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ORIGINAL ARTICLE

A facial microwave-assisted synthesis, spectroscopic characterization and preliminary complexation studies of calix[4]pyrroles containing the hydroxamic-acid moiety

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Abstract The synthesis, spectroscopic characterization and preliminary complexation properties of functionalized calix[4]pyrroles are described. To date, two generalized preparative approaches have been pursued (i) modifying the basic pyrrole-plus-ketone synthesis of calix[4]pyrrole by using microwave irradiation protocol, (ii) the basic *meso*-tetra(methyl) *meso*-tetra(p-nitrophenyl) calix[4]pyrrole skeleton was functionalized to give hydroxamic acids, especially in the *meso*-position of the macrocycles. The structures of novel calix[4]pyrrole hydroxamic acid derivatives were confirmed on the basis of various physicochemical techniques such as elemental analysis, FT-IR, ^{1}H NMR and FAB-Mass. The results of preliminary studies on the extraction of vanadium (V) with the host calix[4]pyrrole hydroxamic acids were elucidated by significant examination of UV–Vis spectroscopy and ICP-AES. Single crystal structure of basic *meso*-tetra(methyl) *meso*-tetra (p-nitro phenyl) calix[4]pyrrole moiety has also been reported.

Keywords Microwave synthesis · Calix[4]pyrrole · Hydroxamic acid · Crystal structure · Liquid–liquid extraction · Vanadium

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Introduction

Design, synthesis, and development of novel macrocyclic molecules are currently receiving importance in the field of supramolecular chemistry. The replacement of calixarene phenolic unit(s) by heterocycle(s), constitute hetero-calixarenes classified according to the category of the subcycle(s). The nature of subcycle(s) reveals electron rich or deficient cavity and varied transformation profile for hetero-calixarene systems. Calixpyrrole [1]—belongs to the family of heterocalixarene [2]. This hetero-calixarene possesses unique supra-molecular characteristics and presents remarkable chemical and physicochemical properties as well as wide application possibilities. Calixpyrrole, as the name implies, offer a cup-shaped skeleton, in which four pyrrole hydrogen bond donors are ideally pre-organized for anions [3–5] and ion pair binding [6]. Thus calixpyrrole derivatives exhibit many novel properties and uncommon chemical behavior when compared with the "classical" calixarenes.

The host properties of calixpyrroles continue to draw research interests due to their potential application as neutral substrates [7, 8], optical sensors [9] and anion transporting agents [10]. Moreover, they have been applied in many aspects, such as biologically active species [11], electro-analytical chemistry [12], colorimetry [13] as well as they have found novel application as cobalt (II) calix[4]pyrrole complex which was screened for its capability to be used as a catalyst in the epoxidation reaction [14]. The hybrid calixpyrroles are being used for biological applications such as anion sensing and antiviral drug delivery due to their amphiphilic binding characteristics [15]. A hybrid calixpyrrole chelating resin has been used for sorption studies of some noble metals like Au(III), Ag(I), Pt(IV), Pd(II) and other metal cations including

Cu(II), Pb(II) and Cd(II) [16–18]. Functionalized calix[4]pyrroles are also distinguished as solid supports for the separation of anionic substrates [19]. They also show promising quality as calix[4]pyrrole modified silica gels for separation of inorganic anions, amino acids, phenols, benzene carboxylic acids, some medicines [20] and lastly for selective separation and preconcentration of Ag^+ and Tl^+ by liquid liquid extraction [21].

Recently, various efforts have been made for the development of milder system for the synthesis of parent calixpyrrole skeleton [22–25]. The *meso*-substituted calix[4]pyrrole has been prepared by condensation of pyrrole with various ketones in the presence of aqueous hydrochloric acid or methanesulfonic acid in alcohol [26–28]. Reported traditional methods suffer from various disadvantages such as large amount of solvent, long reaction time, acid neutralization, low yield and inconvenience of handling (tedious work-up). Thus, the continuing efforts drive to develop more economical and environment friendly chemical process (green chemistry approach) has spurred chemists to seek methods for running reactions with less waste.

In recent years, microwave assisted organic synthesis has become an increasingly popular technique in academic and industrial research laboratories, due to certain advantages like (i) faster reaction times, (ii) reduced solvent volumes, (iii) higher yields, (iv) improved purity, (v) ease of work up after the reaction, and (vi) cleaner chemistries (eco-friendly reaction conditions) [29–31]. Herein, we report the synthesis of *meso*-substituted calix[4]pyrroles using selected aliphatic/aromatic ketones and pyrrole catalysed by concentrated hydrochloric acid under microwave irradiation for the first time. The reaction gives excellent yield (>50–90%) with shorter reaction times (<1–10 min) and does not required harsh conditions.

Calix[4]pyrrole has three potential sites (i) the C-rim, (ii) the N-rim, and (iii) the *meso*-position, which can be used for the introduction of different kinds of fictionalizations. Herewith, we have introduced the hydroxamic acid moiety, as a functional group at the *meso* position of the calix[4]pyrrole. Introduction of the hydroxamic acid group in the macrocycle may enhance the complexing ability towards the metal ions. Hydroxamic acids are versatile metal extractants that have been the subjects of large number of physicochemical investigations because of their wide applications in analytical [32], agriculture [33], and biological fields [34]. In recent years few macrocycles bearing hydroxamic acid as a functional group have been synthesized and used for complexation studies [35–40]. However, so far no work is reported on the synthesis of calix[4]pyrrole containing hydroxamic acid as a chelating-moiety. Thus the incorporation of hydroxamate groups in calix[4]pyrrole can offer additional opportunities to modify the selectivity parameter for binding cations. In this paper we are reporting the single crystal X-ray of the *meso*-tetra(methyl) *meso*-tetra(p-nitrophenyl) calix[4]pyrrole confirming its 1,2 alternate conformation in solid state. It is also interesting to note that the calix-moiety encapsulate two molecules of acetone on either side by strong C–H···O interaction. We have synthesized and characterized six novel tetra-functionalized calix[4]pyrrole hydroxamic acids as chelating site attached at the *meso*-position which were obtained from the basic *meso*-tetra(methyl) *meso*-tetra(p-nitrophenyl) calix[4]pyrrole skeleton. We studied their preliminary analytical application for the liquid–liquid extraction and determination of vanadium (V) by UV–Vis spectroscopy and ICP-AES.

Experimental section

Materials and instrumentation

All the reagents used were of AR grade, purchased from Sigma-Aldrich, Fluka and were used without further purification. Melting points were taken in a single capillary tube using a VEEGO (Model No: VMP-DS, India) melting point apparatus and were uncorrected. Elemental analysis was done on Perkin Elmer, Series II, 2400 elemental analyzer. Microwave synthesis work was carried out using a Kenstar OM-18 MSP domestic microwave oven. FTIR spectra were recorded on Bruker tensor 27 Infrared spectrophotometer as KBr pellets and expressed in cm^{-1}. ^1H NMR spectra were recorded in $CDCl_3$ on a Bruker-ARX 500 instrument, using tetramethylsilane as internal standard. Mass Spectra were recorded on JEOL SX 102/DA 6000 mass spectrometer using Xenon/argon (6 KV, 10mA) as the FAB-gas. The accelerating voltage was 10 KV and the spectra were recorded at room temperature. UV–Vis absorption studies were carried out on a JASCO 570 UV/VIS/NIR spectrophotometer using 10 mm quartz cells.

Plasma scan model 710 sequential inductively coupled plasma atomic emission spectrometer (ICP-AES) with plasma scan multitasking computer and peristaltic pump was used. The following operating conditions were set for ICP-AES.

Rf 27.12 MHz; incident power, 2,000 W; GMK nebulizer; sample concentration, 1 ppm; RF power, 5 W; observation height, 14 mm; argon coolant flow rate, 9.71 min^{-1}; argon carrier flow rate, 0.81 min^{-1}; Intergraph period, 10 s; resolution, 0.004 nm; peristaltic pump flow rate, 1 mL min^{-1}; wavelength, 309.31 nm.

The synthesis of *meso*-substituted calix[4]pyrroles **(3a–g)** by *conventional method*

Parent *meso*-substituted calix[4]pyrrole skeletons **(3a–g)** were synthesized by the acid catalyzed condensation

reaction of pyrrole **(1)** and aliphatic/aromatic ketones **(2a-g)** [26–28, 41].

Modified synthesis of *meso*-substituted calix[4]pyrroles **(3a–g)** by *Microwave Irradiation*

*Compound **3a***

A mixture of pyrrole **1** (1 mL, 0.015 mole), acetone **2a** (1 mL, 0.015 mole) and conc. hydrochloric acid (0.1 mL) in ethanol (5.0 mL) were exposed to microwave irradiation for 0.5 min at 0% output. After completion of the reaction, a white solid material was obtained which was washed by little amount of ethanol and further recrystallized from acetone to give pure product for analysis.

3a: Yield 97%. mp: 300 °C; IR (KBr) *v*: 3,402 (pyrrole NH), 3,100 (β-pyrrole C–H), 2,953, 2,868, 1,577, 1,450, 1,419, 1,226, 1,041, 764; ^{1}H NMR ($CDCl_3$) δ: 7.12 (s, 4H, pyrrole NH), 5.89 (br, d, 8H, pyrrole-βH), 1.48 (S, 24H, CH_3); MS m/z, M+1: 429; Anal. calcd. for $C_{28}H_{36}N_4$: C 78.46, H 8.47, N 13.07; Found: C 77.96, H 8.10, N 12.97.

*Compound **3b***

A mixture of pyrrole **1** (1 mL, 0.015 mole), cyclohexanone **2b** (1.5 mL, 0.015 mole) and conc. hydrochloric acid (0.1 mL) in ethanol (5.0 mL) were exposed to microwave irradiation for 1 min at 0% output. After completion of the reaction, off white solid material obtained, was washed by little amount of ethanol and further recrystallized from acetone to give pure product for analysis.

3b: Yield 95%. mp: 278 °C; IR (KBr) *v*: 3,437 (pyrrole NH), 3,213 (β-pyrrole C–H), 2,970, 2,709, 1,560, 1,405, 1,410, 1,251, 698; ^{1}H NMR ($CDCl_3$) δ: 7.05 (s, 4H, pyrrole NH), 5.84 (br, d, 8H, pyrrole-βH), 1.38–1.68 (m, 24H, cyclohexyl), 1.88–2.12 (m, 16H, cyclohexyl); MS m/z, M+1: 589; Anal. calcd. for $C_{40}H_{52}N_4$: C 81.56, H 8.9, N 9.51; Found: C 81.20, H 7.98, N 9.48.

*Compound **3c***

A mixture of pyrrole **1** (1 mL, 0.015 mole), 3-hexanone **2c** (1.5 mL, 0.015 mole) and conc. hydrochloric acid (0.1 mL) in ethanol (5.0 mL) were exposed to microwave irradiation for 1 min at 0% output. After completion of the reaction, a light yellow precipitates separated which was washed by little amount of ethanol and further recrystallized from acetone to give the pure product for analysis.

3c: Yield 85%. mp: 225 °C; IR (KBr) *v*: 3,443 (pyrrole NH), 3,111 (β-pyrrole C–H), 2,955, 1,576, 1,415, 1,410, 1,251, 1,201, 1,045, 767; ^{1}H NMR ($CDCl_3$) δ: 7.26 (s, 4H, pyrrole NH), 5.89 (br, d, 8H, pyrrole-βH), 0.97–2.17 (48H, overlapping of all hexyl proton); MS m/z, M+1: 598; Anal. calcd. for $C_{40}H_{52}N_4$: C 80.48, H 10.13, N 9.39; Found: C 80.20, H 9.95, N 9.10.

*Compound **3d***

A mixture of pyrrole **1** (1 mL, 0.015 mole), 4-hepatanone **2d** (1.7 mL, 0.015 mole) and conc. hydrochloric acid (0.1 mL) in ethanol (5.0 mL) were exposed to microwave irradiation for 1.5 min at 0% output. After completion of the reaction, a solid material separated (compound **3d**) which was washed by little amount of ethanol and further recrystallized from acetone to give the pure product for analysis.

3d: Yield 80%. mp: 245 °C; IR (KBr) *v*: 3,418 (pyrrole NH), 3,329 (β-pyrrole C–H), 2,978, 1,560, 1,420, 1,396, 1,251, 1,065, 740; ^{1}H NMR ($CDCl_3$) δ: 7.12 (s, 4H, pyrrole NH), 5.94 (br, d, 8H, pyrrole-βH), 1.5–1.89 (32H, overlapping of heptayl proton), 0.95 (d, 24H, CH_2); MS m/z, M+1: 654; Anal. calcd. for $C_{44}H_{68}N_4$: C 80.93, H 10.50, N 8.58; Found: C 80.20, H 9.98, N 8.39.

*Compound **3e***

A mixture of pyrrole **1** (1 mL, 0.015 mole), 3-methyl 2-butanone **2e** (1.3 mL, 0.015 mole) and conc. hydrochloric acid (0.15 mL) in ethanol (5.0 mL) were exposed to microwave irradiation for 2 min at 0% output. After completion of the reaction, a light brown precipitates separated by filtration which was washed by little amount of ethanol to give white crystalline powder, and recrystallized from acetone to give the pure product for analysis.

3e: Yield 75%. mp: 168 °C; IR (KBr) *v*: 3,422 (pyrrole NH), 3,099 (β-pyrrole C–H), 2,934, 1,209, 1,069, 774; ^{1}H NMR ($CDCl_3$) δ: 7.20 (s, 4H, pyrrole NH), 5.88 (br, d, 8H, pyrrole-βH), 2.23 (m, 4H, CH, *i*-propyl), 1.34 (s, 12H, CH_3), 0.85 (d, 24H, CH_3, *i*-propyl); MS m/z, M+1: 540; Anal. calcd. for $C_{36}H_{52}N_4$: C 79.95, H 9.69, N 10.36; Found: C 79.80, H 9.48, N 10.09.

*Compound **3f***

A mixture of pyrrole **1** (7.5 mL, 0.111 mole), p-acetamidoacetophenone **2f** (19.62 g, 0.111 mole) and conc. hydrochloric acid (1.0 mL) in methanol (25 mL), were subsequently subjected to microwave irradiation for 8 min at 0% output with 2 min. intervals. After completion of the reaction, a solid pale pink powder was removed by filtration, washed with methanol, and recrystallized from DMF to give the pure product for analysis.

3f: Yield 40%. mp: >320 °C; IR (KBr) *v*: 3,379 (pyrrole NH), 3,117 (β-pyrrole C–H), 2,979, 1,648, 1,602, 1,539, 1,408, 1,318, 1,264, 841, 767, 664; ^{1}H NMR (DMSO) δ: 10.03 (s, 1H, pyrrole NH), 9.75 (s, 1H, pyrrole NH), 9.63

(s, 2H, pyrrole NH), 9.84 (4H, s, Ar–NH), 7.40 (8H, d, ArH), 7.06 (4H, d, ArH), 6.87 (4H, d, ArH), 5.83 (br, d, 6H, pyrrole-βH), 5.45 (d, 2H, pyrrole-βH), 1.99 (s, 12H, $COCH_3$), 1.77 (s, 12H, CH_3); MS m/z: 905; Anal. calcd. for $C_{56}H_{56}N_8O_4$: C 74.31, H 6.24, N 12.38; Found: C 73.98, H 6.09, N 12.29.

*Compound **3g***

A mixture of pyrrole **1** (7.5 mL, 0.111 mole), p-nitroacetophenone **2g** (18.35 g, 0.111 mole) and conc. hydrochloric acid (1.0 mL) in ethanol (25 mL) were exposed to microwave irradiation for 10 min at 0% output with 2 min intervals. After completion of the reaction, a deep reddish brown material was removed by filtration, thoroughly washed with acetone to give a yellow powder. Crystallization from THF gave light yellow crystals.

3g: Yield 35%. mp: >320 °C; IR (KBr) *v*: 3,410 (pyrrole NH), 3,117 (β-pyrrole C–H), 2,986, 2,934, 1,928, 1,809, 1,599, 1,513, 1,348, 1,218, 1,110, 859, 776, 703, 528; ^{1}H NMR ($CDCl_3$) δ: 7.32 (s, 4H, pyrrole NH), 8.13 (8H, d, ArH), 7.29 (8H, d, ArH), 5.89 (d, 4H, pyrrole-βH), 5.84 (d, 4H, pyrrole-βH), 1.96 (s, 12H, CH_3); MS m/z, M+1: 857; Anal. calcd. for $C_{48}H_{40}N_8O_8$: C 67.28, H 4.71, N 13.08; Found: C 66.98, H 4.60, N 12.92.

General procedure for the synthesis of new hosts (**5a-f**) by *conventional method*

The synthesis of calix[4]pyrrole hydroxamic acids involved the following steps:

*Partial reduction of meso-tetra(methyl) meso-tetra (p-nitrophenyl) calix[4]pyrrole (NPC4P) **3g** to obtain hydroxylamine calix[4]pyrrole **4** (HAC4P)*

To a mixture of 2 g (1 mmole) NPC4P **3g** in 30 mL THF:$CHCl_3$ (1:9 v/v), 200 mL water and 5 g of ammonium chloride were added. The reaction mixture was stirred with gradual addition of Zn-powder (6 g) in small increments over a period of 30 min. The temperature of the reaction mixture was maintained between 55 and 60 °C throughout the addition of Zn-dust. Stirring was continued for another 30 min. The organic layer was separated and washed with water (3 × 25 mL) which was immediately reacted with the aromatic acid chlorides. Evaporation of the organic layer afforded HAC4P **4** in 65% yield.

Preparation of aromatic acid chlorides (general method)

All acid chlorides used in this study were prepared by the action of excess of thionyl-chloride on the corresponding aromatic acids (benzoic acid, p-nitrobenzoic acid, o/p-chlorobenzoic acid, phenylacetic acid, cinnamic acid). After refluxing the solution for about 5 h over the steam bath, excess thionyl-chloride was distilled off under reduced pressure to afford acid chlorides in quantitative yields (85–90%). Except p-nitrobenzoyl chloride all other chlorides were liquid and stored under vacuum until use.

*The synthesis of new hosts calix[4]pyrrole hydroxamic acids **(5a–f)***

A solution of HAC4P **4** (0.65 mmol) in $CHCl_3$ was taken in a 500 mL flat bottom flask containing a fine suspension of 4.87 g $NaHCO_3$ in 25 mL water. The temperature of the heterogeneous mixture was maintained at 0–5 °C by external cooling with ice. 2.6 mmol of acid-chloride (benzoylchloride, p-Nitro-benzoylchloride, phenyl-acetyl-chloride, cinnamoylchloride, p-chloro-benzoylchloride, and o-chloro-benzoylchloride) was added dropwise in 10 mL $CHCl_3$ over a period of 40 min with continuous stirring during addition. After the addition was complete, the mixture was further stirred for 2 h at 0–5 °C. The reaction mixture was then brought to room temperature and solvent was distilled under vacuum to get the crude product. It was recrystallized from ethyl acetate and methanol (75:25, v/v) medium to yield 50–65% of pure calix[4]pyrrole hydroxamic acids **(5a–f)**.

5a; Yield 50%, mp 180 °C; IR (KBr) *v*: 3,402 (pyrrole N–H and –OH), 1,518, 859. ^{1}H NMR ($CDCl_3$), δ: 7.284 (s, 4H, pyrrole NH), 5.881 (d, 4H, pyrrole-βH), 5.842 (d, 4H, pyrrole-βH), 7.792 (d, 8H, ArH), 7.623 (d, 8H, ArH), 7.503 (d, 8H, ArH), 7.426 (d, 12H, ArH), 8.803 (s, 4H, N–OH), 1.961 (s, 12H, CH_3); MS m/z, M+1; 1,217; Anal.calcd.for $C_{76}H_{64}O_8N_8$: C 75.02, H 5.26, N 9.21; Found: C 74.92, H 5.3, N 9.19.

5b; Yield 59%, mp 198 °C; IR (KBr) *v*: 3,402 (pyrrole N–H and –OH), 1,518, 1,349 (NO_2), 859. ^{1}H NMR ($CDCl_3$) δ: 7.294 (s, 4H, pyrrole NH), 5.840 (d, 4H, pyrrole-βH), 5.892 (d, 4H, pyrrole-βH), 7.262 (d, 8H, ArH), 7.628 (d, 8H, ArH), 7.615 (d, 8H, ArH), 7.767 (d, 8H, ArH), 8.809 (s, 4H, N–OH), 1.966 (s,12H, CH_3); MS, m/z, M+1: 1,397; Anal. calcd. for $C_{76}H_{60}O_{16}N_{12}$: C 65.33, H 4.3, N 12.03; Found: C 66.13, H 4.3, N 11.98.

5c; Yield 58%, mp 178 °C; IR (KBr) *v*: 3,408 (pyrrole NH and –OH), 1,620, 1,450, 900. ^{1}H NMR ($CDCl_3$) δ: 7.29 (s, 4H, pyrrole NH), 5.89 (d, 4H, pyrrole-βH), 5.84 (d, 4H, pyrrole-βH), 7.42 (d, 8H, ArH), 7.5 (d, 8H, ArH), 7.66 (q, 8H, ArH), 7.725 (d, 12H, ArH), 8.81 (s, 4H, N–OH), 3.75 (s, 8H, CH_2), 1.99 (s, 12H, CH_3); MS,m/z, M+1, 1,274; Anal. calcd. for $C_{80}H_{72}O_8N_8$: C 75.47, H 5.66, N 8.81; Found: C 74.95, H 5.59, N 8.78.

5d; Yield 60%, mp 189 °C; IR (KBr) *v*: 3,415 (pyrrole NH and –OH), 1,620, 1,450, 900. ^{1}H NMR ($CDCl_3$) δ: 7.292 (s, 4H, pyrrole NH), 5.891 (d, 4H, pyrrole-βH), 5.842

(d, 4H, pyrrole-βH), 7.426 (d, 8H, ArH), 7.509 (d, 8H, ArH), 7.663 (q, 8H, ArH), 7.821 (d, 12H, ArH), 4.761 (d, 4H, CH=CH), 4.682 (d, 4H, CH=CH), 1.96 (s, 12H, CH_3), 8.801 (s, 4H, N–OH); MS, m/z, M+1, 1,369; Anal. calcd. for $C_{80}H_{68}O_8N_8$: C 75.71, H 5.36, N 8.83; Found: C 74.92, H 5.30, N 8.79.

5e; Yield 55%, mp 195 °C. IR (KBr) ν: 3,402 (pyrrole N–H and –OH), 1,518, 859. ^{1}H NMR ($CDCl_3$) δ: 7.294 (s, 4H, pyrrole NH), 5.891 (d, 4H, pyrrole-βH), 5.842 (d, 4H, pyrrole-βH), 7.361 (d, 8H, ArH), 7.621 (d, 8H, ArH), 7.527 (d, 8H, ArH), 7.803 (d, 8H, ArH), 8.803 (s, 4H, N–OH), 1.966 (s, 12H, CH_3); MS, m/z, M+1, 1,213; Anal. calcd. for $C_{76}H_{60}O_8N_8Cl$: C 75.02, H 5.26, N 9.21; Found: C 74.92, H 5.3, N 9.19.

5f; Yield 52%, mp 190 °C; IR (KBr) ν: 3,410 (pyrrole N–H and –OH), 1,620, 1,450, 900. ^{1}H NMR ($CDCl_3$) δ: 7.294 (s, 4H, pyrrole NH), 5.892 (d, 4H, pyrrole-βH), 5.842 (d, 4H, pyrrole-βH), 7.361 (d, 8H, ArH), 7.622 (d, 8H, ArH), 7.529 (d, 12H, ArH), 7.862 (q, 4H, ArH), 8.803 (s, 4H, N–OH), 1.992 (s, 12H, CH_3); MS, m/z, M+1: 1,213; Anal. calcd. for $C_{76}H_{60}O_8N_8Cl$: C 75.25, H 4.95, N 9.24; Found: C 75.10, H 4.92, N 9.21.

X-ray structure determination

X-ray data were collected at 293(2) K on a Bruker diffractometer using Mo Kα X-ray (0.71069 Å) source and a graphite monochromator. The unit cell dimensions were obtained from a least-square fit to setting angles of 25° reflections. Psi scan absorption corrections were applied. The structures were solved by direct methods using CRYSTAL STRUCTURE and refined by full-matrix least square method using SHELXL97. A summary of crystallographic relevant data is given in Table 2.

General course of action for the liquid liquid extraction of Vanadium (V)

For complexation studies, stock solutions of new hosts **(5a–g)** (0.1%, $\approx 10^{-4}$ M) were prepared by separately dissolving 0.1 g of each in 100 mL of ethyl acetate. Standard vanadium stock solution (100 μg mL^{-1}) was prepared by dissolving 0.229 g of ammonium metavanadate (NH_4VO_3) in a minimum amount of concentrated HCl just to solubilize the ammonium meta-vanadate (NH_4VO_3) and then make up 1 L with Millipore Milli-Q water and was standardized spectrophotometrically [42]. Working solution was subsequently prepared by appropriate dilution of the stock solution.

An aliquot of sample solution containing 2–20 μg of vanadium (V) was transferred into a 25 mL separatory funnel and sufficient amounts of concentrated HCl and Millipore Milli-Q water were added to maintain the appropriate molarity (2–7 M) in a total volume of aqueous phase of 10 mL. The mixture was shaken with 8 mL of 0.1% ($\approx 10^{-4}$ M) ligands **(5a–f)** in ethyl acetate. The organic extract was separated, dried over $MgSO_4$ and transferred into a 10 mL volumetric flask. To ensure complete recovery, the extraction was repeated with 2 mL of ligands **(5a–f)**. The combined extracts and washings were diluted to the mark (10 mL) with ethyl acetate. The absorbance of the organic phase was measured against the reagent blank at suitable wavelengths.

The concentration of the metal ion extracted into the organic phase $[VO_2^+]_{(org)}$ as complex was estimated by $[VO_2^+]_{(org)} = [VO_2^+]_{(aq,int)} - [VO_2^+]_{(aq)}$, where $[VO_2^+]_{(aq,int)}$ is the initial concentration of the metal ion in the aqueous phase.

The percent extraction (%E), was calculated by

$$\%E = \left[VO_2^+\right]_{(org)} / \left[VO_2^+\right]_{(aq,int)} \times 100$$

The extracted vanadium (V) complex in ethyl acetate after appropriate dilution was also determined by ICP-AES.

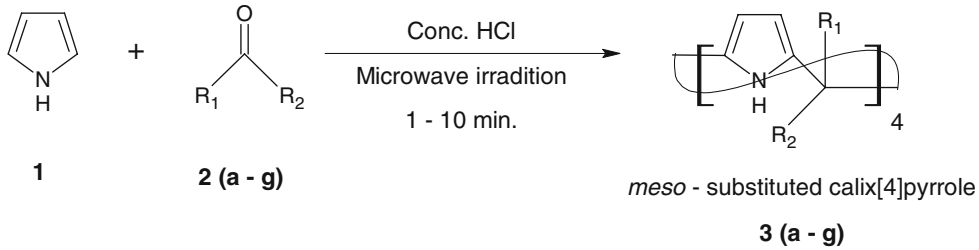
Result and discussion

Synthesis and spectroscopic characterization

A new synthetic protocol has been developed for synthesizing parent *meso*-substituted calix[4]pyrrole macrocycles and are being presented in this article for the first time. Scheme 1 represents the general route for the construction of *meso*-substituted calix[4]pyrrole **(3a–g)** by acid catalyzed cyclo-condensation of pyrrole **(1)** and ketones **(2a–g)**. The selected reaction data obtained from model compounds **3a–g** are illustrated in Table 1 according to different experimental protocols. The process involves microwave irradiation to a mixture containing the pyrrole **1** and ketones **2a–g** with a catalytic amount of concentrated HCl for 1–10 min. The corresponding traditional thermal reaction needs minimum 2–22 h. All the products **(3a–g)** were fully characterized by their spectral data and element analysis. Among these macrocycles **3a–g,** compound **3g** was further determined by X-ray crystal diffraction analysis. The details of data collection and structure refinement are listed in Table 2.

In the IR spectra a strong N–H stretching peak appeared around 3,400–3,450 cm^{-1} of **3a–g**. We carefully analyzed ^{1}H NMR spectra of **3a–e** (aliphatic) and **3f**, **3g** (aromatic). The ^{1}H NMR spectrum of compounds **3a–e** and **3g** displayed a broad singlet peak at around 7.0 ppm which was assigned to the four pyrrolic N–H protons, a doublet nearby 5.8 ppm were assigned to the eight pyrrole ring β-protons. Compound **3a** gives sharp singlet at 1.48 ppm assigned to

Scheme 1 Modified protocol for the synthesis of *meso*-substituted calix[4]pyrroles **(3a–g)** via microwave technique



3a R_1= - CH_3, R_2= - CH_3 **3b** Cyclohexyl **3c** R_1= - CH_2CH_3, R_2= - $CH_2CH_2CH_3$

3d R_1= - $CH_2CH_2CH_3$, R_2= - $CH_2CH_2CH_3$ **3e** R_1= - CH_3, R_2= - $CH(CH_3)_2$

3f R_1= - CH_3, R_2= - $C_6H_4NHCOCH_3$ **3g** R_1= - CH_3, R_2= - $C_6H_4NO_2$

Table 1 Comparison of reaction-time, yield, and melting point of macrocycles **(3a–g)** under classical and microwave conditions

Product	Reaction time		Yield (%)		Melting point (°C)	
	Traditional method[a] (h)	Microwave technique (min)	Traditional method[a]	Microwave technique	Traditional method[a]	Microwave technique
3a	2	0.5	85	97	>300	>300
3b	0.5	1	95	95	276	275–278
3c	2	1	40	85	225	225–227
3d	–	1.5	–	80	–	245
3e	3	2	62	75	168	166–168
3f	22	8	19.7	40	>320	>300
3g	22	10	15.6	35	>320	>300

[a] Reported in literature [22–28, 41]

the eight bridge methyl groups. In the ^{1}H NMR spectrum of **3b,** two multiplets were seen in between 1.2–2.2 ppm for bridge cyclohexyl group. Compound **3c** and **3d** displayed a broad peak between 0.97–2.17 and 1.5–1.89 ppm due to overlapping of all protons of *meso*-hexyl group and heptayl group respectively. In addition compound **3d** displayed one singlet at 0.95 ppm for bridge –CH_2 group. Compound **3e** gave one multiplet at 2.23 ppm, singlet at 1.34 ppm, and one doublet at 0.85 ppm for –CH of *iso*-propyl, four bridge methyl and methyl protons of *iso*-propyl group correspondingly. Compound **3g** exhibited two doublets at 8.13, 7.29 ppm for aromatic protons of the ring attached at the *meso*-position. Compound **3f** showed four singlets, one at 10.03 ppm for single proton of pyrrolic NH, 9.75 ppm for one proton of other pyrrolic NH, 9.63 ppm for two remaining pyrrolic NH protons, and 9.84 ppm for four proton of aromatic amide linkage (Ar–NH). In addition, six pyrrole ring β-protons and two pyrrole ring β-protons appeared at 5.83, 5.45 ppm respectively. Similarly two singlets were obtained at 1.99, 1.77 ppm for –$COCH_3$ and methyl protons of *meso*-position respectively.

The results obtained from elemental analysis, FTIR, ^{1}H NMR and mass data of *meso*-substituted calix[4]pyrrole macrocycles **(3a–g)** match with those of previously reported [22–28, 41]. Thus, microwave irradiation protocol is useful as an alternative to the current available traditional procedures [1]. Analysis of selected reaction data (see Table 1) obtained from model compounds **(3a–g)** confirms the following excellent facts;

(a) The *meso*-substituted calix[4]pyrroles (Particular **3f**, **3g**) have been synthesized after 20–22 h by traditional heating with fairly moderate yields (between 15 and 19%) [41]. Under microwave irradiation, excellent yields (between 35 and 40%) were obtained after just 8–10 min.

(b) One of the goals of "green chemistry" is to avoid or to reduce the use of solvents in organic chemistry. When microwave irradiation was applied, less solvent was required for conducting cyclo-condensation acid catalyzed by concentrated HCl.

(c) In general, the cyclo-condensation worked well with aliphatic ketones compared to aromatic ketones, in term of time and yield due to less steric hinderance.

(d) There is rudimentary difference between microwave irradiation and conventional heating; conventional

Table 2 Summary of crystallographic data for **3g**

Identification code	Compound **3g**
Chemical formula	$C_{54}H_{52}N_8O_{10}$
Formula weight	973.14
Crystal color	Yellow
Crystal size (mm^3)	0.38 × 0.33 × 0.29
Temperature (K)	100
Crystal system	Triclinic
Space group	P − 1
a(Å)	10.713(3)
b(Å)	10.799(3)
c(Å)	11.378(3)
$\alpha(^\circ)$	97.219(5)
$\beta(^\circ)$	104.944(5)
$\gamma\ (^\circ)$	99.179(5)
Z	1
V($Å^3$)	1236.2(6)
Density (Mg/m^3)	1.307
Absorption coefficient (mm^{-1})	0.092
F (000)	434
Reflections collected	7,353
Independent reflections	3,878 [R(int) = 0.0144]
Number of parameters	512
S (Goodness of fit) on F^2	1.031
Final R1, wR2 ($I > 2\sigma(I)$)	0.0645/0.1601
Weighted R1, wR2 (all data)	0.0856/0.1759
Largest diff. peak and hole (e $Å^{-3}$)	0.337 and −0.266
CCDC	638249
(Cambridge crystallographic Data centre No)	

heating is an inward heat transfer (from the heating device, e.g., the wall of the reactors for jacketed tanks, to the medium) while in microwave irradiation, the thermal power is generated in situ due to the interaction of polar molecules or ionic species with the electric field. Physical acceleration (higher temperature) and chemical activation (enhancement in dipole moment) happens using microwaves, which reduce reaction time and enhance yields in comparison with traditional reflux reaction conditions.

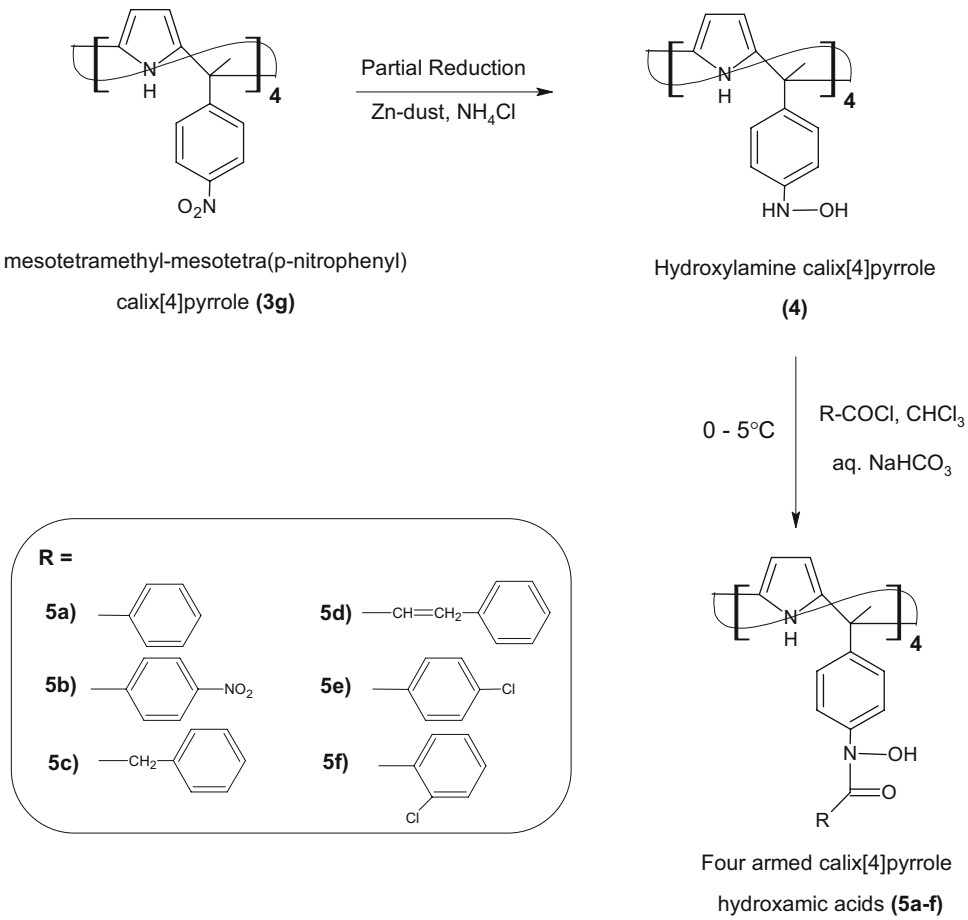
Calix[4]pyrroles are conformationally flexible macrocycles of significant importance because they can bind with anion and neutral substrates under different conditions [1]. In these complexes, guests are bound to the macrocycles by a system of hydrogen bonds of the pyrrolic nitrogen atoms. However, the stability of the complexes is not high enough for analytical use. To improve their binding ability, the macrocycles could be functionalized with some chelating groups. Substitution at the β position (pyrrolic CH) of parent calix[4]pyrrole is often difficult and separation of the product mixtures is very problematic, on the contrary, substitution at the *meso*-position on the bridge is easier.

With this in view, herein we report for the first time the synthesis of tetra-functionalized calix[4]pyrrole hydroxamic acid derivatives **(5a–f)** which were obtained from the basic *meso*-tetra(methyl) *meso*-tetra(p-nitrophenyl) calix[4]pyrrole skeleton **3g** by partially reducing it with Zn-dust and ammonium chloride. Further, coupling with suitable aromatic acid chlorides-benzoyl chloride, p-nitrobenzoyl chloride, cinnamoyl chloride, phenylacetyl-chloride, p-chlorobenzoyl chloride, o-chlorobenzoyl chloride affords calix[4]pyrrole hydroxamic acids **(5a–f)** respectively at low temperature (0–5 °C) in presence of sodium bicarbonate (Scheme 2). Partial reduction of all the four nitro groups in **3g** was tried with hydrazine hydrate in the presence of Raney Nickel as catalyst at 0–5 °C. But the desired product was obtained in low yields which involved tedious separation also. The results were encouraging when partial reduction was tried with Zn-dust in the presence of ammonium chloride [43]. During the preparation of hydroxylamine calix[4]pyrrole, the temperature of the reaction mixture was not allowed to drift above 55–60 °C. The product obtained was isolated from the reaction mixture by extracting in chloroform. Evaporation of the solvent afforded 65% yield of hydroxylamine calix[4]pyrrole **4**. Since compound **4** was unstable in air, it was immediately coupled with different aromatic acid chloride to give the desired products **5a–f**.

The FT-IR (KBr) spectrum of the calix[4]pyrrole hydroxamic acids **5a–f** showed three sharp bands at 3,352, 1,595, and 900 cm^{-1}. The band at 3,352 cm^{-1} is due to N-H stretching (substituted pyrrole ring) and O–H stretching vibrations. It is known that O–H stretching vibrations bands occur at around 3,600 cm^{-1}, hydrogen bonding shifts these bands to lower frequencies. In hydroxamic acids, the –OH group is placed very close to the polar carbonyl C=O group. The band at 1,595 cm^{-1} is assigned to the C=O of the hydroxamic acid group [36, 37]. In unsubstituted amide $RCONH_2$, this band is located between 1,690 and 1,650 cm^{-1}, and in substituted amide RCONHR, it is observed at 1,680 and 1,650 cm^{-1} [38, 39]. The position of the C=O stretching band is highly influenced by the molecular structure and is generally shifted to lower frequencies. Thus hydrogen bonding lowers the C=O band by 10–45 cm^{-1}. The characteristic sharp band for hydroxamic acid (N–O stretching vibrations) was obtained between 975 and 885 cm^{-1} [40] for **5a–f**. In addition, compound **5b** displayed one sharp band at 1,349 cm^{-1} for NO_2 stretching vibrations.

In the ^1H NMR ($CDCl_3$) spectrum, compounds **5a–f** gives various doublets and quartet (not resolvable) between 7.0 and 8.0 ppm for aromatic protons of the ring attached at the *meso*-position and also for the aromatic ring system

Scheme 2 The synthetic route for the new macrocyclic hosts **(5a–f)**



from acid chlorides. Two singlets were observed, one at 7.264 ppm for pyrrole N–H group and the other at 8.803 ppm for hydroxamic acid group. Similarly two doublets at 5.824 and 5.928 ppm were due to the presence of pyrrole β-protons. One singlet at 1.96 ppm was also seen for bridged methyl groups. In addition, compound **5d** displayed two doublets at 4.761 and 4.682 ppm due to—CH=CH—group and **5c** gave one singlet at 3.75 ppm for $-CH_2$ group. Various physical properties of compounds **5a–f** are given in Table 3.

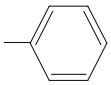
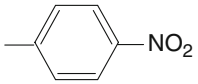
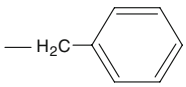
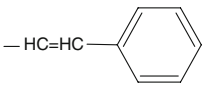
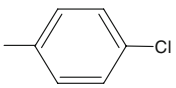
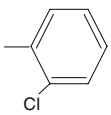
The results obtained from FTIR, ^{1}H NMR, mass data and elemental analysis of new host compound **5a–f**, confirm the presence of hydroxamic acid groups.

Determination of crystal structure

Single crystals of *meso*-tetra(methyl) *meso*-tetra(p-nitrophenyl) calix[4]pyrrole **3g** were grown by slow diffusion of acetone into a THF solution at room temperature. In an attempt to understand the conformation of the **3g** ligand and its interaction with the lattice solvent molecule, we have determined the crystal structure of the compound. ORTEP diagram of **3g** with atom numbering scheme is depicted in Fig. 1 and the summary of the crystallographic data is given in Table 2. Compound **3g** possesses a center of symmetry at the mid point of the plane involving the methylene carbon bridging the pyrrole units with two molecules of acetone as solvent of crystallization per calix unit. It is observed that in compound **3g**, the calixpyrrole macrocycle adopted a *1, 2 alternate*-conformation. The distances between methylene bridge connecting the pyrrole rings ranges from 5.05 to 5.06 Å in along the C1–C6 rectangle while the diagonal distances ranges from 6.96 Å (between C1····C1) to 7.34 Å (between C6····C6), respectively. The two diagonals of the C1–C6 rectangle show significant difference (0.38 Å). The Pyrrole ring (N1–C2 to C5) makes an angle of 57.7° where as the second pyrrole ring (N2–C7 to C10) makes an angle of 42.2° with respect to the plane involving the methylene carbon atoms. The symmetry related *1, 3-alternate* pyrrole rings (N1–C2–C5) and 2, 4 pyrrole rings parallel to each other whereas the adjacent 1, 2 and 3, 4 pyrrole rings makes an angle of 68.1° with overall *1, 2-alternate* conformation for calix molecule**.**

Calix compounds are well known for inclusion of solvents/guest molecules in the calix-cones. Compound **3g** encapsulate two acetone molecules symmetrically on either side of the calix cone with strong N–H···O interaction

Table 3 Various physical parameters of host macrocycles **5a–f**

Macrocycle hosts	R	Molecular weight (g)	Color	Melting point (°C)	Yield (%)
5a		1,216	Creamish	180	50
5b		1,396	Light brown	198	59
5c		1,273	Brownish	178	58
5d		1,368	Brown	189	60
5e		1,212	Dark brown	195	55
5f		1,212	Brown	190	52

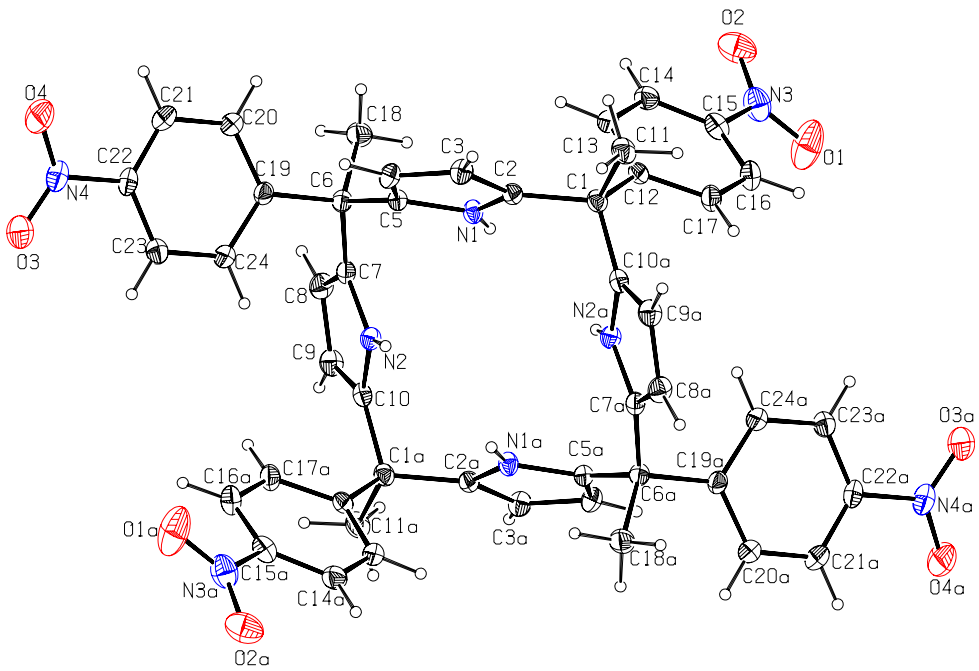


Fig. 1 ORTEP diagram of the calix[4]pyrrole ligand **3g** with atom numbering scheme (50% probability factor for the thermal ellipsoids and the lattice acetone molecule is omitted for clarity)

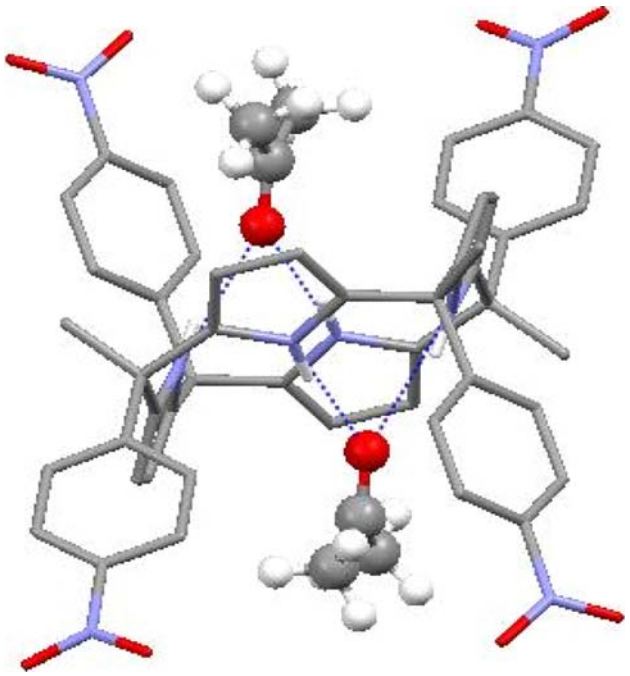


Fig. 2 Mercury diagram showing the N–H···O interaction (dotted blue line) between the lattice acetone with the pyrrole amino hydrogen in *1, 2-alternate* calix[4]pyrrole ligand **3g**

between the pyrrole amino hydrogen's H1 and H2 with the oxygen atom of the encapsulated acetone (Fig. 2).

Thus, the oxygen atom O5 of the symmetrically disposed acetone, on either sides of the calix moiety acts as an acceptor with the adjacent pyrrole amino hydrogen's H1 and H2 with the following H-bonding parameters : N(1)–H(1)····O(5): H1····N5 = 2.10(2) Å, N1····N5 = 2.899(3) Å < N(1)–H(1)····O(5) = 161(2)° symmetry code: x, y, z and N(2)–H(2)····O(5): H(2)····O(5) = 2.11(2) Å, H(2)····O(5) = 2.968(3) Å, N(2)–H(2)····O(5) = 169(2)°, symmetry code : −x, 1 − y, 1 − z. In addition to this H-bonding interaction, various other intermolecular C–H····O hydrogen bonds between the phenyl hydrogen's and methyl hydrogen's (from acetone) with nitro oxygen's stabilizes the molecule in the crystal lattice. The crystal structure shows the presence of two molecules of acetone symmetrically placed above and below the molecule forming hydrogen bonds with two adjacent pyrrole of **3g**. The molecule adopts a 1, 2-alternate conformation.

Liquid–liquid extraction of Vanadium (V) by new macrocyclic host **5a–f**

The preliminary complexation performance of vanadium (V) with ligand **5a–f** was studied under optimum conditions of the acidity, λ_{max}, molar absorptivity (ε_M), the composition of Vanadium (V)-host **(5a–f)** complex. Maximum color intensity of vanadium-host **(5a–f)** complex

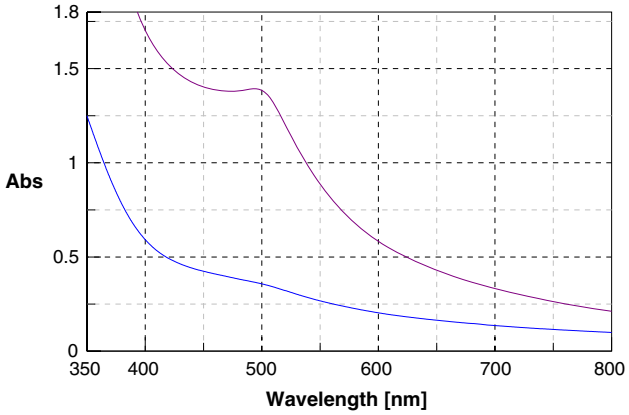


Fig. 3 Comparative Spectra of ligand **5b** (7.1×10^{-4} M) (Blue line) and its Vanadium *(V)* complex in ethyl acetate (Violet line)

was obtained with 6 M HCl. The maximum absorption of the pinkish violet colored complex was measured at 505 nm and showed a bathochromic shift of 282 nm from that of the reagent blank (Fig. 3). The molar absorptivity value for complexes of **5a–f** fluctuates in the range 4,150–4,429 L mole^{-1} cm^{-1}. The high value of molar absorptivity indicate that **5a–f** are tremendously receptive host for vanadium and can be used for trace level detection, particularly **5b**, which shows a high ε_M value of 4,429 L mole^{-1} cm^{-1}, due to the high inductive and mesomeric effect of the nitro group, which make the N–OH protons more labile, thus smooth the progress of complex construction.

The composition of *V*-reagent **5b** complex extracted into ethyl-acetate has been studied by *Slope-Ratio Method* viz. by plotting the graph of logarithm of distribution coefficient of the metal (logDm) against the negative logarithm of the concentration (−log ligand). The extraction is carried out by taking a fixed concentration of vanadium solution and varying amounts of host **(5b)**. The plot of (logDm) against −log (host **5b**) gave a straight line of slope 1.86 indicate that the extracted species V: host **5b** is 2:1. Thus, 1 mole of host **5b** is required for 2 mole of Vanadium (Fig. 4).

The possible extraction mechanism of the metal species in solution, VO_2^+ with the ligand is as follows,

$$2VO_2^+ + 4(HL) \rightarrow 2[H^+(VO_2L_2)^-] + 2H^+$$

One mole of host **5a–f** consists of four hydroxamic acid groups which was represented by 4 HL in above equation and hence forms a 2:1 complex with VO_2^+ in the solution. The anionic complex thus formed, $[VO_2L_2]^-$ takes up a proton to yield the neutral ion pair complex $H^+[VO_2L_2]^-$ which gets extracted into ethyl acetate.

To obtain more information about the nature of the extracted complex; a known weight of the dry complex was digested with a perchloric and nitric acid mixture. It was

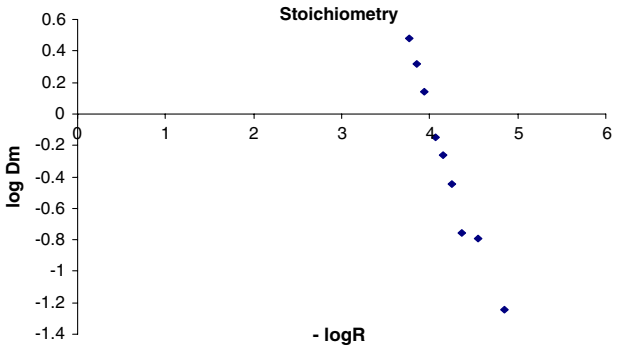


Fig. 4 Slope ratio plot for determination of stoichiometry[a] of vanadate complex of host **5b** (Plot of distribution ratio of vanadium [D_m] against host **5b**) [[a] Extraction conditions—organic phase (ligand **5b** in ethyl acetate) = 0.5−6 mL, 7.1×10^{-4} M; aqueous phase = 10 mL, 500 μg of Vanadium solution containing 6 M HCl. 25 °C for 5 min stirring and $\lambda_{max} = 505$ nm]

centrifuged and the vanadium (V) content was determined by ICP-AES. The obtained results are in conformity with the complex formula.

Thus, the preliminary studies carried out for the extraction of vanadium (V) show that the new tetra-functionalized calix[4]pyrrole hydroxamic acids can be effectively used as spectrophotometric reagent.

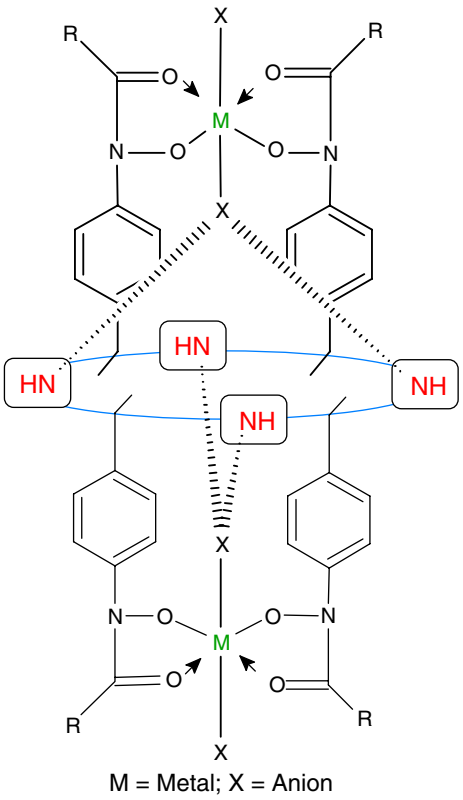


Fig. 5 Proposed complex structure of *cation/anion* with heteroditopic receptor calix[4]pyrrole hydroxamic acid

Conclusion

The chemistry of calixarene has been "rejuvenated" by the appearance of calixpyrroles. We have developed an excellent approach for the safe, rapid, inexpensive and simple synthetic protocol for the construction of *meso*-substituted calix[4]pyrroles, using an efficient and simple methodology based on focused microwave irradiation. The most important result of this approach, compared with the previously reported methods, is the optimization of yields and reaction times. The present versatile method is an important addition to microwave-assisted synthetic methodologies. The resulting changes in calix[4]pyrrole macrocycle (hydroxamic acid, the versatile metal extractants and calixpyrroles being healthy institute of anion sensors) can be used to increase the absolute affinity towards cations such that the system as a whole can act as ditopic receptors. This article could see its utility in further design and synthesis of hetero-ditopic receptors, competent of binding both cation and anion simultaneously (Fig. 5). The synthesized calix[4]pyrrole-hydroxamic acid **5a–f** display high affinity for vanadium (V) metal ion. Under preliminary investigations they were found to be extremely capable vanadophiles. The work of using the synthesized host compound **5a–f** as ditopic receptors for bivalent, trivalent and other important metal ions is under progress in our laboratory. We believe that the almost all the important results presented in this paper will open up a potentially novel chapter in the chemistry of calixpyrroles and as well as will add to a series of buoyant novel host compound in the field of pyrrole based hetero-calixarene.

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