

# Design, synthesis, characterization, and preliminary complexation studies of chromogenic vanadophiles: 1,3-alternate thiacalix[4]arene tetrahydroxamic acids

Mitesh H. Patel, Vijay B. Patel, Pranav S. Shrivastav\*

*Chemistry Department, School of Sciences, Gujarat University, Ahmedabad 380009, India*

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## Abstract

New chromogenic supramolecular vanadophiles were designed and synthesized by incorporating hydroxamic acid chains on a 1,3-alternate thiacalix[4]arene scaffold and were found to show high affinity toward vanadate ions. The article describes a comprehensive design process to devise a tailor-made co-ordination cavity for vanadate ions by pre-organization of hydroxamic acid chelating moieties on a 1,3-alternate thiacalix[4]arene scaffold. These receptors simultaneously co-ordinate two vanadate ions giving a highly ‘staggered’ geometry with almost  $D_{2d}$  symmetry. Proposed structures and complexation behavior of the receptors were explained by critical examination of FTIR, UV–visible, mass, and  $^1\text{H}$  NMR data.

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**Keywords:** 1,3-Alternate thiacalix[4]arene; Vanadophiles; Hydroxamic acid; Co-ordination cavity

## 1. Introduction

Thiacalixarenes, the calixarene analogs having sulfide bridges instead of methylene bridges, are recent members of the calixarene family.<sup>1,2</sup> Thiacalixarenes are preferred over classical calixarenes as molecular platforms (scaffolds) for the design of sophisticated complexing systems<sup>3</sup> as (i) they are more flexible than calixarene by virtue of their larger framework,<sup>4</sup> which means the appended binding sites can fine-tune themselves according to incoming guests, (ii) they can be locked into the desired conformer preferentially through an easy one-step transformation,<sup>5</sup> and (iii) they include surplus binding sites in the form of sulfur. The synthesis of thiacalix[4]arene was first reported by Sone et al. in 1997 via a stepwise procedure.<sup>6</sup> In the same year Miyano et al.

reported a single step procedure<sup>7</sup> to synthesize thiacalixarenes with higher yields. Since then several lower rim modifications<sup>8–10</sup> have been realized to enhance their complexing properties toward metal ions.

The role of vanadium complexes is highly critical in biological processes as they mimic the functions of peroxidases, catalases, and nitrogenases.<sup>11</sup> The chemistry and biochemistry of vanadium and its different species have been extensively reviewed by Crans et al.<sup>12</sup> Recently, Duhme-Klair et al.<sup>13</sup> have proposed some chemosensors for biologically important oxovanadates and studied their solid state structures and spectroscopic properties.

Hydroxamic acids are versatile extractants and have achieved significant importance as analytical tools for separation and determination of a large number of metal ions, especially as a reagent for the determination of different species of vanadium.<sup>12</sup> With this in view, herein we report for the first time the synthesis of 1,3-alternate thiacalix[4]arene tetrahydroxamic acid derivatives as chromogenic vanadophiles and their preliminary complexation studies.

\* Corresponding author. Tel.: +91 79 26300969; fax: +91 79 26308545.

E-mail addresses: [mitesh9@gmail.com](mailto:mitesh9@gmail.com) (M.H. Patel), [pranav\\_shrivastav@yahoo.com](mailto:pranav_shrivastav@yahoo.com) (P.S. Shrivastav).

## 2. Design of receptors

As has been known for some time, two hydroxamic acid groups, *cis* with respect to each other, co-ordinate one vanadate ion.<sup>14</sup> Thus, if two hydroxamic acid groups are pre-organized on a single molecular scaffold, this may result in just the right kind of *co-ordination cavity*,<sup>15</sup> to engage ions like vanadate. Hence, our approach was to construct hydroxamic acid chains, on four phenolic oxygens of a 1,3-alternate thiacalix[4]arene scaffold. Thus, in solution, two hydroxamic acid chains located on opposite faces of the  $\sigma_v$  ( $\sigma_{yz}$  in Fig. 1) plane would form a pair by inter-chain H-bonding, giving rise to a cavity. Alternatively, the pair may also sustain itself by trapping a solvent molecule and hence the metal ion to be complexed would replace the solvent to occupy the cavity. Two pairs created in this way would reside on opposite faces of the  $\sigma_d$  plane of the scaffold, and would therefore simultaneously co-ordinate with two vanadate ions independent of each other giving a highly ‘staggered’ geometry with almost  $D_{2d}$  symmetry. It was evident from a molecular modeling exercise that, the cone conformer would experience enormous steric hindrance in binding bulky guests such as vanadate ions due to the presence of four large hydroxamic acid chains positioned on the same side of the scaffold, giving a highly ‘eclipsed’—high energy orientation.

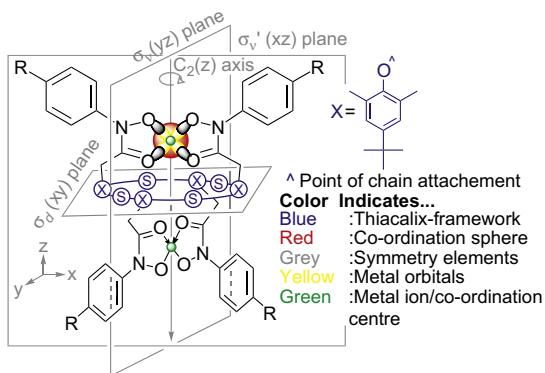


Figure 1. Schematic complexation of vanadium with proposed ligand.

## 3. Results and discussion

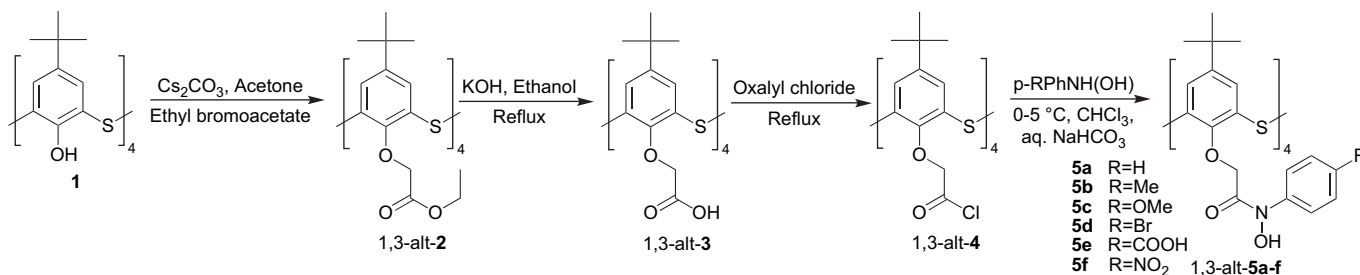
To construct the anticipated ligands, thiacalix[4]arene **1** was first alkylated with ethyl bromoacetate using cesium carbonate as base template to furnish tetra-ester **2** locked in 1,3-alternate

conformation, which was subsequently hydrolyzed to obtain the tetra-acid derivative<sup>16</sup> **3**. The tetra-acid was then converted into acid chloride<sup>17</sup> **4** by simple reflux with oxalyl chloride and finally coupled with the phenyl hydroxylamine of choice to obtain desired hydroxamic acids **5a–f** (Scheme 1).

To establish the proposed structures, the synthesized thiacalix[4]arene hydroxamates **5a–f** were studied through HPLC, elemental analysis, FTIR, MS, and <sup>1</sup>H NMR (Tables 1 and 2). To ascertain the purity, **5a–f** were chromatographed through HPLC under isocratic conditions. A single peak at a retention time of 2.16 min was observed for **5a** with negligible baseline noise (Fig. 2). The other compounds **5b–f** were similarly chromatographed and the purity obtained was greater than 98% for all the compounds. The elemental analysis revealed stoichiometric presence of H, N, and S, however, %C values were little lower than expected, the reasons for which have been documented earlier.<sup>18</sup> FTIR spectra of **5a–f** showed three significant peaks around 2960, 1770, and 880 cm<sup>−1</sup>, which characterize >N–O–H, >C=O, and >N–O–H stretching vibrations, respectively.

The mass spectrum of **5a** exhibits a cluster of peaks at *m/z* 1317, 1316, 1315, 1314, and 1313 corresponding to M+1 (protonated molecular ion), M (molecular ion), and M−1, M−2, and M−3 (mono-, di-, and tri-deprotonated molecular ions). This deprotonation can be attributed to the labile N–OH protons. The most abundant fragments were also identified, which were at *m/z* 1224=[M−(OH+C<sub>6</sub>H<sub>5</sub>)+2H], *m/z* 1166=[1224−(CH<sub>2</sub>•CO•NH<sub>2</sub>)] base peak, *m/z* 1071=[1166−(OH<sub>2</sub>+C<sub>6</sub>H<sub>5</sub>)], and *m/z* 1017=[1071−(CH<sub>2</sub>•CO•NH)+3H]. It can be noticed that the fragmentation follows an interesting pattern, i.e., disintegration of one hydroxamic acid chain completely upto the phenolic oxygen, followed by the next chain in identical manner (Scheme 2). The fragmentation of **5b–f** also follows the same trend.

Comparison of <sup>1</sup>H NMR spectra of products **5a–f** with tetra-acid **3** exhibits emergence of a new peak around  $\delta$  value ~10–11 corresponding to strongly hydrogen bonded N–OH functionality (Fig. 3). Conversely, in conventional hydroxamic acids like *N*-phenyl benzohydroxamic acid, the N–OH protons are found around  $\delta$  value 8–9. This downfield shift of N–OH protons of **5a–f** may be attributed to surplus H-bonding of N–OH protons as compared to simple hydroxamic acids, consequently, this supports aforesaid pairing of chains through H-bonding. All other peaks in the <sup>1</sup>H NMR spectra of products **5a–f** were in good agreement with the values expected from comparison with the precursor **3**.



Scheme 1. Synthetic route for **5a–f**.

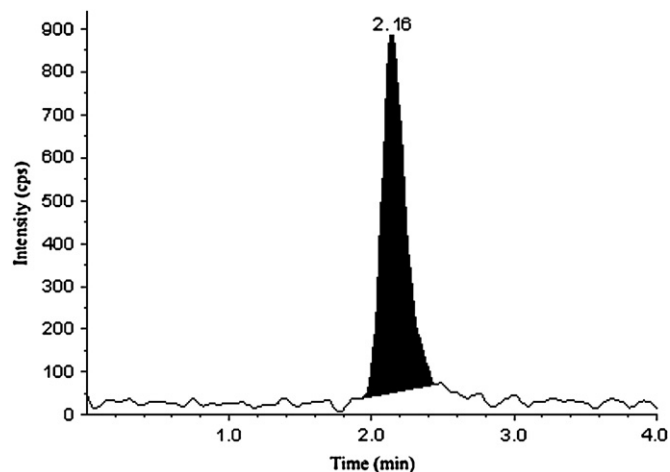
Table 1

Mp, significant IR peaks, and elemental analysis data of **5a–f** and vanadate complex of **5a**

| Ligand                                                                      | R               | Yield (%) | Mp (°C) | $\nu_{\text{O-H}}$ (cm <sup>-1</sup> ) | $\nu_{\text{O-N}}$ (cm <sup>-1</sup> ) | %C <sub>Exp</sub> (calcd) | %H <sub>Exp</sub> (calcd) | %N <sub>Exp</sub> (calcd) | %S <sub>Exp</sub> (calcd) |
|-----------------------------------------------------------------------------|-----------------|-----------|---------|----------------------------------------|----------------------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| <b>5a</b>                                                                   | H               | 70        | 223 (d) | 2960                                   | 883                                    | 64.48 (65.63)             | 5.72 (5.81)               | 4.21 (4.25)               | 9.66 (9.73)               |
| <b>5b</b>                                                                   | Me              | 68        | 227 (d) | 2964                                   | 883                                    | 65.28 (66.45)             | 6.10 (6.16)               | 4.02 (4.08)               | 9.29 (9.34)               |
| <b>5c</b>                                                                   | OMe             | 68        | 234 (d) | 2964                                   | 884                                    | 62.52 (63.49)             | 5.77 (5.89)               | 3.81 (3.90)               | 8.88 (8.92)               |
| <b>5d</b>                                                                   | Br              | 73        | 258 (d) | 2958                                   | 883                                    | 51.45 (52.95)             | 4.39 (4.44)               | 3.39 (3.43)               | 7.80 (7.85)               |
| <b>5e</b>                                                                   | COOH            | 63        | 272 (d) | 2952                                   | 890                                    | 59.88 (61.11)             | 5.10 (5.13)               | 3.68 (3.75)               | 8.52 (8.59)               |
| <b>5f</b>                                                                   | NO <sub>2</sub> | 64        | 278 (d) | 2950                                   | 891                                    | 56.24 (57.74)             | 4.75 (4.85)               | 7.43 (7.48)               | 8.49 (8.56)               |
| [ <b>5a</b> - <sup>4</sup> (VO <sup>3+</sup> ) <sub>2</sub> ] <sup>+2</sup> | H               | —         | —       | —                                      | 890                                    | 55.76 (56.95)             | 4.69 (4.78)               | 3.60 (3.69)               | 8.41 (8.45)               |

Before extensive study of the synthesized ligands for complexation/quantitative extraction with various cations, it was thought appropriate to examine the complexation behavior of the synthesized ligands with vanadate ion. In practice, appropriately diluted solutions of the ligands and vanadium solution were shaken manually for 5 min. The formation of a complex was evident from instantaneous appearance of a deep-purple coloration in organic layer (thus, chromogenic). To determine the qualitative parameters— $\epsilon_M$  and  $\lambda_{\text{max}}$ , and the quantitative parameter—%*E* and ligand/metal stoichiometry, organic layer was separated, diluted appropriately, and scanned through a UV–visible spectrophotometer against reagent blank. The results were verified by ICP-OES measurements.

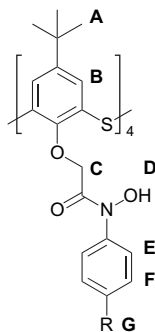
As can be inferred from the complexation results with different ligands (Table 3), the molar absorptivity values for complexes of **5a–f** varies in the range 6350–7300. The high value of molar absorptivity indicates that **5a–f** are extremely sensitive ligands for vanadium and can be used for trace level detection and quantification of vanadium, especially **5f**, which shows a high  $\epsilon_M$  value of 7300 l mol<sup>-1</sup> cm<sup>-1</sup>. This high sensitivity of **5a–f** toward vanadate ions may be attributed to the pre-organization of chelating sites on a stable molecular platform. To the best of our information, this is the highest value reported for any hydroxamic acid based vanadophile. Within

Figure 2. HPLC chromatogram of **5a** [Time (min) vs. Intensity (cps)].

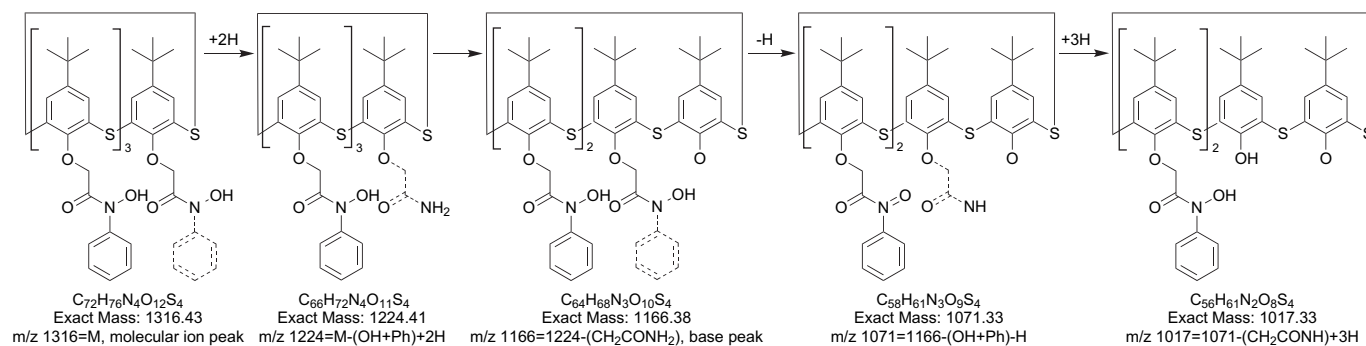
the group **5a–f**, the superiority of **5f** may be accredited to the high inductive and mesomeric effects of the nitro group, which make the N–OH protons more labile, thus facilitating complex formation.

The composition of complexes (e.g., [**5a–f**-<sup>4</sup>(VO<sub>x</sub><sup>+</sup>)<sub>y</sub>]<sup>+m</sup>) was studied by 'slope ratio method' viz. by plotting the graph

Table 2

<sup>1</sup>H NMR and mass data of **5a–f** and vanadate complex of **5a**

| Ligand                                                                      | R               | A (δ)    | B (δ)    | C (δ)    | D (δ)     | E (δ)    | F (δ)    | G (δ)    | m/z (M <sup>+</sup> ) |
|-----------------------------------------------------------------------------|-----------------|----------|----------|----------|-----------|----------|----------|----------|-----------------------|
| <b>5a</b>                                                                   | H               | 1.20 (s) | 7.57 (s) | 4.96 (s) | 10.60 (s) | 7.77 (d) | 7.41 (t) | 7.17 (t) | 1316                  |
| <b>5b</b>                                                                   | Me              | 1.21 (s) | 7.55 (s) | 4.89 (s) | 10.59 (s) | 7.72 (d) | 7.21 (d) | 2.15 (s) | 1372                  |
| <b>5c</b>                                                                   | OMe             | 1.20 (s) | 7.55 (s) | 4.90 (s) | 10.65 (s) | 7.84 (d) | 6.98 (d) | 3.51 (s) | 1436                  |
| <b>5d</b>                                                                   | Br              | 1.20 (s) | 7.58 (s) | 4.90 (s) | 10.65 (s) | 7.70 (d) | 7.58 (d) | —        | 1628                  |
| <b>5e</b>                                                                   | COOH            | 1.24 (s) | 7.58 (s) | 4.93 (s) | 10.72 (s) | 8.02 (d) | 8.04 (d) | —        | 1492                  |
| <b>5f</b>                                                                   | NO <sub>2</sub> | 1.25 (s) | 7.58 (s) | 4.97 (s) | 10.80 (s) | 8.05 (d) | 8.24 (d) | —        | 1496                  |
| [ <b>5a</b> - <sup>4</sup> (VO <sup>3+</sup> ) <sub>2</sub> ] <sup>+2</sup> | H               | 1.21 (s) | 7.56 (s) | 4.96 (s) | —         | 7.75 (d) | 4.41 (t) | 7.18 (t) | —                     |



Scheme 2. Proposed mass fragmentation pattern for **5a**. Dashed (---) portion is the fragment removed.

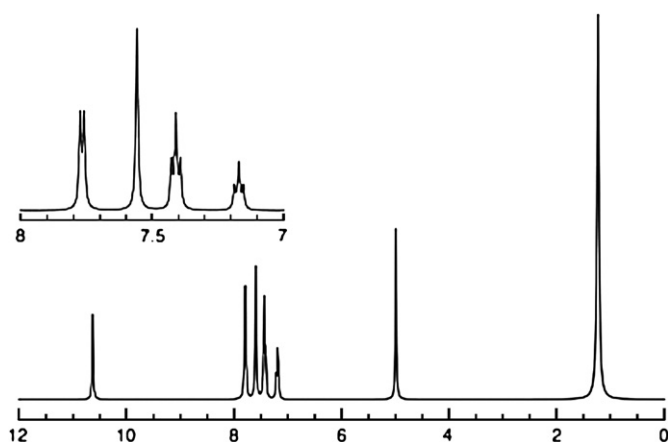


Figure 3. <sup>1</sup>H NMR spectrum of **5a** with all aromatic protons resolved.

of logarithm of distribution coefficient of the metal ( $\log D_m$ ) against the negative logarithm of the ligand concentration ( $-\log[\text{ligand}]$ ) as shown in Figure 4. The extraction was carried out by taking a fixed concentration of vanadium solution in 6 M HCl and varying amounts of ligand.  $D_m$  was calculated by ICP-OES measurements of organic and aqueous phases. The plot of  $\log D_m$  against  $-\log[\mathbf{5a}]$  gave a straight line with slope equal to 1.98, indicating the stoichiometry of the extracted complex to be 1:2 (**5a**/metal). Thus, 1 mol of **5a** co-ordinates with 2 mol of vanadate ions. Similarly, the plots for other ligands **5b–f** showed 1:2 stoichiometry, i.e., the species formed is  $[\mathbf{5a-f}^{-4}(\text{VO}^{+3})_2]^{+2}$ . Further, <sup>1</sup>H NMR spectra of complexes do not show any peak around  $\delta$  value 9–12 suggesting deprotonation of N–OH function of hydroxamic acid group by the vanadate ion, which further supports the proposed mode of complexation.

Table 3  
Results for extraction of vanadium with ligands **5a–f**

| Ligand (L) | $\lambda_{\text{max}}$ (cm <sup>−1</sup> ) | $\epsilon_M$ (l mol <sup>−1</sup> cm <sup>−1</sup> ) | %E  | L/M stoichiometry |
|------------|--------------------------------------------|------------------------------------------------------|-----|-------------------|
| <b>5a</b>  | 520                                        | 6470                                                 | >99 | 1:2               |
| <b>5b</b>  | 516                                        | 6350                                                 | >99 | 1:2               |
| <b>5c</b>  | 521                                        | 6600                                                 | >99 | 1:2               |
| <b>5d</b>  | 520                                        | 6545                                                 | >99 | 1:2               |
| <b>5e</b>  | 524                                        | 7105                                                 | >99 | 1:2               |
| <b>5f</b>  | 525                                        | 7300                                                 | 100 | 1:2               |

M—vanadium.

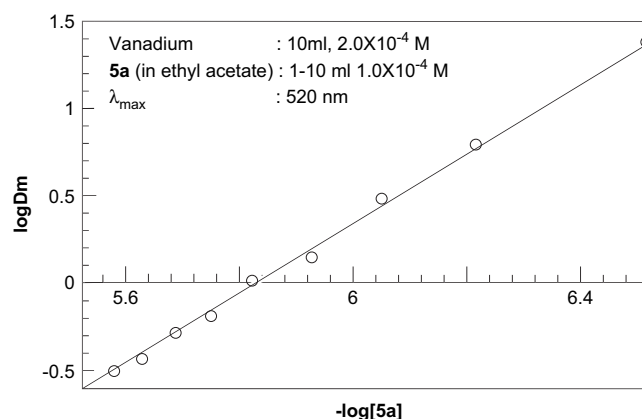


Figure 4. Slope ratio plot for determination of stoichiometry of vanadate complex of **5a**.

## 4. Conclusion

New chromogenic ligands comprising hydroxamic acid units anchored to 1,3-alternate thiocalix[4]arene scaffold were designed, synthesized, and characterized successfully. They were found to be very promising vanadophiles under preliminary observations. The synthesized receptors may also complex other suitable guests by virtue of the bridging sulfide moiety. Extensive studies for evaluation of these ligands as selective/specific agents for various metal ions are underway.

## 5. Experimental

### 5.1. Materials and instrumentation

All the reagents used were of AR grade, procured from Sigma-Aldrich. The reagents were used without further purification. The solvents were dried appropriately wherever required. Melting points were taken in a single capillary tube using a Toshniwal melting point apparatus and are uncorrected. Elemental analysis was carried out on Heraeus CarloEbra 1108 elemental analyzer. FTIR spectra were recorded on Bruker tensor 27 Infrared Spectrophotometer as KBr pellets and expressed in cm<sup>−1</sup>. UV absorption studies were carried out on a JASCO 570 UV/VIS/NIR Spectrophotometer. <sup>1</sup>H NMR spectra were recorded on Bruker DPX-400 AVANCE in DMSO-*d*<sub>6</sub>

with tetramethylsilane as internal standard. Mass measurements were done on Thermo Finnigan TQS Quantum Discovery Mass Spectrometer using electrospray ionization. Thermal studies were carried out on Mettler Toledo DSC 822<sup>o</sup>. Powder XRD analysis was performed on Panalytical X'Pert PRO X-ray Diffractometer. Purity of the synthesized compounds was ascertained on Perkin–Elmer 200 Series Liquid Chromatograph with Thermo Electron Betasil C-18 reversed phase column (3  $\mu$ m particle size, 100 mm long and 3.0 mm internal diameter) maintained at 45  $^{\circ}$ C, mobile phase composition was methanol–0.01% acetic acid (90:10 v/v).

## 5.2. Protocol for extraction of vanadium

For complexation studies, stock solution of ligands ( $1.0 \times 10^{-2}$  M) were prepared by separately dissolving 0.01 mol of each in 1 l of ethyl acetate. The vanadium stock solution ( $1.0 \times 10^{-2}$  M) was prepared by dissolving 0.01 mol of ammonium metavanadate in 5 ml concd HCl and diluting to 1 l with 6 M HCl. The stock solutions were diluted appropriately to obtain working solutions of ( $1.0 \times 10^{-4}$  M) and ( $2.0 \times 10^{-4}$  M) for ligands and vanadium, respectively. For extraction studies, appropriate volumes of ligand and metal solutions were mixed, shaken for 5 min and separated through a separatory funnel, dried with  $\text{MgSO}_4$ , and diluted uniformly. Solutions thus prepared were examined for UV–visible absorptions at suitable wavelengths. The quantitative studies were carried out by ICP-OES measurements at the 309.31 nm emission line for vanadium.

## 5.3. Synthesis

Compounds **1**, **2**, **3**, and **4** were synthesized according to procedures reported in literature with appropriate modifications to simplify the procedures and/or improve yields, employing commonly available/low cost chemicals. Also, the use of hazardous chemical like  $\text{SCl}_2$  was deliberately avoided. Simple precipitation and/or fractional crystallization techniques were preferred over column chromatography for the purpose of purification/isolation/isomeric separation.

### 5.3.1. Modified method for synthesis of thiacalixarene (syn **1**)

A mixture of *p*-*tert*-butyl phenol (64.5 g, 0.43 mol), elemental sulfur  $\text{S}_8$  (14 g, 0.44 mol), and NaOH (8.9 g, 0.22 mol) in super-dry diphenyl ether (100 ml) was stirred for 15 min, heated gradually to 160  $^{\circ}$ C over a period of 1 h and kept at this temperature for further 3 h. Then, the temperature of the reaction mixture was brought down to 80  $^{\circ}$ C and additional sulfur (14 g, 0.44 mol) was added carefully. The temperature was raised to 230  $^{\circ}$ C over a period of 3 h and maintained for further 3 h. The reaction was continuously monitored by TLC [hexane–chloroform 1:1 (v/v)]. The resulting dark brown reaction mixture was cooled to ambient temperature and diluted with cold acetonitrile (250 ml). The precipitates thus produced were of thiacalix[4]arene **1** and were collected by filtration over a sintered glass funnel (preferably G2), and washed with 1 M HCl to remove any traces of alkali. Further purification was achieved

by recrystallization from chloroform. The yield obtained was 74%. The method described is devised by partial modification of two procedures<sup>7,19</sup> reported by Miyano et al. Though one of these methods describes a two step procedure with 83% yield in cyclization step, it employs hazardous  $\text{SCl}_2$  in the first step and the overall yield is  $\sim 62\%$ . Thus, the present method is comparatively more efficient with reduced steps.

### 5.3.2. General method for synthesis of phenyl hydroxylamine (partial reduction)

The nitro derivative (7.5 g, ca. 60 mmol) of choice was dissolved in chloroform (100 ml), added to a solution of  $\text{NH}_4\text{Cl}$  (7.5 gm in 100 ml water) and stirred for 10 min with the aid of magnetic stirrer. Zn powder (10 gm) was then added in small portions (0.3–0.5 g) every 4–5 min until the reduction was complete. After additional stirring of 15 min the contents were allowed to cool to ambient temperature. The organic layer was collected, dried with  $\text{MgSO}_4$ , and concentrated in vacuo until pale yellow crystals of hydroxylamine were observed. The concentrate along with crystals was cooled to  $-10$   $^{\circ}$ C and filtered rapidly over a glass frit under vacuum. The yield was 60–75%. As aromatic hydroxylamines are very unstable in air, they were redissolved in dry chloroform and kept at low temperature (0–4  $^{\circ}$ C) until coupled with acyl chloride.

### 5.3.3. Synthesis of 1,3-*alt* thiacalix[4]arene tetraacetate (syn **2**)

Compound **1** (18 g, 25 mmol) was suspended in dry acetone (500 ml) containing a sixfold excess of anhydrous cesium carbonate (38 g, 150 mmol) and an eightfold excess of ethyl bromoacetate (33.4 g, 22.3 ml, 200 mmol). The mixture was heated under reflux for 6 h. After cooling, the solid residue was filtered and washed with dichloromethane (50 ml) three times. The combined filtrates were evaporated and maintained at 1 mm Hg vacuum and 80  $^{\circ}$ C for 3 h to ensure complete removal of unchanged ethyl bromoacetate. From the mixture of conformational isomers, the 1,3-alternate isomer **2** was separated by fractional crystallization from ethanolic solution (reported procedure<sup>5</sup> employs column chromatography for separation of conformational isomers). It was recrystallized from chloroform–ethyl acetate mixture (4:1 v/v). Yield obtained was 72%.

### 5.3.4. Synthesis of 1,3-*alt* thiacalix[4]arene tetra-acid (syn **3**)

To a solution of **2** (18 g, 17 mmol in 1000 ml ethanol) was added KOH (9 g in 500 ml 50% ethanol) and the mixture was refluxed on a water bath with rapid stirring for 2 h. The mixture was cooled to ambient temperature and acidified to pH=1 using 1 M HCl to precipitate compound **3** in quantitative yield (98%). The precipitates were filtered, washed with water, and dried in vacuo.

### 5.3.5. Synthesis of 1,3-*alt* thiacalix[4]arene tetraacyl chloride (syn **4**)

Compound **3** (1 g, 1 mmol) was suspended in a 20-fold excess of oxalyl chloride (1.3 ml, ca. 20 mmol) and refluxed until the reaction mixture became homogeneous (ca. 30 min). The contents were cooled and dry chloroform was added. To



remove excess oxalyl chloride vacuum distillation was repeated three times with the addition of dry chloroform after each distillation. Finally, the yellowish product obtained was redissolved in chloroform and coupled with previously prepared hydroxylamine derivative.

#### 5.3.6. Synthesis of **5a** (general method for synthesis of **5a–f**)

N-Phenyl hydroxylamine (ca. 4.5 mmol in 100 ml chloroform) was covered with saturated solution of  $\text{NaHCO}_3$  (150 ml) and a cold solution of **4** (ca. 1 mmol in dry chloroform) was added dropwise directly into chloroform layer with slow stirring by means of magnetic needle. After the addition was complete (ca. 30 min), the stirring was continued until the liberated HCl was completely neutralized. The organic layer was collected and washed with water and concentrated to 1/4th volume with a flash evaporator. Dropwise addition of acetonitrile to this concentrate afforded off-white to pale brown colored precipitates of the desired compound. The precipitates were filtered over a sintered glass funnel and purified by recrystallization from chloroform–acetone (2:3 v/v) mixture. The yield obtained for **5a** was 70%. The characterization details along with yields for all six compounds **5a–f** are listed in Tables 1 and 2.

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#### Supplementary data

FTIR, Mass, DSC, and PXRD spectra of **5a**. Supplementary data associated with this article can be found in the online version, at [doi:10.1016/j.tet.2007.12.048](https://doi.org/10.1016/j.tet.2007.12.048).

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