Synthesis and applications of functionalized (thia)calixarenes

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Macrocyclic platforms
Calixarenes

Calix

CPK-Model

X=O, S, NH
The characteristic advantages of calix[4]arenes for the constructing of receptors are followed:
- the low cost and accessibility of parent macrocycles by one-pot synthesis;
- calixarenes can incorporate the small hydrophobic organic molecules into their molecular cavities with the formation of the stable host-guest complexes;
- the existence of variety of calixarene conformations: cone, partial cone, 1,2-alternate, 1,3-alternate etc.;
- calix[4]arene conformations are rather rigid and are able to fix the required spatial orientation of binding centers;
- nontoxicity of calixarene platforms.
- calixarene platform gives an unique possibility to decorate the upper and lower rim of macrocycle by the suitable heteroatom groups and to form the molecular system possessing the several binding centers;
Background of Calixarene Chemistry

Main Problem:

Stereo and Regio Selective Functionalization of Lower and Upper Rim

Mono, Di, Tri and Tetra Substituted Derivatives

Cone  Partial Cone  1,3-Alternate  1,2-Alternate
Main topics

1. Design of new types of cavitands
2. Design of hosts molecules
3. Design of tectons for MOFs
Design of new types of cavitands

\[ \text{Br-X-Br} \]

1 \( X = \) \( \sim \sim \sim \)

2 \( X = \)

3 \( X = \)

1 (30%)

2 (33%)

3 (45%)

4 (23%)
Lower rim complexes: recognition of the charged species and surfaces

Low selectivity

High selectivity

Stereoselective synthesis using template effect

Y = group capable to bind cations:
-\(\text{C(O)NEt}_2\), -\(\text{C(O)-Ph}\), \(n = 1\)
## Stereoselective synthesis using template effect

<table>
<thead>
<tr>
<th>R</th>
<th>Base</th>
<th>Reagents ratio</th>
<th>Products distribution, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TCA:XR : M2CO3</td>
<td>Cone</td>
</tr>
<tr>
<td>CH₂C(O)NEt₂</td>
<td>Na₂CO₃</td>
<td>1 : 8 : 4</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>K₂CO₃</td>
<td>1 : 8 : 4</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>K₂CO₃</td>
<td>1 : 8 : 6</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Cs₂CO₃</td>
<td>1 : 8 : 4</td>
<td>-</td>
</tr>
<tr>
<td>CH₂C(O)Ph</td>
<td>Na₂CO₃</td>
<td>1 : 6 : 6</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>K₂CO₃</td>
<td>1 : 6 : 6</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Cs₂CO₃</td>
<td>1 : 6 : 6</td>
<td>7</td>
</tr>
</tbody>
</table>
Organophosphorus Derivatives of Thiacalix[4]arenes

1 δ(31P): 170.2 ppm  
 m/z = 848[M+H⁺]

2 δ(31P): 170.2 ppm  
 m/z = 848[M+H⁺]

[O₂]

3 δ(31P): -4.2 ppm  
 m/z = 880[M+H⁺]

4 δ(31P): 134.3, 140.4 ppm  
 m/z = 924[M+H⁺]

2PCl₃(NEt₃)

HNEt₂
2h, 90°C
Organophosphorus Derivatives of Thiacalix[4]arenes

Stabilization of monosubstituted derivative
Table: Reaction of BrCH$_2$C(O)NHC$_6$H$_4$NO$_2$ with p-tert-butyithiicalix[4]arene

<table>
<thead>
<tr>
<th>Base</th>
<th>Solvent</th>
<th>Time, h</th>
<th>Yield, %</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na$_2$CO$_3$</td>
<td>CH$_3$C(O)CH$_3$</td>
<td>72</td>
<td>37</td>
<td>-</td>
<td>-</td>
<td>11</td>
<td>26</td>
<td>-</td>
</tr>
<tr>
<td>K$_2$CO$_3$</td>
<td>CH$_3$C(O)CH$_3$</td>
<td>72</td>
<td>60</td>
<td>54</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cs$_2$CO$_3$</td>
<td>CH$_3$C(O)CH$_3$</td>
<td>72</td>
<td>52</td>
<td>10</td>
<td>42</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Na$_2$CO$_3$</td>
<td>CH$_3$CN</td>
<td>20</td>
<td>56</td>
<td>-</td>
<td>-</td>
<td>51</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>K$_2$CO$_3$</td>
<td>CH$_3$CN</td>
<td>20</td>
<td>51</td>
<td>44</td>
<td>7</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cs$_2$CO$_3$</td>
<td>CH$_3$CN</td>
<td>20</td>
<td>73</td>
<td>20</td>
<td>53</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Effect of binding sites preorganization on calixarene platform

Cone, paco, 1,3-alternate; Li, Na, K, Cs

$\Delta \lg K \approx 6-10$
Macrocycle conformation effect

The extraction constants of alkali metal ions by conformers I and II.

Complexes stoichiometry of I (R= CH₂COPh)

I – R= Ph;

II – R= NEt₂

Log $K_{ex}$

The extraction constants of alkali metal ions by conformers I and II.
Array of fluorescent chemosensors for molecular recognition of halide anions

- C(O)Naphtyl

<table>
<thead>
<tr>
<th></th>
<th>F⁻</th>
<th>Cl⁻</th>
<th>Br⁻</th>
<th>I⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>–</td>
</tr>
<tr>
<td>3b</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>–</td>
</tr>
<tr>
<td>3c</td>
<td>↓</td>
<td>–</td>
<td>–</td>
<td>↓</td>
</tr>
</tbody>
</table>
Transfection DNA into the cells by synthetic receptors
Aggregation effects at the complex formation with tetra-amides (DLS method)

**Extraction data**

\[ C(\text{Me}^{n+}) = 0.1 \text{M}, C(\text{L}) = 10^{-4} - 2.5 \times 10^{-3} \text{ M}, C(\text{Pic}^{-}) = 2.3 \times 10^{-4} \text{ M} \]

<table>
<thead>
<tr>
<th></th>
<th>Li(^{+})</th>
<th>Ag(^{+})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>LogK(_{ex})</td>
</tr>
<tr>
<td>Cone-5</td>
<td>0.8</td>
<td>3.3</td>
</tr>
<tr>
<td>Cone-6</td>
<td>1.9</td>
<td>8.4</td>
</tr>
<tr>
<td>Paco-5</td>
<td>0.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Paco-6</td>
<td>1.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Alternate-5</td>
<td>0.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Alternate-6</td>
<td>0.8</td>
<td>3.3</td>
</tr>
</tbody>
</table>

**Nanoparticles size (nm)/Polydispersity**

<table>
<thead>
<tr>
<th></th>
<th>Free ligand</th>
<th>Li(^{+})</th>
<th>Ag(^{+})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cone-5</td>
<td>-</td>
<td>-</td>
<td>84 / 0.18</td>
</tr>
<tr>
<td>Cone-6</td>
<td>-</td>
<td>143 / 0.19</td>
<td>153 / 0.08</td>
</tr>
<tr>
<td>Paco-5</td>
<td>-</td>
<td>-</td>
<td>134 / 0.16</td>
</tr>
<tr>
<td>Paco-6</td>
<td>-</td>
<td>-</td>
<td>131 / 0.17</td>
</tr>
<tr>
<td>Alternate-5</td>
<td>-</td>
<td>-</td>
<td>140 / 0.19</td>
</tr>
<tr>
<td>Alternate-6</td>
<td>-</td>
<td>-</td>
<td>141 / 0.23</td>
</tr>
</tbody>
</table>

**Cone**

**Paco**

**1,3-Alternate**
Nanoparticles size distribution of Ag complex in CH$_2$Cl$_2$
SEM nanoparticles image of Ag(I) complex in CH2Cl2

1,3-alt - 10
Design of tectons for MOFs

- Binding sites: -COOH; -C(O)NR2; -CN; -Pyr; etc...

cone 1,3-alternate partial cone 1,2-alternate
Strategies of MOFs formation on the basis of 1,3-alternate

M/L=2/1 (tubular system)

M/L=1/1 (nontubular system)

Collaboration with M.W. Hosseini

1D

2D

M/L=2/1

3D

M/L=1/1
Preorganized calixarene ligands (1,3-alternate)

\[
R = t\text{-Bu; H}
\]
X-Ray structure of the synthesized calixarene ligands
1D structure of (3-cyanopropoxy)-p-tert-butylthiacalix[4]arene with silver ion

X – non coordinating anion
PF$_6^-$, SbF$_6^-$, BF$_4^-$

Space group P2, Z = 1

(C$_{56}$H$_{68}$N$_4$O$_4$S$_4$Ag)(PF$_6$)$_2$(CH$_2$Cl$_2$)

Infinite linear 1D- structure, M/L=1/1
Structure of decanuclear cluster of AgNO₃ with (p-cyanobenzyloxy)-p-tert-butyl-thiacalix[4]arene

The 1D arrangement along the c axis

Space group P4₂/n, Z = 4

25.77 Å
The solid-state structure of clusters Ag10

Ag1 - pentacoordinated with a NSO3 environment
Ag2 – heptacoordinated with a SO6 environment
Ag3 - tetracoordinated with O4 environment

<table>
<thead>
<tr>
<th>Distance (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag1-Ag2</td>
</tr>
<tr>
<td>Ag1-Ag3</td>
</tr>
<tr>
<td>Ag2-Ag3</td>
</tr>
<tr>
<td>Ag1-S</td>
</tr>
<tr>
<td>Ag2-S</td>
</tr>
</tbody>
</table>
The arrangement of the decanuclear cluster in the (001) plane
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