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Macrotricycles Featuring a π-Basic Tetrahedral Cavity: Preference for NH_4^+ Detected by Electrospray Ionization Mass Spectrometry

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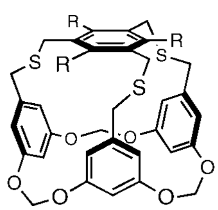
ABSTRACT



1: R = H
2: R = Et

Cation-π interactions play an important role in biology. The title compounds are C_3-symmetric macrotricycles built from resorcinol, a π electron-rich arene. They were prepared in up to 18% yield by intramolecular cyclization of 1,3,5-trisubstituted benzene tripods bearing pendant resorcinol groups, with methylene acetal bridges. Positive ESI-MS showed that these receptors recognize NH_4^+ over K^+, and poorly respond to the large *t*-$BuNH_3^+$ cation, suggesting that they bind NH_4^+ intramolecularly, presumably via cation-π interactions.

Since their discovery and characterization in the gas phase,[1] the occurrence of cation-π interactions[2] in several biological systems has been amply demonstrated,[3] and synthetic receptors for alkali metal[4] and quaternary ammonium[5] cations relying on these interactions have been reported. Cation-π interactions, complementing highly directed hydrogen bonds, are involved in a few NH_4^+-specific receptors,[6] but were

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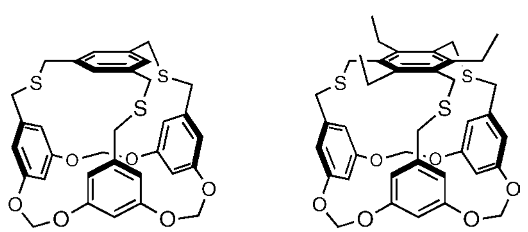
shown to operate marginally[7] in the uptake of the ammonium cation by the ammonium transporters (Amts) found in bacteria and archae.[8−10]

Recently, cylindrical cage-type molecules with π cavities were described, which bind NH_4^+ and Li^+ preferably to other alkali metal cations, via a gate-selective process, as shown by ESI-MS measurements.[11]

In this letter, we present a class of conformationally rigid macrotricycles featuring a potentially tetrahedral π cavity, that are reminiscent of the spheriphanes[12] and use the same technique to probe the selective binding of NH_4^+ over the alkali metal cations and the large t-$BuNH_3^+$ primary ammonium, possibly by intramolecular cation-π interactions.

As carcerands and cavitands,[13] cages **1** and **2** are derived from resorcinol: this π electron-rich arene is incorporated as its methylene acetal and forms a C_3 symmetric macrocyclic substructure that is capped by 1,3,5-trisubstituted benzene at the upper rim via benzylic thioether links. They

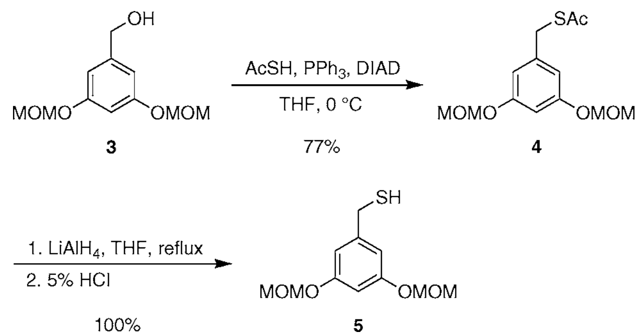


1 **2**

complement the cages derived from hexahomotrioxacalix-[3]arene, which feature CH_2OCH_2 benzylic ether instead of the present OCH_2O acetal bridges.[14] The latter were synthesized by capping of the functionalized hexahomotrioxacalix-[3]arene macrocycle with 1,3,5-trisubstituted benzene. The alternative synthetic strategy was chosen for the present study, that is, intramolecular cyclization of functionalized tripod precursors.[5f,12a,15]

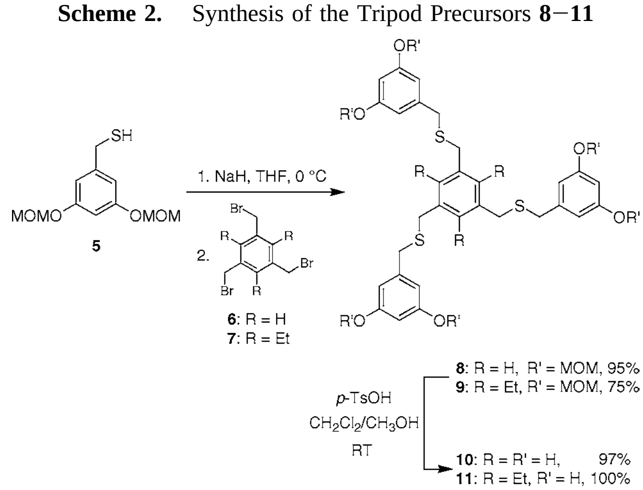
Resorcinol-based tripods **10** and **11** were synthesized in four steps from known 3,5-bis(methoxymethyloxy)benzyl alcohol **3**.[16] At first (Scheme 1), treatment of **3** with

Scheme 1. Preparation of Benzyl Thiol **5**



thiolacetic acid in Mitsunobu reaction conditions (PPh_3, DIAD, THF, 0 °C)[17] afforded the benzylthiolacetate derivative **4** in 77% yield after chromatography. Subsequent reduction of thiolacetate **4** ($LiAlH_4$, THF, reflux) followed by acidification (5% HCl) released the corresponding thiol (**5**) quantitatively. Next (Scheme 2), **5** was deprotonated

Scheme 2. Synthesis of the Tripod Precursors **8**−**11**



(NaH, THF, 0 °C) and condensed at room temperature with stoichiometric amounts of 1,3,5-tribromomethylbenzene **6**

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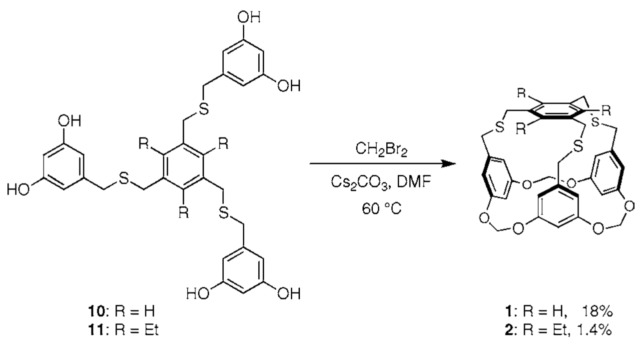
and 1,3,5-triethyl-2,4,6-tribromomethylbenzene **7**, respectively. The resulting protected (MOM) tripods **8** and **9** were obtained in 95 and 75% yields after crystallization (Et_2O). Standard cleavage conditions of the MOM protections (6 N HCl) led to decomposition of the polybenzylic framework. However, nonaqueous conditions (excess *p*-TsOH, 1:1 CH_2Cl_2/MeOH, room temperature)[18] successfully afforded the target resorcinol-based tripods **10** and **11** as beige solids in quantitative yields.

The intramolecular cyclization (Scheme 3) was accomplished by slow addition of a mixture of **10** or **11** and dibromomethane (3 equiv) in DMF to a suspension of Cs_2CO_3 (7.5 equiv) in DMF at 60 °C in high dilution conditions (1 mM). The resulting cages **1** and **2** were isolated in 18 and 1.4% yields, respectively, after chromatography.

Scheme 3. Synthesis of Macrotricycles **1** and **2**



Cage **1** was formed in acceptable yield, as compared to related systems.[12,15] The 1,3,5-triethyl substitution of tripod **11**, by forcing the three resorcinol moieties to be on the same side of the benzene cap,[19] was expected to direct its closure to the cage **2**. However, the low yield of formation of the latter could be ascribed to strain effects arising from steric interactions between the ethyl substituents and the benzyl thioethers upon bridging the pendant resorcinols with the short methylene connectors. As shown by ^{1}H NMR, the macrotricycles have C_{3v} symmetry in solution. Proof of the closed structures rests in the characteristic pairs of doublets of the diastereotopic methylene acetal protons (e.g., for **2**: ^2J = 7.2 Hz and $\Delta\nu$ = 46 Hz in $CDCl_3$), as previously observed for methylene groups of calixarenes fixed in the cone conformation.[20] Noteworthy, these protons show up as a sharp singlet in d^6-dmso.

In the crystal, the structure of cage **2** deviates from C_3 symmetry, because one of the methylene acetal bridges differs from the others (Figure 1). In addition, the aryl cap is only slightly helically twisted. As a consequence, the centroids of the four aryl groups form an elongated tetrahedron: the separation between the resorcinol-derived groups ranges from 4.31 to 5.11 Å, while their average distance to the aryl cap is approximately 6.15 Å.

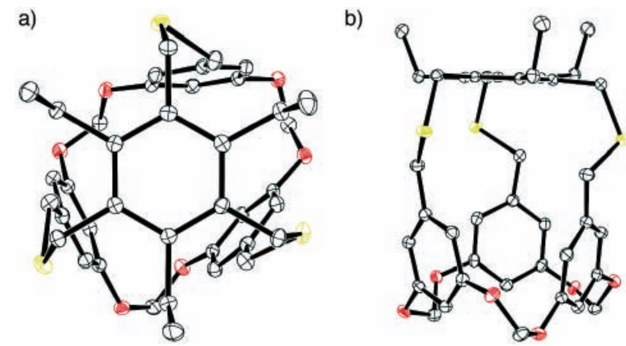


Figure 1. (a) Top and (b) side views (ORTEP) of the X-ray crystal structure of **2**.

The complexation properties of cages **1** and **2** toward the ammonium and alkali cations in solution (MeOH) were investigated by positive electrospray ionization mass spectrometry (+ESI-MS) in the 0−3000 *m/z* range.[21] Both cages (10^{-4} M in MeOH) show very intense signals in the presence of equimolar amounts of NH_4^+ (Figures S9 and S10). In a first series of experiments, a mixture of **1**, LiCl, NaCl, KCl, and CsCl all at 10^{-4} M in MeOH was examined (Figure 2).

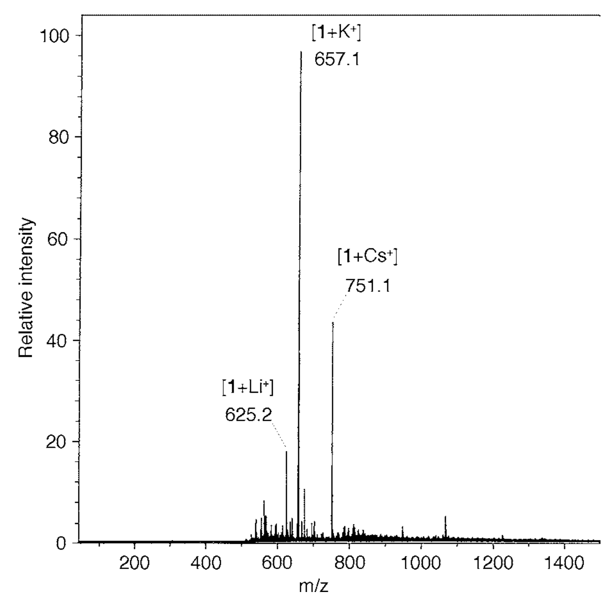


Figure 2. ESI-MS of **1** and a mixture of Li^+, Na^+, K^+, and Cs^+. An enlarged view is shown in Figure S11.

Only signals corresponding to the 1:1 complexes were observed. The absolute signal intensities of $[1 + M]^+$ followed the order $K^+ > Cs^+ > Li^+$, $[1 + Na]^+$ being hardly detected. The signals were left unchanged upon variation of the voltage at the capillary exit between 70 and 300 V. In a

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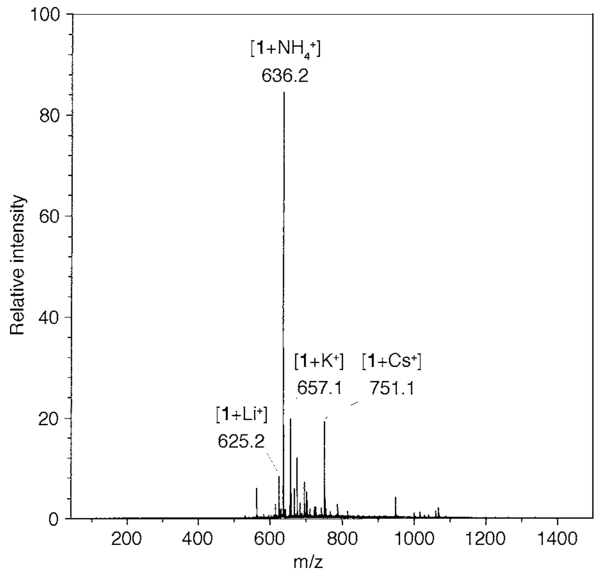

Figure 3. ESI-MS of **1** and a mixture of Li^+, Na^+, K^+, Cs^+, and NH_4^+. An enlarged view is shown in Figure S12.

second series of experiments (Figure 3), an equal amount of NH_4PF_6 in MeOH was added to the mixture. The most intense signal was then due to the ammonium cation and the intensities of $[\mathbf{1} + K]^+$ and $[\mathbf{1} + Cs]^+$ were similar: $NH_4^+ > K^+ \approx Cs^+ > Li^+$. Finally, when NH_4PF_6 and KPF_6 were opposed, the intensity of $[\mathbf{1} + NH_4]^+$ was nearly three times as much as that of $[\mathbf{1} + K]^+$ (Figure S13). Similar observations could be made for cage **2**: examination of a mixture of **2**, LiCl, NaCl, KCl, CsCl, and NH_4PF_6 did not show any trace of Li^+ or Na^+ adduct, and the K^+ and Cs^+ complexes appeared as minor species by comparison with the ammonium complex (Figures S14 and S15).

Selective complexation of NH_4^+ over K^+ has always been challenging,[22a] as these monovalent cations have similar ionic radii (1.43 and 1.33 Å, respectively),[1b] and several synthetic receptors that fulfill this function have been described.[6,22] The most efficient ones (selectivity >400) also form among the most stable complexes with NH_4^+ ($K_a \approx 10^6$ M^{-1}), and all take into account the preference of NH_4^+ for tetrahedral coordination, while K^+ favors coordination numbers of 6 and more. The orientation of NH_4^+ within the cavities of the receptors is imposed by highly directing hydrogen bonds. As a result, in the few examples of complexes involving also cation-π interactions, which have all been characterized crystallographically,[6] NH_4^+ assumes a C_3-symmetrical orientation with respect to the aromatic platforms of the receptors, whereas theoretical studies of the benzene NH_4^+-π complex agree on the preference of a C_2-symmetrical positioning in the absence of any other constraint.[1b,23] In either case the N•••aryl distance is ca. 3 Å.[1b,6c]

As shown by the X-ray crystal structure of **2**, the dimensions of the cages are large enough to accommodate NH_4^+ in a cation-π bonding mode similar to what has been observed in earlier studies,[6] but external binding by the acetal oxygens cannot be ruled out. Indirect indications for inclusion of NH_4^+ into macrotricycle **1** come from comparative +ESI-MS experiments with t-$BuNH_3^+$, a large primary ammonium cation which, according to CPK models, cannot enter the cavities of either **1** or **2**.[22a] As shown in Figure S16, a 1:1 mixture of t-$BuNH_3Cl$ and **1** is hard to detect cleanly, t-$BuNH_3^+$ competing with trace amounts of K^+. This suggests that t-$BuNH_3^+$ interacts only weakly with the macrotricycle. Expectedly, addition of one equivalent of NH_4PF_6 to the mixture gave rise to the strong signal of $[\mathbf{1} + NH_4]^+$ (Figure S17). By contrast, the ^1H NMR spectrum of a solution of **1** (≈5 mM in d^6-dmso)[24] in the presence of a large excess (>50 equiv) of $^{15}NH_4Cl$ did not differ significantly from that obtained with t-$BuNH_3Cl$ (Figures S18 and S19).[25] In particular, the signal of the ammonium proton was left unchanged in both cases, and no additional high field resonance could be found either in the ^1H or ^{15}N NMR spectrum of the former mixture (Figure S19). This indicates that encapsulation of NH_4^+ by **1** is not effective in these latter experimental conditions.

In conclusion, +ESI-MS shows that macrotricycle **1** has a clear preference for binding NH_4^+ over isosteric K^+ or the larger t-$BuNH_3^+$ cation. Definitive proof of inclusion of NH_4^+ in the cavity of the macrotricycles reported here awaits X-ray crystal structure studies.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds, copies of the ^1H NMR and ESI-MS spectra, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) The choice of this solvent was dictated by solubility reasons.

(25) Interestingly, NH_4PF_6 changed the singlet observed for the OCH_2O protons in this solvent to the expected AB system ($^2J = 7.2$ Hz, $\Delta\nu = 8.0$ Hz at ≈ 120 equiv), whereas NH_4Cl and t-$BuNH_3Cl$ did not.