attracting attention.[3] Design of chemosensors by incorporatiion of fluorophores can be based on either fluorescent ON−OFF[4] or OFF−ON[5] phenomenon. Many of the reported fluorescent sensors for Hg^{2+} that operate through fluorescence quenching are often hampered by interference from chemically related cations like Cu^{2+} which also causes nonspecific fluorescent

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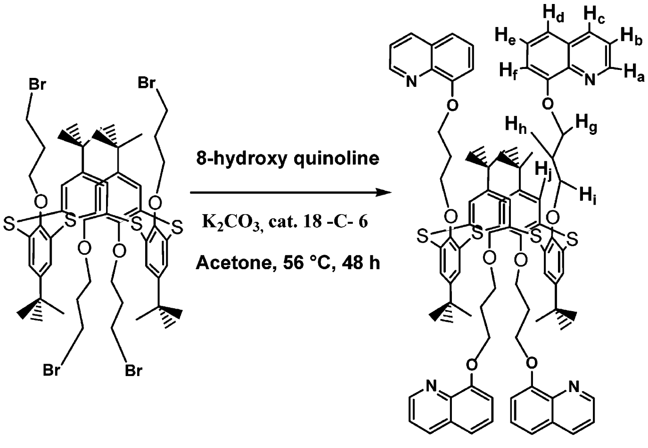
quenching.[6] In this regard, development of extremely selective and sensitive sensors with respect to Hg^{2+} ion assumes importance. The 8-hydroxyquinoline moiety has been receiving much attention in the design of efficient fluorophores because of the appreciable change in fluorescence upon metal binding.[7] A few 8-hydroxyquinoline-based Hg^{2+} selective fluorophores, which act by anchoring it to scaffolds like azacrown ethers, are documented.[8] Calixarene and thiacalixarene have also been appended with 8-hydroxyquinoline moieties affording molecular chemosensors.[9,12]

Among the macrocyclic complexing agents, thiacalixarenes with electron-rich sulfur bridges are efficient ionophores for transition metal ions even in the absence of additional ligating groups and are considered to be superior to the classical calixarenes in complexation capabilities.[10] To combine the complexation capabilities of both 8-hydroxyquinoline and thiacalix[4]arene, we have anchored four 8-quinolinoloxy groups to 4-*tert*-butylthiacalix[4]arene through flexible propyl chains in 1,3-alternate conformation. On the basis of the report that 1,3-alternate calixarene derivatives are superior in metal binding compared to their cone counterparts,[11] it is envisaged that this 1,3-alternate derivative would show interesting complexation properties toward metal ions especially in the utilization of the lone pairs of the sulfur atoms. Thiacalix[4]arene in the cone conformation with diagonal quinolinoloxy pendant groups through oxyethylene spacers and its coordination properties have been reported earlier by Chen and co-workers.[12] However, the compound showed poor selectivity toward Ni(II), Co(II), and Zn(II). A decrease in the number of neutral oxygen donor sites (by attaching the 8-quinolinoloxy groups through shorter alkyl chains) would make it possible to utilize the lone pair electrons of the donor sites of bridging sulfur of the thiacalixarene moiety for imparting selectivity toward soft metal ions like Hg^{2+}. As expected, because of the cooperative effects of the 8-quinolinoloxyl groups and the bridging sulfur of the thiacalixarene unit, the receptor in the 1,3-alternate conformation was found to exhibit high selectivity and sensitivity toward the Hg^{2+} ion among the transition metals ions selected for this study. The compound also exhibited marked selective fluorescence quenching upon complexation with Hg^{2+} with no interference from Cu^{2+} and hence can be used as a selective ON−OFF type fluorescence sensor.

Scheme 1. Synthesis of the Receptor **2**



1 **2**

Experimental Section

General Remarks. All reactions were carried out in oven-dried glassware. Progress of the reactions was monitored by thin layer chromatography, while purification was effected by column chromatography using silica gel (60−120 mesh). The perchlorate salts of Cr(II), Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Hg(II), Ag(I), Pb(II), Cd(II), Na(I), K(I), and Ca(II) used in this study were purchased from Aldrich. Aluminum(III) nitrate nonahydrate and 8-hydroxyquinoline were purchased from S.D. Fine Chemicals, India. All other chemicals used were of analytical reagent grade. Melting points were recorded on a Buchi melting point apparatus and are uncorrected. NMR spectra were recorded at 300 (^1H) and 75 (^{13}C) MHz on a Bruker Avance DPX-300 FT NMR spectrometer. Chemical shifts are reported in δ (ppm) relative to TMS (^1H) or $CDCl_3$ (^{13}C) as internal standards. IR spectra were recorded on Bomem MB series FT-IR spectrometer; absorbances are reported in cm^{-1}. Fluorescence studies were carried out with Spex-Flourolog DM3000F spectrofluorometer with double grating 0.22 M Spex 1680 monochromator and a 450 W Xe lamp as excitation source using right angular mode. Absorption studies were carried out using Shimadzu UV-1601 spectrophotometer. Mass spectra were recorded using JMS 600H (JEOL) and Ultraflex MALDI-TOF (Bruker Daltonics) mass spectrometers.

Synthesis. The synthesis of the thiacalix[4]arene receptor **2** was carried out as outlined in Scheme 1. The tetrabromo derivative **1** was synthesized as reported.[13] Exhaustive O-arylation of the tetrabromo derivative with 8-hydroxyquinoline was carried out in the presence of K_2CO_3 and a catalytic amount of 18-C-6 in refluxing acetone. K_2CO_3 (0.36 g, 2.5 mmol) was added to a solution of **1** (500 mg, 0.42 mmol) in dry acetone under argon atmosphere, followed by the addition of catalytic amount of 18-C-6 and 8-hydroxyquinoline (0.57 g, 4.15 mmol), and the resulting solution was refluxed for 48 h. After removal of the solvent, the reaction

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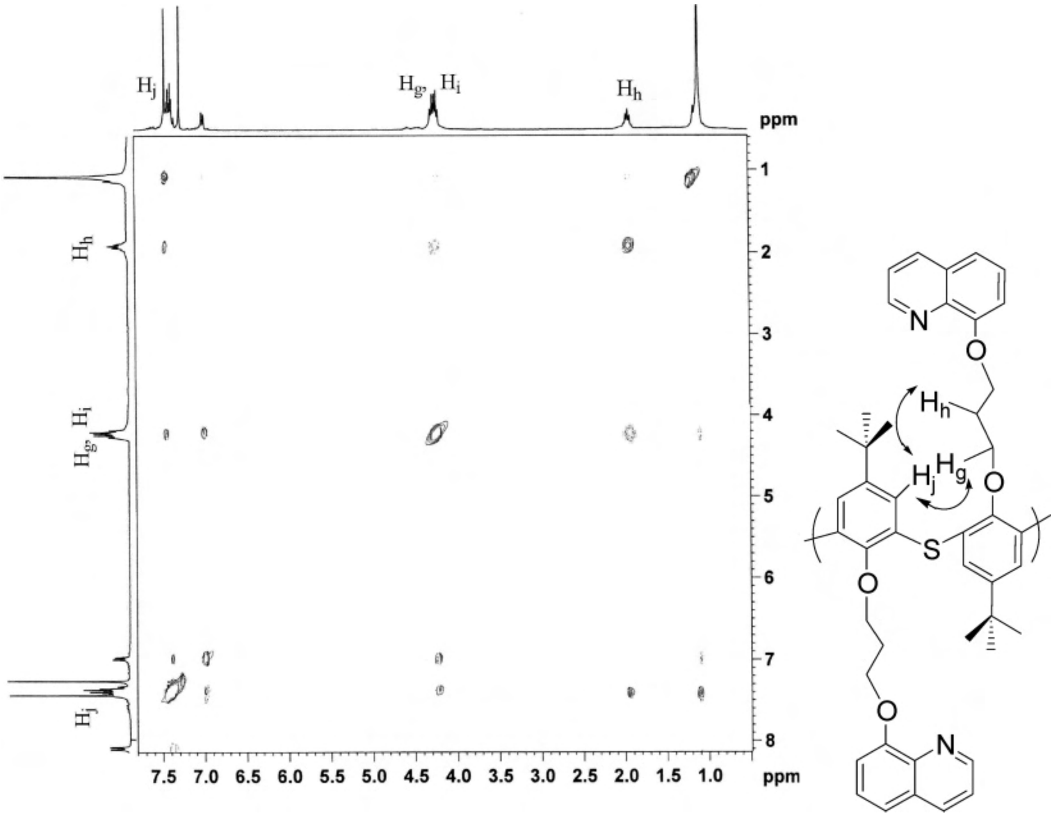

Figure 1. NOESY spectrum of receptor **2** in the range of 0−8 ppm in $CDCl_3$.

mixture was quenched with 10% aqueous HCl (30 mL). The resulting solution was extracted with 15 mL of dichloromethane twice. The organic extracts were combined, washed with water, brine, dried over anhydrous sodium sulfate, and evaporated under vacuo to obtain the crude product. It was then subjected to chromatography on a silica gel (60−120 mesh) column using 7:3 hexane−ethyl acetate mixture to afford **2** (0.35 g, 43%) as an off-white solid. mp: 118−119 °C. IR (KBr): ν_{max} 2959, 1570, 1500, 1466, 1451, 1377, 1316, 1263, 1179, 1107, 1037, 1015, 875, 820, 790 cm^{-1}. ^1H NMR: δ 8.91 (dd, $J_1 = 1.7$ Hz, $J_2 = 4.1$ Hz, 4H, Quin H_a), 8.09(dd, $J_1 = 1.6$ Hz, $J_2 = 8.3$ Hz, 4H Quin H_c), 7.43 (s, 8H, thiacalix H_j), 7.44−7.33 (m, 12H Quin H_b, H_d, H_e), 6.98 (d, $J = 7.2$ Hz, 4H Quin H_f), 4.27−4.16 (merged t, 16H, H_g, H_i), 1.89−1.82 (m, 8H, H_h), 1.09 (s, 36H). ^{13}C NMR: δ 157.2, 155.0, 149.0, 145.8, 145.5, 140.8, 135.8, 135.5, 129.5, 129.1, 128.5, 127.9, 126.6, 121.4, 119.5, 109.3, 66.9, 66.7, 34.2, 31.2, 29.0. MS (FAB) $[M + Na]^+$ for $C_{88}H_{92}N_4O_8S_4Na$: calcd 1483.5; found 1483.9

Fluorescence Quantum Yield. Fluorescence quantum yield (Φ_f) was determined in spectroscopic grade THF using optically matching solutions of resublimed anthracene ($\Phi_f = 0.21$ in ethanol) as the standard at an excitation wavelength of 280 nm, and the quantum yield was calculated using eq 1 where A_s and A_r are the

$$\Phi_f = \Phi_r(A_rF_s/A_sF_r)(\eta_s^2/\eta_r^2) \quad (1)$$

absorbances of the sample and reference solutions, respectively, at the same excitation wave length, F_s and F_r are the corresponding relative integrated fluorescence intensities, and η is the refractive index of the solvent.

Results and Discussion

A well-defined and simple ^1H NMR spectrum showed a highly symmetric structure for receptor **2**. The ^{t}Bu groups and aromatic protons of the thiacalix[4]arene moiety appeared as singlets at δ 1.09 and 7.43, respectively. These δ values are in good agreement with the values obtained for 1,3-alternate conformers reported elsewhere.[13] The 1,3-alternate receptor exhibited a $(M + Na)^+$ peak at m/z 1483.9 in the FAB-MS spectrum. Further confirmation of the 1,3-alternate conformation of **2** was obtained by NOESY experiments. The NOESY spectrum of **2** displayed NOE cross-peaks between the aromatic protons of the thiacalix moiety and one of the $-OCH_2$ groups and also the central methylene protons of the propyl chain (Figure 1).

Absorption Studies. Because of solubility limitations of **2**, in the present study, THF was chosen as the solvent. The UV−vis absorption spectrum of **2**, recorded in THF solution, exhibited a strong band at 240 nm ($\epsilon = 1.58 \times 10^5$ M^{-1} cm^{-1}) and another at 267 nm ($\epsilon = 5.06 \times 10^4$ M^{-1} cm^{-1}) which are attributed to the $\pi-\pi^*$ transitions of the aromatic rings of the thiacalixarene moiety. The weak band at 308 nm is assigned to the $\pi-\pi^*$ transitions of the 8-quinolinoloxy groups. To obtain insight into the binding properties of **2** toward various metal ions (Cr^{3+}, Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Hg^{2+}, Ag^+, Pb^{2+}, Cd^{2+}, Na^+, K^+, Ca^{2+}, Al^{3+}), the UV−vis spectral changes upon addition of metal perchlorates to the THF solution of **2** were investigated. Except for Hg^{2+}, Ag^+, and Cr^{3+}, the other metal ions had no effect on the absorption spectrum of **2** (Supporting Information. SI). Upon complexation with Hg^{2+}, the absorption band at 240 nm experienced a bathochromic shift by 14 nm, while with Ag^+ and Cr^{3+}, the shifts were relatively small (SI). Upon progressive addition of Hg^{2+} ions to a solution of **2** in THF

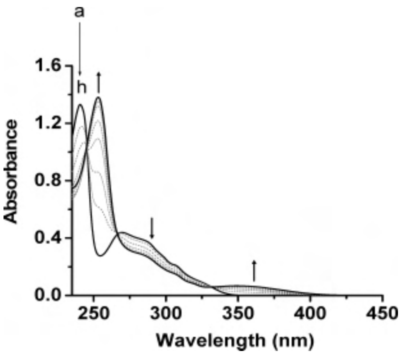

Figure 2. UV−vis titration curve of **2** in THF (8.5×10^{-6} M) with $Hg(ClO_4)_2$ (1.7×10^{-3} M) in THF at 25 °C: equiv of Hg^{2+} ion from a−h = 0, 0.66, 1.33, 2.00, 2.67, 3.33, 4.00, and 4.67, respectively.

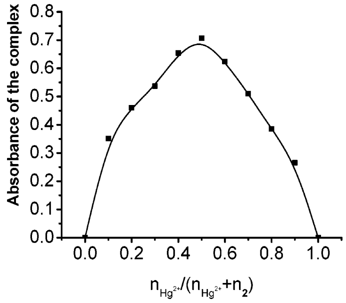

Figure 3. Job's plot of **2** and Hg^{2+} where absorption at 254 nm was plotted against the mole fraction of **2** (8.5×10^{-6} M) and Hg^{2+} (3.4×10^{-5} M) in THF.

(8.5×10^{-6} M), the absorption band at 240 nm gradually decreased in intensity with the concomitant formation of a new band at 254 nm which increased in intensity (Figure 2). Well-defined isosbestic points at 267 and 336 nm clearly indicate the formation of a specific complex. The stoichiometry of the $\mathbf{2}\cdot Hg^{2+}$ complex was ascertained by the method of continuous variations (Job's method). The classical procedure of mixing aliquots of equimolar solutions (8.5×10^{-6} M) of **2** and Hg^{2+} ions in THF failed because no significant absorption changes resulting from complex formation were observed in the absorption spectrum. The procedure was repeated with four times the concentration of Hg^{2+} (3.4×10^{-5} M), and the Job's plot obtained is given in Figure 3. The stoichiometry of the complex $\mathbf{2}\cdot Hg^{2+}$ is thus 1:4 if one considers the tetra-8-quinolinoloxy substituted 1,3-alternate thiacalix[4]arene as four individual chelating units, each one binding with one Hg^{2+} ion each as in the proposed structure shown in Figure 9.

Fluorescence Study. The fluorescence spectrum of **2** (λ_{exc} = 267 nm) in THF exhibited a characteristic emission band at 385 nm. Upon addition of increasing amounts of Hg^{2+} to a solution of **2** in THF (8.5×10^{-6} M), complete quenching of fluorescence at 385 nm was observed instantaneously (Figure 4). The fluorescence of **2** was completely quenched when the Hg^{2+} concentration reached 4 equiv (inset of Figure 4). The result suggests that the association constant for the tetramercury complex is very large.

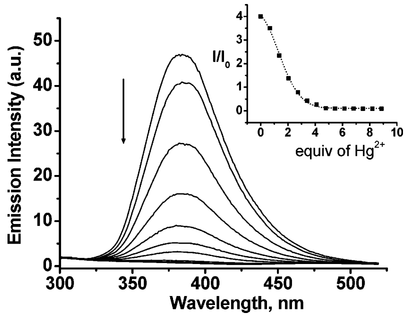

Figure 4. Fluorescence spectra (λ_{exc} = 267 nm) of **2** (8.5×10^{-6} M) in THF with increasing amount of Hg^{2+}(1.7×10^{-3} M) in THF. Inset shows variation of fluorescence intensity against equivalents of Hg^{2+}.

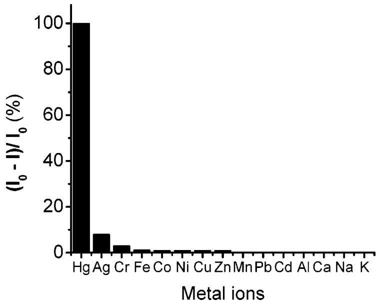

Figure 5. Quench ratio [$(I_0 - I)/I_0$] of fluorescent intensity of **2** (8.5×10^{-6} M) in THF upon addition of 4 equiv of metal ions.

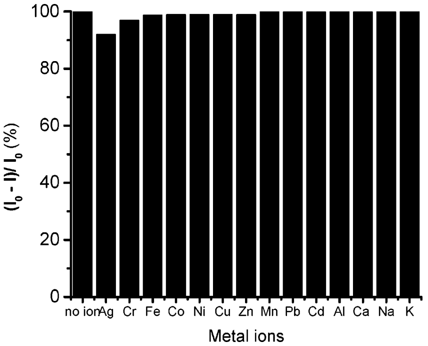

Figure 6. Quench ratio [$(I_0 - I)/I_0$] of fluorescent intensity of **2** (8.5×10^{-6} M) in THF upon the addition of 4 equiv of Hg^{2+} in the presence of 10 equiv of background metal ions.

Under the above conditions, the fluorescence response of **2** to other metal ions was also investigated. As shown in Figure 5, although the fluorescence of **2** at 385 nm was strongly quenched by Hg^{2+}, no significant spectral changes occurred in the presence of 4 equiv each of Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+}, Cd^{2+}, Na^{+}, K^{+}, Ca^{2+}, and Al^{3+}. Of practical significance is that even 10 equiv each of these metal ions did not interfere in the sensing of Hg^{2+}, and the results of the competition experiments are shown in Figure 6. Ag^{+} and Cr^{3+} showed marginal quenching of fluorescence (7 and 3%, respectively). Unlike many Hg^{2+}sensors reported to date, it is noteworthy that **2** shows highly selective fluorescence quenching toward Hg^{2+} over paramagnetic Cu^{2+}, probably because of very selective and strong binding of the latter with **2**. The quenching mechanism can be explained as being caused by the electron transfer from the quinoline nitrogen to the Hg^{2+}. The fluorescence quantum yields (Φ_F) of **2** in the free and Hg^{2+}-bound form were found to be 0.110 and 0.004, respectively. The Φ_F of **2** is comparable or better than many of the macrocyclic systems containing 8-hydroxyquinoline fluorophore reported earlier.[14] The substantial decrease in the quantum yield of **2** in the

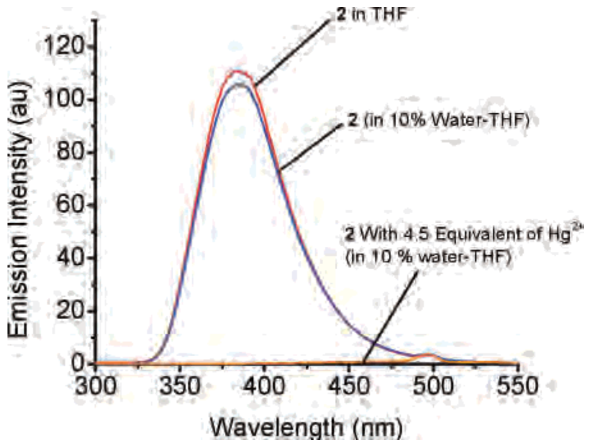

Figure 7. Emission intensity of receptor **2** (8.5×10^{-6} M) in THF, in 10% H_2O-THF solvent system, and with 4.5 equiv of Hg^{2+} (1.7×10^{-3}M) in 10% H_2O-THF solvent system.

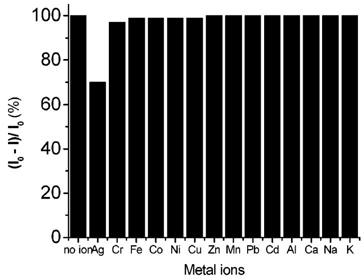

Figure 8. Quench ratio [$(I_0 - I)/I_0$] of fluorescent intensity of **2** (8.5×10^{-6} M) in 10% H_2O-THF solvent system upon addition of 8−10 equiv of Hg^{2+} in the presence of 10 equiv of background metal ions.

presence of 4 equiv of Hg^{2+} and its high Hg^{2+} selectivity show its credibility as a good Hg^{2+} sensor.

From a practical point of view, additional experiments were conducted to test the sensitivity of **2** toward Hg^{2+} in mixed H_2O-THF system (Figure 7). At an optimum of 10% H_2O-THF system, although the emission of **2** was slightly less ($\Phi_F = 0.078$), almost 98% quenching of fluorescence at 385 nm was observed in the presence of 4.5 equiv of Hg^{2+}. Competition experiments were also carried out in this mixed solvent system for evaluation of the sensing ability of **2** toward Hg^{2+} in the presence of 10 equiv each of background metal ions, and the results are shown in Figure 8. While Ag^+ recorded 29% and Cr^{3+} had 3% background quenching, other metal ions did not cause any effect. However, the sensitivity was found to be moderately lower in the mixed solvent system as compared to pure THF. The detection limit[15] was calculated as three times the standard deviation of the background noise and was found to be 2.5×10^{-6} M in THF and 2.0×10^{-6} M in the 10% H_2O-THF system. Reversibility experiments showed that Hg^{2+} binding to **2** is reversible (SI). In the presence of ∼ 4.5 equiv of thiourea, which is a strong chelator to Hg^{2+}, in the 10% H_2O-THF system, the decomplexation of Hg^{2+} with **2** occurred instantaneously, thereby regaining its fluorescence intensity to the original value. These experiments also show the capability of **2** as a highly selective sensor toward Hg^{2+}.

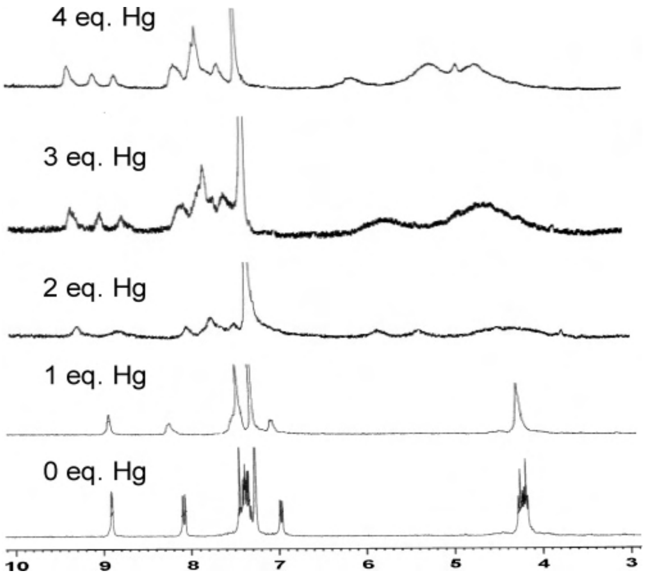

Figure 9. NMR spectral changes of **2** (1.64×10^{-3} M) by the addition of Hg $(ClO_4)_2$ (59×10^{-3} M) at 300 MHz in $CDCl_3/CD_3CN$ = 7:3.

^{1}H NMR Study. To get first hand information about the coordinating sites of receptor **2** upon complexation, ^{1}H NMR titration of **2** (in $CDCl_3$) was carried out with $Hg(ClO_4)_2$ (in CD_3CN) (Figure 9). The calixarene based ionophores have tendency to encapsulate solvents and neutral molecules causing shifts in δ values of the aromatic protons of the calixarene unit.[16] Control NMR titration of **2** taken in $CDCl_3$ with CD_3CN in the absence of Hg^{2+} ions did not show significant shifts in the δ values of any protons, particularly, the aromatic protons of the thiacalixarene moiety, indicating the absence of interaction between CD_3CN and the hydrophobic cavity of the thiacalixarene. Large shifts of proton resonances of $Ar-O-CH_2$ (H_i), $Quin-O-CH_2$ (H_g), quinoline protons H_f, H_c, and H_a, and aromatic protons (H_j) of the thiacalixarene units of the receptor **2** on complexation with four equivalents of Hg^{2+} point toward the coordination of both the oxygen atoms, quinoline nitrogen, and the S atom with the Hg^{2+}. Further corroborative evidence for the tetramercury complex was observed in the MALDI-TOF mass spectrum of the solid complex which showed mass peak corresponding to ($M + 4Hg^{2+}$) at m/z 2264.51 (SI). Thus the formation of a tetracoordinate tetramercury complex authenticated with ample spectral evidence prompted us to propose the structure of the complex as **3** (Figure 10). Each rigid terminal 8-quinolinoloxy moiety along with phenoxy oxygen connected with a propyl chain organizes in such a way as to involve the bridging S of the thiacalix moiety to form a mixed N/S/O podand-like structure encapsulating one Hg^{2+} ion each in the four cavities thus formed. It is believed

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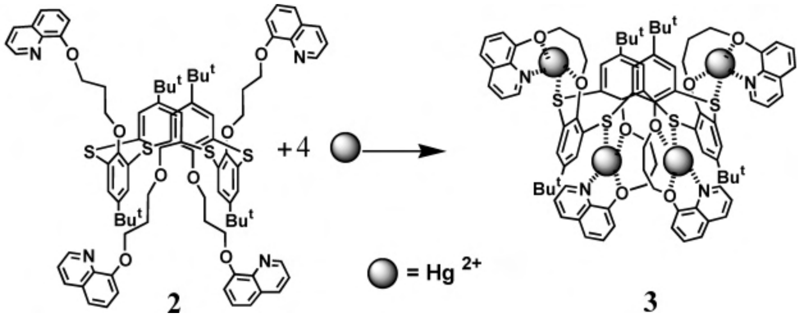

Figure 10. Proposed binding mode of **2** with Hg^{2+}.

that the presence of S atoms in the receptor contributes to the selectivity toward Hg^{2+} according to the HSAB principle.

Conclusions

In conclusion, a new 1,3-alternate thiacalix[4]arene derivative bearing four 8-quinolinoloxy groups through flexible propyl chains has been synthesized which exhibited a high affinity toward Hg^{2+}. The highly selective fluorescence quenching behavior of the receptor toward Hg^{2+}, its sensing ability in partially aqueous systems, and its reversible binding with Hg^{2+}, reinstating its fluorescence in the presence of stronger ligands, suggest that it can be used as an ON−OFF fluorescent sensor toward Hg^{2+}. The receptor exhibited only marginal affinity toward Cr^{3+} and Ag^{+}, and no affinity to other transition metal ions tested including Cu^{2+}, thereby reducing the possibility of interference by these metal ions. The system behaved as four independent units of mixed N/S/O donor sites in a thiacalixarene framework. The unusual formation of a tetramercury complex with **2** was confirmed by UV−vis, fluorescence, NMR, and MALDI-TOF mass spectral studies.

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Supporting Information Available: ^1H NMR spectrum, ^{13}C spectrum, UV−vis absorption spectra of **2** with Hg^{2+}, Ag^{+}, and Cr^{3+}, effect of metal ions other than Hg^{2+}, Ag^{+} and Cr^{3+} on absorption profile of receptor **2**, Job's plot analysis, reversibility experiment, and MALDI-TOF spectrum of **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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