Development of tBu-phenyl acetamide appended thiacalix[4]arene as “*Turn-ON*” Fluorescent Probe For Selective Recognition of Hg(II) Ions

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Abstract

Herein, a novel N-(4-(tert-butyl)-phenyl)-2-chloroacetamide functionalized thiacalix[4]arene architecture, viz TCAN2PA has been synthesized and the sensing behaviour towards metal ions was explored. The probe, TCAN2PA displayed a “*Turn-ON*” fluorescence response towards Hg(II) ions in acetonitrile over a series of competing common metal ions. A bathochromic shift in absorption band along with a significant “*Turn-ON*” fluorescence behaviour of TCAN2PA was observed upon interaction with Hg(II) ions. The lower rim modification of thiacalixarene with N-(4-(tert-butyl)-phenyl)-2-chloroacetamide actively contributes toward the fluorescence property due to the presence of strong electron-donating aryl amido substituent. Fluorescence titration experiments were conducted to find out the limit of detection and to understand binding stoichiometry as well. The electron transfer interactions between the electron-rich TCAN2PA host with Hg(II) ions have been postulated which is also supported by computational modelling insights.

1. Introduction

In recent years, there has been a curiosity in the invention of fluorescent sensors for detection of various heavy metal ions concerning its toxicity and negative environmental impact^{1,2}. Among different hazardous species and specifically metal ions, mercury is a highly toxic heavy metal³. Mercury is broadly used for manufacturing of various materials, agricultural chemicals due to which pollution of air and water originates. Mercury-containing compounds, particularly methyl mercury, accumulates in human brain and dislocates the blood-brain wall disturbing the metabolism of the nervous system. Inorganic mercury, during the anaerobic conditions, can be converted into methyl mercury⁴. Mercury causes various diseases like kidney failure, lack of coordination, sensory impairment, allergic reactions, negative reproductive effects, acrodynia, and Mina Mata disease^{5,6}. Mercury can be determined by various methods i.e. spectrophotometry⁷, neutron activation analysis⁸, anodic stripping voltammetry⁹, X-ray fluorescence spectrometry¹⁰, electrothermal atomic absorption spectrometry¹¹, atomic fluorescence spectrometry¹², atomic absorption spectrometry (AAS)^{13–15}, potentiometric ion-selective electrodes¹⁶, inductively coupled plasma mass spectrometry (ICP-MS), capillary electrophoresis and high-performance liquid chromatography (HPLC) and inductively plasma-atomic emission spectroscopy (ICP-AES)¹⁷. Fluorescence-based measurements are mostly used due to their high sensitivity and simplicity, which converts molecular recognition into actual fluorescence signals. Cation binding by fluorescent sensors occurs through the mechanisms like photo-induced charge transfer (PCT), photo-induced electron transfer (PET)^{18–21}, formation of monomer/excimer and recently most of fluorescence resonance energy transfer (FRET)²².

The third-generation “calixarene” is an interesting research area in supramolecular chemistry that functions as a receptor for cations, anions and neutral analytes. In recent decades, various developments are seen, for molecular recognition of cations species²³. Thiacalix[4]arene containing four sulfur atoms is easily available and therefore imparts new features compared to conventional calixarenes^{24–27}. The

thiacalix[4]arene assembly has an inherent hydrophobic cavity that allows recognition of various cationic, anionic, and neutral guests^{28–33}. The selectivity to bind any particular guest or metal ion by thiacalix[4]arene can be controlled by functionalizing with several binding units as amides, acids, imines, esters, amines and thioethers. The incorporation of soft binding sites such as -N and -S into the thiacalix[4]arene scaffold shifts the binding ability from hard to soft metal ions. Therefore, the thiacalix[4]arene scaffold exhibits many interesting binding features as a chemosensor for metal ions³⁴.

In this article, a novel thiacalixarene derivative, i.e., thiacalix[4]arene N-(4-(tert-butyl) phenyl)-2-chloroacetamide (TCAN2PA) has been synthesized and characterized. N-(4-(tert-butyl)phenyl)-2-chloroacetamide moiety has been functionalized to the lower rim of the parent thiacalix[4]arene and photochemical measurements including absorption and emission techniques were introduced to investigate its selectivity and sensitivity toward Hg(II) ions. Spectrophotometric and spectrofluorimetric results confirmed the binding of Hg(II) ions with TCAN2PA. The stoichiometry, binding constant and quantum yield of the TCAN2PA-Hg(II) complex have also been calculated. Additionally, molecular docking calculation helps to find the bind interaction between TCAN2PA and Hg (II) ions.

2. Experimental Section

2.1 Materials and Instrumentations

All metal salts, chemicals, reagents and solvents of analytical grade were purchased from commercial sources and used without further purification. 4-tert-Butyl aniline and chloroacetyl chloride were obtained from Sigma Aldrich. Fluorescence active TLC plates (F-2009) were obtained from Merck. Fluorescence spectra were recorded on a Jasco FP-8300 spectrofluorometer (Tokyo, Japan) with EHCS-813. Absorption spectra were recorded using a Jasco V-750 UV-Vis recording spectrophotometer (Tokyo, Japan) with EHCS-750 in the range of 200–800 nm. ¹H NMR, ¹³C NMR, and ¹³C DEPT spectra were obtained on a Bruker AV- (III) -400 MHz spectrometer using a BBFO probe. Mass spectra were recorded on a Micromass Q-TOF micro mass spectrometer with a capillary voltage of 3000 V and a source temperature of 120°C.

2.2 Synthesis of TCAN2PA

To a solution of thiacalix[4]arene (0.5 g, 0.00069 mol), K₂CO₃ (0.19 g, 0.0014 mol) in dry acetone, N-(4-(tert-butyl)phenyl)-2-chloroacetamide (0.31 g, 0.0014 mol) was added. The reaction mixture was then refluxed for 8 hrs. The progress of the reaction was monitored through TLC. After completion, the reaction mixture was cooled to room temperature, and the solvent was evaporated to dryness. The pure compound (Scheme 1) was obtained by silica gel column chromatography by using (hexane: ethyl acetate) as eluents (9:1) to get the solid product with 70 % yield.

MS (ESI): m/z for C₆₃H₇₅N₂O₆S₄ Calcd: 1084.5 [M], Found 1123.4 [M + Na]⁺ (**Fig. S8**), **¹H-NMR** (400 MHz, DMSO-*d*₆): δ (ppm): 0.94 (18H, s, -CH₃), 1.38(36H, s, -CH₃), 5.1(4H, s, -CH₂), 8.8(2H, s, -OH) (**Fig. S9**) 10.1

(2H, s, -NH), 7.5(8H, s, Ar-H), 7.3(4H, s, Ar-H), 2.5(DMSO); ^{13}C NMR (100 MHz, DMSO): δ (ppm): 30.61, 34.69, 76.71, 77.03, 77.35, 120.54, 136.42, 144.71, 155.63 (Fig. S10); M.P: 275.0°C.

2.3 Spectrophotometric and spectrofluorimetric measurements

Stock solutions of TCAN2PA (2×10^{-4} M) and the nitrate salts (2×10^{-3} M) of various metal ions [Fe(III), Cu(II), Cd(II), Zn(II), Cr(III), Ca(II), Co(II), Mg(II), Ag(I), Pb(II), Sr(II), Hg(II), Ba(II), K(I), Na(I), Bi(III)] were prepared in acetonitrile (ACN). The absorption spectra were recorded in the range of 200–700 nm, whereas the emission spectra were recorded within the range of 300 to 700 nm. The emission titration experiments were carried out by successive addition of mercury into the solution of TCAN2PA. A Job's plot study was performed based on the emission studies.

2.4 In silico Insight

Molecular docking is an outstanding tool for computational modeling. Molecular docking can also be used to estimate the stability of host-guest complex that provides the structural descriptions of the host-guest complex to gain insights into the binding conformations, mechanistic information and the elucidation of ligand-induced conformational changes^{35,36}. Design of ligands with specific electrostatic and stereochemical attributes can be developed by molecular docking to procure high receptor binding affinity. It imparts three-dimensional structures for scrupulous inspection of the topology at the binding site for the presence of clefts, cavities and sub-pockets. With molecular docking, careful inspection of the electrostatic properties such as charge distribution can also be done^{37,38}.

Initially, the chemical structures of TCAN2PA and Hg(II) were developed by using the geometry optimization technique. The developed structures of TCAN2PA and Hg(II) were then set as starting host and guest, respectively using the Schrodinger software (Maestro 12.0). 3D knowledge-based shapes from the superimposed pair of the host and guest are utilized to calculate the energy scores for the host-guest complex. The best-docked score of the complex was retrieved by Hex 8.0 software. Identification of the complex possessing the lowest free energy is done. The equation used to calculate the binding energy is as under:

$$\Delta E_{total}(\text{kcal/mol}) = \Delta E_{complex} - \Delta E_{receptor} - \Delta E_{ligand}$$

The insights for the possible host-guest interactions are procured by molecular docking, particularly the non-covalent interactions as they are not explained by the spectrofluorimetric results. Accelry's Discovery Studio visualizer version 16.1 is used to observe the non-covalent interactions that play a major role within the various host-guest interactions. It reveals that π -lone pair, π -alkyl, π - π stacking and π - π T-shape stacking, metal-donor interactions are the main interactions for the host-guest complex formation.

2.5 Molecular dynamics (MD) simulation

MD simulation was carried out using the Desmond v3.6 (Academic version)³⁹ package taking the complex with lowest free energy as an input. It is performed to know the thermodynamic stability of the complex. As per classical mechanics, MD implements Newton's equations of motion, to acquire the details of speed and position of each atom in the system under investigation. Thus, examination of the trajectory and temporal evolution of host-guest complex can be examined⁴⁰. In the first step, a particular configuration is attributed to the atoms to replicate the conditions like temperature and pressure of the real system. The position and velocity of each of the atoms at some points later are attainable from the computation of the forces that act on each particle. For the integration of the molecular trajectories for a given time interval, these calculations are repeatedly performed⁴¹. The simulation cell was created using the device builder module TIP3P (transferable intermolecular potential with three points) water model and the cubic periodic box containing the Simple Point Charge (SPC) (10×10Å) with the Integrated Liquid Simulations Potential (OPLS) all-atom force field 2005. MD simulation for this case was carried out for a duration of 20 ns with a relation time if 1 ps at a constant temperature of 300 K, along with constant volume and shape (NVT) with a Nose-Hoover thermostat 9, constant volume, Smooth Particle Mesh Ewald (PME) method. After that root mean square deviation (RMSD), root means square fluctuation (RMSF), Hydrogen bond, a radius of gyration (Rg), the histogram for torsional bonds were analyzed for the identification of structural changes with the dynamic role of the selected host-guest complex^{42,43}.

3. Results And Discussion

3.1 Selectivity towards metal ions

In order to obtain the selectivity of the probe, absorption as well as emission studies were performed. The receptor TCAN2PA exhibits an absorption band at 295 nm. The characteristic absorption band of TCAN2PA at 295 nm indicates a strong $n \rightarrow \pi$ transitions in both the phenolic groups of thiocalix[4]arene. Upon interaction with a series of common metal ions, including [Fe(III), Cu(II), Cd(II), Zn(II), Cr(III), Ca(II), Co(II), Mg(II), Ag(I), Pb(II), Sr(II), Hg(II), Ba(II), K(I), Na(I), Bi(III)] a significant redshift of 39 nm was observed only in the case of Hg(II), as shown in (Fig. 1a). The electronic perturbation induced by the coordination with -NH and -OH groups of TCAN2PA accelerates the sensing of Hg(II) ions^{44,45}. This certain change in absorption band indicates strong interaction of mercury ions with the receptor TCAN2PA, whereas no change in the absorption band of TCAN2PA was observed upon interaction with other metal ions. On similar lines, upon excitation at 325 nm, the receptor TCAN2PA exhibits an emission maximum at 399 nm (Fig. 1b). A sharp enhancement in emission intensity of TCAN2PA was observed only with the addition of Hg(II) ions, whereas no change in emission maxima was observed with other metal ions. This enhancement in fluorescence intensity may be attributed to the transfer of electrons between electronic rich -NH and -OH group of the receptor to Hg(II) ions.

3.2 Sensitivity towards Hg (II) ions

Further to gain in-depth insight about the sensitivity of TCAN2PA towards Hg(II) ions, fluorescence titration experiments were carried out (Fig. 2a). A significant enhancement in fluorescence intensity was observed upon gradual addition of mercury ions to the solution of TCAN2PA. The Stern-Volmer plot further shows that the probe TCAN2PA can detect mercury ions over a wide range of concentrations (50nM-700nM) and the value of R^2 was determined to be 0.9917 (Fig. S15). The jobs plot analysis further reveals that the receptor TCAN2PA interacts with Hg(II) ions in 1:1 stoichiometry (Fig. S14). A plot of $\log [(F_0-F)/(F-F_1)]$ versus $\log [M]$ help us to find out the binding constant (K_S), where F_0 and F_1 denote the relative fluorescence intensities of the complex without addition of guest metal ion and with maximum concentration of metal ion $[M]$, respectively. The binding constant for TCAN2PA-Hg(II) system was determined to be $1.8344 \times 10^6 \text{ M}^{-1}$, which indicates a strong binding interaction between host molecule and guest analyte^{46–50}. It is noteworthy to mention that no significant interference of the competitive metal ions was observed during the Sensing process (Fig. 2b). A comparison between some recently reported probes toward the recognition of Hg(II), their LOD values and detection methods have been incorporated as Table 1.

Table 1
Detection limits of present work to compare with other reported values.

Sr No.	Probe	Method	Medium	LOD	Ref.
1	Calixarene-based di-imine based probe	Fluorescent	THF-H ₂ O	600 nM	51
2	Anthracene anchored calix [4]arene pyridine amide based probe	Fluorescent	MeOH/CHCl ₃	380 nM	52
3	Rhodamine-Based Conjugate Polymer	Electrochemical	EtOH/H ₂ O	97.7 nM	53
4	Pyrene-amino mercapto thiadiazole based probe	Fluorescent	ACN: H ₂ O	100 nM	54
5	Carbazole Schiff base (CBS) probe	Colorimetric, Fluorescent	H ₂ O	14.7 nM	55
6	Diarylethene-rhodamine Unit Based	Colorimetric, Fluorescent	ACN	24.6 nM	56
7	Symmetrical Derivative of Anthrone based probe	Electrochemical	ACN: H ₂ O	610 nM	57
8	perylene diimide based probe	Fluorescent	DMSO-H ₂ O	350 nM	58
9	Coumarin-based probe	fluorescent	H ₂ O	120 nM	59
10	Thiacalix[4]arene N-(4-(tert-butyl) phenyl)-2-chloroacetamide (TCAN2PA)	fluorescent	ACN	50 nM	This work

3.3 In silico Insight

3.3.1 In silico Metal ion sensing

Initially, the geometry of the host molecule was optimized and then the Hg(II) ion was incorporated during the docking study. The pose with the lowest energy and most favourable geometry have been captured using Accelry's Discovery Studio visualizer. The geometry optimized structures of the receptor have been displayed as (Fig. 3). Among all the cations, the lowest docking energy was obtained for the TCAN2PA-Hg(II) system, suggesting stable complex formation between them. This lowest energy complex formation only with Hg(II) ions further support the experimental observation and signifies the selectivity of the probe. Host-guest interactions reveal that the complex formation between TCAN2PA and Hg(II) ions is due to one type of interaction namely, metal-donor in two pairs with the distance of 2.22 and 2.43 Å (Fig. 4).

3.3.2 Analysis of MD simulation

Molecular dynamics simulations have been accomplished to examine the stability and conformational changes of host-guest inclusion complex for 20 ns time trajectory. Different parameters of the Chitosan Nanoneedle stability testing have been evaluated during the whole event which includes root mean square deviations (RMSD), root mean square fluctuations (RMSF), radius of gyration (ROG), intramolecular hydrogen bonds, and energy contributions were plotted as the time dependant function of MD simulations. Two types of analysis have been done for the MD simulations including quality analysis and whole event analysis **Table S1**. The total energy of -13023.999 kcal/mol was retrieved at initiation of MD simulations while potential energy (kcal/mol), temperature (K), pressure (bar), volume (Å³) noted with the values of -13023.999, -16099.142, 298.735, 4.798 and 51434.883 respectively. Further, the statistical analysis has revealed the fluctuation and contribution of its higher stability except total energy which possessed exponential growth **Fig. S16**.

To assess the structural integrity, favourable conformational space and stability of the host-guest inclusion complex MD simulations were performed in a water solvent system. During this event, various parameters were identified which contained intramolecular hydrogen bonds, coulomb, van-der Waals interactions and total energy at 20 ns time interval (Fig. 5).

3.4 Sensing mechanism

The receptor TCAN2PA exhibits weak fluorescence at 399 nm. Upon interaction with Hg(II) ions, an enhancement in fluorescence intensity was observed. This may be due to the inhibition of photoinduced electron transfer (PET) from receptor to mercury ions. The molecular docking studies further indicate that the electron-rich -OH and -NH sites of the receptor involved in complexation with Hg(II) ions. This study indicates that upon complexation with mercury ions, the receptor became more rigid, which may lead toward the enhancement in emission maxima.

4. Conclusion

In summary, a novel thiacalix[4]arene N-(4-(tert-butyl) phenyl)-2-chloroacetamide (TCAN2PA) has been designed and synthesized toward the selective recognition of Hg(II) ions. A redshift in absorption maxima followed by the significant enhancement in emission intensity indicates its exceptional selectivity toward Hg(II) ion over a series of common metal ions. The emission titration experiments reveal that this fluorescent “*Turn-ON*” sensing probe strongly bind Hg(II) ions, as the binding constant was found to be $1.8344 \times 10^6 \text{ M}^{-1}$. The binding stoichiometry for TCAN2PA-Hg(II) system was determined to be 1:1. Additionally, this thiacalix based probe can determine Hg(II) concentrations up to 50 nM. The molecular docking studies further confirm that the -OH groups associate to the lower rim of thiacalix and the “N” sites of the fluorophore strongly involve in binding interaction of mercury ions. Theoretical studies further predict a lowest energy complex for Hg(II) ions which supports the enhancement in the emission intensity by Hg(II) signifying a stable complex of TCAN2PA with Hg(II) ions. Therefore, this probe can act as an efficient probe towards the sensing of Hg(II) ions.

Declarations

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Code availability: Not applicable

Authors' Contributions: Ashukumar Verma: Methodology, Data curation, Writing - original draft; Krunal Modi: Formal analysis, Software; Shuvankar Dey: Validation; Anita Kongor: Writing - review & editing; Manthan Panchal: Formal analysis; Manoj Vora: Checked the literature; Falak Panjwani: Designed the experimental scheme; V. K. Jain: Funding acquisition, Resources, Supervision.

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Figures

Figure 1

(a) UV–visible spectra and (b) fluorescence spectra of TCAN2PA (2×10^{-4} M) in the presence of various metal ions (2×10^{-3} M) in ACN

Figure 2

(a) Change in fluorescence maxima of the probe TCAN2PA upon addition of varying amounts of Hg(II) in ACN. Inset: limit of detection (b) Variation in emission intensities of TCAN2PA-Hg(II) system upon addition of competitive ions.

Figure 3

Geometrically optimized 3D structure of TCAN2PA (A) front view, (B) Top view

Figure 4

(A) Front view and (B) top view of TCAN2PA-Hg (II) complex after molecular docking

Figure 5

MD simulations event analysis graph plots during the 20 ns time trajectory

Figure 6

Plausible sensing mechanism for the binding of Hg(II)

Supplementary Files

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