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Abstract – Recent developments in the field of sensing and recognition revealed that artificial receptors based on calix[4]arenes with π-conjugated fluorophoric or chromophoric moieties are efficient in enhancing selectivity/sensitivity as well as the binding affinity for ionic or molecular recognition. Herein, via studying the reaction of dimethylformamide dimethyl acetal (DMF–DMA) with p-tert-butylthiacalix[4]arene tetrahydrazides in three different conformers (i.e., cone, partial-cone, and 1,3-alternate), the formation of novel lower rim p-tert-butylthiacalix[4]arene derivative (cone, partial-cone, and 1,3-alternate) conformers in high yields (80, 95, and 85%, respectively) was achieved. The structure of isolated products was confirmed using different spectroscopic and analytical techniques such as FT-IR, \textsuperscript{1}H NMR, \textsuperscript{13}C NMR, and elemental analysis. Importantly, the synthesized receptors showed preferential uptakes of alkali (Na\textsuperscript{+}, K\textsuperscript{+} and Cs\textsuperscript{+}), heavy (Pb\textsuperscript{2+}, Cd\textsuperscript{2+}, Hg\textsuperscript{2+}, and Ag\textsuperscript{+}) and transition (Ni\textsuperscript{2+}, Co\textsuperscript{2+}, and Cu\textsuperscript{2+}) metal ions via liquid–liquid extraction method. The finding of this work adds new compounds to the growing family of thiacalix[4]arenes and validates their high sensitivity and selectivity in detection of heavy metal ions.

INTRODUCTION
Calix[n]arenes\textsuperscript{1-4} are bowl-shaped macrocyclic compounds that have been widely used in catalysis,\textsuperscript{5} molecular recognition,\textsuperscript{6} metal ion receptors,\textsuperscript{7} and sensors.\textsuperscript{8} Among the calixarene family, thiacalix[4]arenes\textsuperscript{9-11} are the most popular members as the presence of sulfur atoms in their structure
makes them ideal compounds for facile complexation with various metal ions. In this respect, metal-recognition abilities of thiacalixarenes can be tuned by introducing different functional groups to the active sites in their structures including the upper / lower rims or bridging sulfur atoms. However, the hydroxyl's lower rim groups are considered to be the easiest sites for preparing a large number of thiacalixarenes with various functional groups in different conformers.

Thiacalixarenes lower rim functionalization is carried out mainly through alkylation with halo-reagents. In a previous work, alkylation using halo-reagent enabled the synthesis of three different conformers (i.e., cone, partial-cone and 1,3-alternate) at the lower rim of p-tert-butylthiacalix[4]arene tetraesters, tetraethers, tetraketones, and tetraamides. Among these conformers, p-tert-butylthiacalix[4]arene tetraesters were the best precursors for further functionalization of thiacalixarenes to synthesize tetra-acids, tetraethioesters, and tetrahydrazides. In addition, the p-tert-butylthiacalix[4]arene tetrahydrazides have been successfully used for the synthesis of other thiacalixarene derivatives through coupling with carbonyl compounds as well as addition to unsaturated carbon–carbon double bond or carbon–nitrogen triple bonds.

As a continuation of our ongoing interest in thiacalixarenes and their potential applications in voltammetric sensors and receptors, we report herein the synthesis of lower rim derivatives, in three different conformers, by reacting N,N-dimethylformamide dimethyl acetal (DMF-DMA) with p-tert-butylthiacalix[4]arene tetrahydrazides. Moreover, the affinity of the prepared compounds to recognize and bind to different metal ions such as alkali (Na+, K+ and Cs+), heavy (Pb2+, Cd2+, Hg2+ and Ag+) and transition (Ni2+, Co2+ and Cu2+) metal ions using liquid–liquid extraction protocol in picrate solutions has been evaluated.

RESULTS AND DISCUSSION

Novel p-tert-butylthiacalix[4]arene derivatives 4a-c, in three different conformers (i.e., cone, partial-cone and 1,3-alternate) as shown in Scheme 2, were prepared through three steps. Firstly, following Miyano et al., who have selectively converted p-tert-butylthiacalix[4]arene 1 to p-tert-butylthiacalix[4]arene tetraesters 2a-c in three different conformers (cone, partial-cone, and 1,3-alternate) using alkali metal carbonates (M2CO3, M = Na, K, and Cs). Secondly, hydrazinolysis of different tetraesters conformers produced the corresponding p-tert-butylthiacalix[4]arene tetrahydrazides 3a-c. Finally, p-tert-butylthiacalix[4]arene tetrahydrazides 3a-c were reacted with N,N-dimethylformamide dimethyl acetal (DMF-DMA) in boiling dry toluene to afford p-tert-butylthiacalixarene derivatives 4a-c in good yields (80 to 90%) as illustrated in Scheme 1.

The proposed structures (Scheme 2) of the prepared thiacalixarene derivatives 4a-c were confirmed by various spectroscopic and analytical methods including FT-IR (Supplementary Materials Figures S1-S3).
$^1$H NMR (S4-S6), and $^{13}$C NMR (S7-S9) as well as elemental analysis. As can be seen in Figures S1-S3, IR spectra obtained for compounds 4a - 4c showed the appearance of characteristic IR bands at $\nu = 3378$, 3395, and 3400 cm$^{-1}$ assigned for free NH group, along with strong bands at $\nu = 1701$, 1674 and 1676 cm$^{-1}$ for CO group in the three compounds, respectively. Additionally, the compounds exhibited IR band at 1270, 1265, and 1263 cm$^{-1}$, which are attributed to (COC) group, respectively.

The fact that symmetrical structures of cone 4a and 1,3-alternate 4c conformers are originated from their corresponding cone 3a and 1,3-alternate 3c conformers, respectively; it is expected to exhibit the same number of peaks in NMR spectra. However, it is possible to differentiate between these conformers by considering the chemical shifts associated with different proton groups. Thus, as illustrated in Figures S4 and S6, the protons of the –OCH$_2$C(O)– group in the 1,3-alternate conformation, are located in the shielding area of two adjacent benzene rings, and consequently the signals of these protons were detected in a higher field than the signals of the corresponding protons in cone conformer (4.21 ppm and 4.88 ppm, respectively). Whereas, the tert-butyl protons of the 1,3-alternate conformer are noted in the deshielding zone of the attached phenyl unit and the two adjacent benzene rings. Thus, the tert-butyl protons signal of 1,3-alternate should appear in a lower field compared to tert-butyl protons signals of the cone conformer (1.20 ppm and 1.11 ppm, respectively). In view of these results, the structures of compounds 4a and 4c can be unambiguously assigned to cone and 1,3-alternate conformers, respectively.

The structure of compound 4b is predicted to be unsymmetrical and therefore, the $^1$H NMR spectrum (S5) exhibited marked increase in splitting and multiplicity of protons from different group. The obtained $^1$H NMR spectrum of compound 4b showed the presence of three non-equivalent peaks associated with the tert-butyl groups; and the -N(Me)$_2$ group should exhibit a 2:1:1 ratio of resonance patterns in the proton spectrum. Thus, tert-butyl has the following peaks $\delta = 1.15$ (s, 18H), 1.29 (s, 9H), 1.36 (s, 9H) whereas peaks at $\delta = 2.84$(s, 3H), 2.92(s, 3H), 2.96(s, 6H) are assigned to -N(Me)$_2$ group. In addition, there are three peaks for OCH$_2$C(O)– protons at $\delta = 4.69$(s, 2H), 4.8(s, 2H), 4.82(d, 2H); similar peaks are observed for Ar-H and –NH protons.

In consistence with $^1$H NMR results, $^{13}$C NMR spectra (Figures S7-S9) also confirmed the symmetrical structure of both 4a (cone) and 4c (1,3-alternate) with the detection of 10 peaks in their spectra. As for the unsymmetrical structure, compound 4b (partial-cone) showed similar number of peaks but with the splitting of each peak in the spectrum of the unsymmetrical structure 4b (partial-cone) (see EXPERIMENTAL).
Scheme 1. Reagents and conditions: i, $^7$; ii, $^{13}$; and iii, DMF-DMA, toluene, reflux

Scheme 2. Structures of stereoisomers 4a-c

Although the proposed structures of $p$-tert-butylthiacalix[4]arene derivatives 4a-c contained at their lower rim various functional groups such as C=O, C=N, and NH, which is expected to easily coordinate with the desired metal ion, the conditions used in this study (acidic aqueous/organic) mixture (pH 4.5) are most likely to favor the –C=N group to interact with the metal. Thus, To evaluate the ability of $p$-tert-butylthiacalix[4]arene derivatives 4a-c to bind/host metal ions, a liquid–liquid extraction experiment from aqueous/organic biphas system (i.e., H$_2$O/CHCl$_3$ mixture) was carried out using different metal picrate salts with the metal being either monovalent (M = Na$^+$, K$^+$, and Cs$^+$) or divalent heavy and transition metals (Pb$^{2+}$, Cd$^{2+}$, Hg$^{2+}$, Ni$^{2+}$, Co$^{2+}$, Cu$^{2+}$, and Ag$^+$). The prepared sample solutions were analyzed via UV–Vis spectroscopy. The extraction percent ($E\%$) for alkali and transition metal ions
by using the studied derivatives of $p$-tert-butylthiacalix[4]arene are listed in Table 1 and Figure 1. It is observed that all $p$-tert-butylthiacalixarene derivatives 4a–c, unlike tertiary amide analogues,21-23 are good extractants for all alkali metal ions. However, $1,3$-alternate conformer 4c is highly selective for $K^+$ compared to other alkali metals with a percent of 52% is determined for $K^+$ detection. This finding is unusual given that the analogous $p$-tert-butylthiacalixarene tetrahydrazides,24 are only suitable for detection of transition metal ions. Moreover, it can be noted that $p$-tert-butylthiacalixarene derivatives 4a–c are also highly selective extractants for $Cd^{2+}$, $Hg^{2+}$, and $Cu^{2+}$ by cone, 4a (59-75%); $Pb^{2+}$, $Cd^{2+}$, and $Ag^+$ by partial-cone 4b (68-80%). In view of these results, it is clearly established that these conformers have higher selectivity for the environmentally harmful transition metal cations such as $Cd^{2+}$, $Hg^{2+}$, and $Ag^+$.

Table 1. Competition between extraction extent ($E$) for different metal ions by $p$-tert-butylthiacalix[4]arene derivatives 4a–c

<table>
<thead>
<tr>
<th>Ligand</th>
<th>$Na^+$</th>
<th>$K^+$</th>
<th>$Cs^+$</th>
<th>$Pb^{2+}$</th>
<th>$Cd^{2+}$</th>
<th>$Hg^{2+}$</th>
<th>$Ni^{2+}$</th>
<th>$Co^{2+}$</th>
<th>$Cu^{2+}$</th>
<th>$Ag^+$</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>33.4</td>
<td>5.2</td>
<td>0.0</td>
<td>47.0</td>
<td>59.6</td>
<td>69.1</td>
<td>52.8</td>
<td>14.9</td>
<td>74.9</td>
<td>52.2</td>
</tr>
<tr>
<td>4b</td>
<td>4.3</td>
<td>52.2</td>
<td>0.5</td>
<td>80.0</td>
<td>68.0</td>
<td>5.8</td>
<td>24.0</td>
<td>19.0</td>
<td>37.9</td>
<td>75.1</td>
</tr>
<tr>
<td>4c</td>
<td>17.7</td>
<td>24.0</td>
<td>12.9</td>
<td>22.1</td>
<td>30.7</td>
<td>22.0</td>
<td>20.1</td>
<td>22.1</td>
<td>42.4</td>
<td>30.7</td>
</tr>
</tbody>
</table>

Figure 1. Extraction percent ($E$) of different metal ions using $p$-tert-butylthiacalix[4]arene derivatives 4a–c

The protocol used for extraction of various metal ions involve using aqueous solution phase of metal picrate with concentration of $1.0 \times 10^{-4}$ M and organic solution phase of the $p$-tert-butylthiacalix[4]arene derivatives 4a–c ($1.0 \times 10^{-3}$ M) in chloroform. The extraction percentage is estimated using the formula $E\% = (\text{initial aqueous cation concentration}) - (\text{final aqueous cation concentration}) / (\text{initial aqueous cation concentration}) \times 100$. 
The stoichiometry and extraction constants of the instantly formed ligand–metal complexes were also determined. Extraction equilibrium is described by Eq. (1), where $M^{n+}$, $L$, Pic$^-$, $ML^{n+}$, and $ML^{n+}nPic^-$ are the metal ion, ligand (here, 4a, 4b and 4c), picrate anion, metal complex and ion-pair, respectively, while $n$ is the number of ligands that react with one metal ion.

$$M_{aq}^{n+} + nL_{org} + nPic_{aq}^- \leftrightarrow ML_{n}^{n+} nPic_{org}^- \quad (1)$$

The percentage extraction, $E\%$, and extraction degree, $\alpha$, were calculated according to Eq. (2).

$$E\% = \alpha \times 100\% = \frac{[ML^{n+}nPic^-]_{org}}{[Pic^-]_{aq,init}} \times 100 \quad (2)$$

The thermodynamic extraction constant, $K_{ex}$, is given by Eq. (3).

$$K_{ex} = [ML^{n+}nPic^-]_{org}.fM,L,Pic^-[M^{n+}].fM^{n+}[nPic^-]_{aq}.fPic^-[L]_{org}f[L] \quad (3)$$

Where $f$ is the activity coefficient. The activity coefficients of different species and ion-pair for diluted solution were $1.0 \times 10^{-4}$ M; thus, they were neglected and assumed to be unity.

To determine the stoichiometric coefficient ($n$) of the complexes, which is formed in the organic phase using Eq. (4) as the modified form of Eq. 3.

$$\log K_{ex} = \log \left( \frac{\alpha}{1-\alpha} \right) - \log [M^{n+}]_{aq} - n\log [L]_{org} \quad (4)$$

Virtually, the plot of $\log(\alpha/1 - \alpha)$ versus $\log[L]_{org}$ gave rise to a straight lines, and its slope equals to the ($n$) value. Furthermore, the extraction constants ($K_{ex}$) are calculated using the intercept values ($b$).

$$b = \log K_{ex} + \log [M^{n+}]_{aq} \quad (5)$$

Our obtained results demonstrated that plotting of $\log(\alpha/1 - \alpha)$ vs. $\log[L]_{org}$ for selected metal ions that gave highest extraction percentage such as Ag$^+$, Cd$^{2+}$, and Hg$^{2+}$ (Figure 2) in saturated water/chloroform mixture was linear in all cases, therefore, Eq. 4 is valid, with the values of $\log K_{ex}$, $Kex$ and $n$ are depicted in Table 2.
Figure 2. Plot of log(α/1 - α) vs. log[L]_org for metal picrate extraction by *p*-tert-butylthiacalixarenes 4a–c in a mutually saturated water–chloroform solvent system

Table 2. Extraction constants log $K_{ex}$ and stoichiometry complexes for different metal–ligand complexes formed in the organic phase

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Metal</th>
<th>log$K_{ex}$</th>
<th>$K_{ex}$</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>Cd$^{2+}$</td>
<td>10.38</td>
<td>2.39x10$^{10}$</td>
<td>1.5</td>
</tr>
<tr>
<td>4b</td>
<td>Ag$^{+}$</td>
<td>11.92</td>
<td>8.31x10$^{11}$</td>
<td>1.8</td>
</tr>
<tr>
<td>4c</td>
<td>Hg$^{2+}$</td>
<td>8.95</td>
<td>8.90x10$^{8}$</td>
<td>1.0</td>
</tr>
</tbody>
</table>

The obtained results (Table 2) revealed that the stoichiometric calculations associated with formation of metal-thiacalixarene complexes are highly dependent on the type of *p*-tert-butylthiacalixarenes (4a–c) conformers as well as the size and valance of metal ion. Thus, the ligand: metal (L:M) ratio in these type of host-guest associations does not follow a specific trend. In this respect, we found in the case of *cone* conformer (4a) with Cd$^{2+}$ n = 1.5, thereby implying L:M ratio of 3:2. Whereas for *partial-cone* 4b with Ag$^{+}$ (n = 1.8), the L: M ratio is ~ 1: 2 and for *1,3-alternate* conformer (4c) with Hg$^{2+}$ a 1:1 stoichiometric ratio of L: M is accomplished. The unusual finding of 3:2 L:M ratio in case of cadmium can be explained in terms of the fact that the 4a conformer of the ligand has four -C=N- (azomethine) groups available for host-guest association with the metal ion, and Cd$^{2+}$ favors an octahedral geometry that required the association of six – C=N groups. In order to achieve such stoichiometry three molecules of 4a have to react with two Cd$^{2+}$ ions, thus, giving rise to a 3:2 ratio.
CONCLUSION

A facile synthesis of novel \( p \)-\textit{tert}-butylthiacalixarene derivatives in three different conformers at the lower rim is achieved by the reaction of thiacalixarene tetrahydrazides with dimethylformamide dimethyl acetal. The ability of new thiacalixarene derivatives to recognize/bind alkali metal ions (Na\(^+\), K\(^+\), and Cs\(^+\)), heavy metals (Pb\(^{2+}\), Cd\(^{2+}\), and Hg\(^{2+}\)), and transition metal ions (Ni\(^{2+}\), Co\(^{2+}\), Cu\(^{2+}\), and Ag\(^+\)) has been studied by the liquid–liquid extraction method. This study revealed that these new compounds are very sensitive and extremely selective towards a wide range of metal ions. Furthermore, given that these new compounds containing good leaving -N(Me)\(_2\) group at their lower rim, it can be used as a starting precursors for various transformations in organic/organometallic reaction processes.

**General method for picrate extraction:**

Solutions of metal picrates were prepared from an aqueous solution of picric acid and metal hydroxide (i.e., NaOH, KOH or CsOH) or metal nitrate [i.e., Pb(NO\(_3\))\(_2\), Cd(NO\(_3\))\(_2\), Hg(NO\(_3\))\(_2\), Ni(NO\(_3\))\(_2\), Co(NO\(_3\))\(_2\), Cu(NO\(_3\))\(_2\) or AgNO\(_3\)] solutions and analyzed by a pH meter. In the latter case, solutions were weakly acidic with the final pH of 4.5. An aqueous picrate solution (5 mL, 1.0 × 10\(^{-4}\) M) and a chloroform solution of the ligand (5 mL, 1.0 × 10\(^{-3}\) M) were stirred together for 0.5 h and then kept for 0.5 h at 25 °C. Blank experiments showed that metal picrate extraction did not occurred in the absence of \( p \)-\textit{tert}-butylthiacalixarene derivatives 4a-c. The absorbance of aqueous phase before (\(A_0\)) and after extraction (\(A_i\)) was measured at 355 nm. The percent extraction (\(E\%\)) was calculated using the following expression:

\[
E\% = \frac{A_0 - A_i}{A_0}
\]

EXPERIMENTAL

All chemicals and reagents were of analytical grade and used as received without further purification. Melting points (°C, uncorrected) were determined using an open glass capillary via a Melting Point Apparatus (Stuart, model SMP10). The Fourier transform infrared (FT-IR) analysis of the prepared compounds was conducted on a Perkin Elmer Spectrum 1000 FT-IR Spectrometer. \(^1\)H and \(^{13}\)C NMR spectroscopic analyses were performed in deuterated chloroform (CDCl\(_3\)) and dimethyl sulfoxide (DMSO) at room temperature using JEOL ECP-400 MHz spectrometers. The chemical shifts were expressed in δ 7.28 downfield from CDCl\(_3\), which was used as a reference. Absorbance A was measured by a JENWAY, 64OS UV - Vis spectrophotometer.
Synthesis of compounds 4a-c (general methods).

A mixture of p-tert-butylthiacalixarene tetrahydrazides 3a, 3b or 3c (1 g, 0.99 mmol) with DMF-DMA (0.58 g, 4.95 mmol) in 40 mL dry toluene, was heated under reflux for 12 h. The mixture was concentrated to approximately 10 mL then left to cool. The white solid product was separated, filtrated and washed with MeCN. The product was recrystallized from EtOH.

4a, cone, yield 80%; white powder; Mp 170 °C, IR (KBr, ν/cm⁻¹): 3378 (NH-free), 1701 (CO), 1270 (COC). ¹H NMR (400 MHz, CDCl₃) δ: 1.11 (s, 36H, Buᵗ), 2.96 (s, 24H, N(CH₃), 4.88 (s, 8H, OCH₂CO), 7.38 (s, 8H, ArH), 8.02 (s, 4H, N=CH). 13C NMR (100 MHz, CDCl₃) δ: 31.0, 34.2, 37.8, 75.9, 128.4, 135.0, 147.7, 158.1, 158.6, 164.2. Anal. Calcd for C₆₀H₈₄N₁₂O₈S₄: C, 58.61; H, 6.89; N, 13.67. Found: C, 58.50; H, 6.48; N, 13.35.

4b, partial-cone, yield 90%; white powder; Mp 242 °C. IR (KBr, ν/cm⁻¹): 3395 (NH), 1674 (CO), 1265 (COC). ¹H NMR (400 MHz, CDCl₃) δ: 1.15 (s, 18H, Buᵗ), 1.29 (s, 9H, Buᵗ), 1.36 (s, 9H, Buᵗ), 2.84 (s, 3H, NCH₃), 2.92 (s, 3H, NCH₃), 2.96 (s, 6H, NCH₃), 4.62 (d, 2H, OCH₂CO), 4.69 (s, 2H, OCH₂CO), 4.8 (s, 2H, OCH₂CO), 4.82 (d, 2H, OCH₂CO), 7.41-8.42 (m, 8H, ArH + 4H, N=CH). ¹³C NMR (100 MHz, CDCl₃) δ: 31.0, 31.2, 34.3, 34.5, 34.9, 37.8, 70.7, 73.4, 74.0, 125.2, 126.7, 128.1, 128.8, 129.0, 131.8, 133.5, 135.2, 135.7, 137.8, 147.9, 148.1, 156.8, 157.2, 157.6, 157.9, 158.1, 163.6, 164.0, 164.40. Anal. Calcd for C₆₀H₈₄N₁₂O₈S₄: C, 58.61; H, 6.89; N, 13.67. Found: C, 58.65; H, 6.54; N, 13.30.

4c, 1,3-alternate, yield 80%; white powder; Mp 190 °C. IR (KBr, ν/cm⁻¹): 3400 (NH), 1676 (CO), 1263 (COC). ¹H NMR (400 MHz, DMSO) δ: 1.20 (s, 36H, Buᵗ), 2.80 (s, 24H, N(CH₃), 4.21 (s, 8H, OCH₂CO), 7.42 (s, 8H, ArH), 8.07 (s, 4H, N=CH), 8.38 (s, 4H, CONH). ¹³C NMR (100 MHz, DMSO) δ: 31.2, 34.5, 37.5, 69.2, 127.2, 128.9, 147.9, 155.1, 157.9, 162.9. Anal. Calcd for C₆₀H₈₄N₁₂O₈S₄: C, 58.61; H, 6.89; N, 13.67. Found: C, 58.68; H, 6.51; N, 13.43.

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