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Supporting Information Placeholder

ABSTRACT: A missing, inherently chiral member of the calix[4]arene family denoted “catechol[4]arene” was synthesized. Its properties were studied and compared to the ones of its close relatives resorcin[4]arene and pyrogallol[4]arene. This novel supramolecular host exhibits binding capabilities that are superior to its sister molecules in polar media. The enantiomerically pure forms of the macrocycle display modest recognition of chiral ammonium salts.

In the broad field of supramolecular chemistry, macrocycles have always played a key role.1 Among the synthetic macrocycles, the calix[4]arene family (Figure 1a) stands out as one of the most functional and versatile ones.2 Calix[4]arene along with its sister molecules resorcin[4]arene (RS) and pyrogallol[4]arene (PG) are rigid and easily derivatizable3 macrocyclic structures that enabled a variety of applications across the fields of material sciences, molecular sensing and drug delivery.4 The latter two systems are of particular interest as they are known to self-assemble in apolar media; resulting in the formation of hexameric capsules held together by hydrogen bond networks.5 The emerging enclosed space supplemented with its capability to take up neutral and cationic guests resembles enzymatic pockets to some extent.6 In the case of RS, these properties have been successfully applied to the catalysis of a growing number of reaction classes.7

While there are examples of successful asymmetric catalysis employing achiral RS, these reactions exclusively rely on the presence of an optically active co-catalyst to carry the chiral information.8 One way of overcoming this limitation would be the use of inherently chiral building blocks. The calix[4]arene fami-
ily of macrocycles is achiral. Interestingly, a missing chiral relative (±)-1 (Figure 1b) can be envisioned, we propose the name catechol[4]arene, which to the best of our knowledge has not been reported so far. This inherently chiral constitutional isomer of RS could potentially open access to a range of applications known from other inherently chiral macrocycles, such as asymmetric catalysis, chiral molecular recognition and chiral self-assembly.9

The known calix[4]arene family can be easily obtained through electrophilic aromatic substitution of the respective phenols with aldehydes.10 However, the directing effects in catechol prevent the direct formation of 1. Catechol derivatives reacting with formaldehyde under acidic conditions yield mainly the tricyclic cyclotherivatrylenes (Figure 1a), and no formation of cat-


Table 1. X-ray crystal structure of (±)-1 with the distances a and b and the tetrahedral angle Δα. Values for a, b and the maximum variability of the tetrahedral angle Δαmax for 1, RS and PG.16

<table>
<thead>
<tr>
<th>Property</th>
<th>1</th>
<th>RS</th>
<th>PG</th>
</tr>
</thead>
<tbody>
<tr>
<td>a (Å)</td>
<td>7.73</td>
<td>7.81</td>
<td>7.75</td>
</tr>
<tr>
<td>b (Å)</td>
<td>9.31</td>
<td>9.25</td>
<td>8.95</td>
</tr>
<tr>
<td>Δαmax</td>
<td>4.7</td>
<td>1.4</td>
<td>0.7</td>
</tr>
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</table>

In order to investigate the chiral properties of 1 in solution, its enantiomers were analyzed by CD-spectroscopy and optical rotation measurements. These characterization methods along with DFT calculations17 allowed to assign the axial chirality and...
optical activity for \( M^-(+) \) and \( P^+(+) \) (Figure 2, see Supporting Information Chapter 2.5).\(^{18} \)

![Graph](image)

**Figure 2.** a) Experimental CD spectra of enantiomers \( M^-(+) \) and \( P^+(+) \) in chloroform; b) Calculated CD spectrum for \( M^-(+) \) (TD DFT B3LYP/6-31G(dp)) in chloroform.

After having confirmed the structure, its ability to self-assemble was explored. \((\pm)-1\) turned out to be poorly soluble in chloroform and no evidence for the formation of larger self-assembled structures was obtained by NMR spectroscopy (see Supporting Information Chapter 2.2). Also forcing conditions like prolonged heating, ultrasonication, templating and ball-milling failed to induce any form of soluble higher structure.\(^{19} \) The same was true for the optically active forms, \( M^-(-) \) or \( P^+(-) \). We suspect that the absence of hydrogen bonds between the aromatic units of the macrocycle, which stabilize the crown conformation in case of RS and PG, is detrimental to its aptitude for self-assembly. In polar solvents such as acetone, diethyl ether or methanol, \( 1 \) exhibited good solubility. The latter solvent is particularly interesting, as RS and PG are practically insoluble in alcoholic solvents. The solvation of \( 1 \) is presumably facilitated through the increased flexibility of the macrocyclic framework.

The DFT calculations of \( 1 \) suggest a conformation with \( C_{2v} \)-symmetry as major species in solution (see Figure S12, Table S3 and Supporting Information Appendix C). Nevertheless, the \(^1\)H-NMR spectra suggest a well-defined \( C_{2v} \)-symmetric macrocycle, independent of the solvent and devoid of any signal splitting typically expected for \( C_{2v} \)-symmetry. Consequently, it can be proposed that two rapidly interconverting pseudo-boat conformers are present in solution. Similar observations have been made for a related system.\(^{20} \)

In light of the systematic differences between \( 1 \) and its sister macrocycles, the question arose to which extent their guest binding capability differs. We investigated the binding of organic ammonium guests. Acetone was chosen as solvent due to the good solubility of all three hosts (see Figure S2). Initial experiments with \( (\pm)-1 \) and varying concentrations of methylpyridinium guests \( G1 \) and \( G2 \) showed considerable shifts of the host and guest signals indicating the formation of host-guest complexes in fast-exchange on the NMR timescale (Figure 3, see Supporting Information Chapter 3.1).

![Diagram](image)

Figure 3. Host guest interactions of \((\pm)-1\) with guests \( G1 \) and \( G5 \). a) Partial \(^1\)H-NMR spectra of \( G2; (\pm)-1 + G2 \) (1:1, 4 mM); (\pm)-1; (\pm)-1 + G1 (1:1, 4 mM); \( G1 \); b),c) NMR shifts \( \Delta \delta \) of \((\pm)-1\) signals with increasing equivalents of \( G1 \) and \( G2 \) and their corresponding binding constants \( K_b \) for \((\pm)-1\)c\( G1 \) and \((\pm)-1\)c\( G2 \). All spectra were recorded in acetone-\(d_6 \).

Interestingly, binding of \( G1 \) and \( G2 \) was substantially higher in \( RS \) and \( PG \). A small library of five achiral guest molecules was investigated, comprising mono- and dicationic \((G1, G2)\) methylpyridinium salts, as well as benzylic \((G3)\) and phenyllic \((G4, G5)\) tri- and dimethylammonium salts. The hexafluorophosphate counterion ensured good solubility of these salts in acetone. As all three macrocycles were in fast exchange with their respective guests, the binding constants \( K_b \) for the host-guest complexes were determined by means of \(^1\)H-NMR titration in acetone-\(d_6 \) (Table 2).\(^{21} \)

**Table 2.** Binding constants \( K_b \) of \((\pm)-1\), RS and PG and the corresponding guest \((M^+)\), determined by \(^1\)H-NMR titration in acetone-\(d_6 \). Titrations performed at 4 mM of host. n.d.: \( K_b \) could not be determined by means of NMR titration.

<table>
<thead>
<tr>
<th>G#</th>
<th>((\pm)-1)</th>
<th>RS</th>
<th>PG</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>992 ± 17 M(^{-1})</td>
<td>47.2 ± 0.80</td>
<td>152 ± 3.2</td>
</tr>
<tr>
<td>G2</td>
<td>117 ± 0.80 M(^{-1})</td>
<td>10.5 ± 0.18</td>
<td>34 ± 0.10</td>
</tr>
<tr>
<td>G3</td>
<td>32.7 ± 0.22 M(^{-1})</td>
<td>n.d.</td>
<td>15.8 ± 0.045</td>
</tr>
<tr>
<td>G4</td>
<td>83.3 ± 1.3 M(^{-1})</td>
<td>12.5 ± 0.22</td>
<td>39.0 ± 0.61</td>
</tr>
<tr>
<td>G5</td>
<td>56.5 ± 0.19 M(^{-1})</td>
<td>8.75 ± 0.076</td>
<td>34.3 ± 0.33</td>
</tr>
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</table>
While all host-guest complexes showed only weak to moderate binding affinities, (±)-1 outperformed the other systems in every case tested. Surprisingly, RS demonstrated the weakest binding capabilities which stands in stark contrast to its properties as a hexameric capsule in apolar solvents.

Upon assessing the achiral binding capabilities we shifted our attention towards chiral recognition using enantiopure (+)-1 and P(+)-1. Initial tests were performed with (S)-G6, a methylated derivative of 1-indamine, an important drug intermediate. The 1H-NMR in acetone-d6 of a 1:2 mixture of (±)-1 and (S)-G6 demonstrated two distinguished sets of signals for the each of the diastereomeric complexes M(−)-1c(S)-G6 and P(+)-1c(S)-G6 (Figure 4b). An exact assignment of the peaks was accomplished by comparison with spectra of pure P(+)-1 and (S)-G6 (Figure 4c).

In order to identify any form of enantioselective binding, a library of four chiral ammonium salts was compiled and the binding constants K of each host-guest pair were determined via 1H-NMR titration in acetone-d6 (Table 3, see Supporting Information Chapter 3.2).

Table 3. Binding constants K of M(−)-1 and P(+)-1 and the corresponding chiral guest (M+), determined by 1H-NMR titration in acetone-d6. Titration performed at 4 mM of host.

<table>
<thead>
<tr>
<th>GF</th>
<th>M(−)-1</th>
<th>P(+)-1</th>
<th>K(M+)/K(M−)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S)-G6</td>
<td>58.4 ± 0.11</td>
<td>47.3 ± 0.085</td>
<td>1.23:1</td>
</tr>
<tr>
<td>(R)-G6</td>
<td>63.8 ± 0.14</td>
<td>79.4 ± 0.23</td>
<td>1.19:1</td>
</tr>
<tr>
<td>(R)-G7</td>
<td>37.7 ± 0.16</td>
<td>55.8 ± 0.26</td>
<td>1.14:1</td>
</tr>
<tr>
<td>(S)-G9</td>
<td>273 ± 0.66</td>
<td>268 ± 0.66</td>
<td>1.02:1</td>
</tr>
</tbody>
</table>

For the structurally related guests (S)-G6, (R)-G7 and (R)-G8 a trend for selectivity of M(−)-1 towards S and P(+)-1 towards R configured guests was observed. In the case of the structurally closely related guests (S)-G6 and (R)-G7, a chiral binding preference is detectable with K(M)/K(P) values amounting to 1.23:1 and 1:1.24, respectively. The overall binding affinity increased with the dicaticonic guest (S)-G9 in accordance to our previous findings with G1. At the same time, binding selectivity with (S)-G9 became almost negligible. This observation may be explained by examining the binding motifs of this particular guest. While (S)-G9 possesses two cationic sites, our results from titration of the achiral guests G2 and G5 with racemic (±)-1 suggest (S)-G9 to primarily bind via its methylpyridinium moiety. Since the chiral information, located on the pyrrolidinium moiety, points away from the chiral cavity of 1, the selectivity might be lost. The strongest chiral recognition was observed for (R)-G8. In this case, the chiral center at the benzylic position displays a high degree of rotational freedom, which may be translated into an enhanced adaptability towards the chiral environment of the host, thus expressing the highest selectivity.

In summary, we have developed a short, high yielding (39% overall yield), and scalable synthesis of a missing member of the calix[4]-arene family denoted “catechol[4]-arene”. This new, inherently chiral macrocycle was characterized in detail and compared to its sister molecules resorcin[4]-arene and pyrogalol[4]-arene. 1 is well soluble in alcohols, while showing poor solubility in apolar solvents such as chloroform, which sets it apart from its close relatives RS and PG. In contrast to RS and PG, no evidence for the formation of larger self-assembled structures was found. However, (±)-1 exhibited guest binding capabilities in polar solvents which exceeded those of RS and PG. This property may be attributed to its more flexible conformation that adapts to maximize the interaction with the individual guests. The enantiomers M(−)-1 and P(+)-1 were accessed by preparative, chiral HPLC and their absolute configuration was assigned by CD-spectroscopy and quantum mechanical calculations. The optically active macrocycles showed modest chiral recognition of optically active ammonium salts. We believe that I could serve as a readily available, inherently chiral macrocyclic platform for further derivatization and applications in chiral recognition, asymmetric catalysis and chiral self-assembly.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and NMR spectra of new compounds (PDF)
Crystallographic data for (±)-1 (CIF)

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REFERENCES


