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Synthesis of 1,5-(2,6-dimethylpyridyl)-calix[8]arene: solid-state structure of its dicesium complex

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ABSTRACT

Reaction of *p*-*tert*-butylcalix[8]arene **1** with 2,6-bis(chloromethyl)pyridine results in the regioselective introduction of the nitrogen-containing heterocycle to the 1 and 5 phenolic positions. The deprotonated form of the 1,5-bridged compound **2** acts as a dianionic ligand toward Cs^+. The dicesium complex [**2**·$Cs_2O(H_2O)$], which has water molecules as additional ligands for the cesium cations, was characterized by X-ray crystallography.

Calixarenes and their derivatives are an interesting class of compounds due to their potential applications in diverse areas such as host–guest chemistry, coordination chemistry, catalysis, biomimetic chemistry, sensors, and ion transport.[1] In the specific case of calix[4]arenes, the ease of modification by introduction of several types of functional groups at the phenolic rim has led to the development of numerous examples of versatile compounds.[1,2] The variety of derivatives reported to date is related to the well-established synthetic protocols, which allow the preparation of calix[4]arenes with regio- and atropisomeric control by deprotonation of the phenolic OH groups with specific alkali-metal bases. While a considerable number of studies have focused on the chemistry of *p*-*tert*-butylcalix[4]arenes derivatives, the number of reports on *p*-*tert*-butylcalix[8]arene-derived compounds remains relatively scarce.[3] This can be partly ascribed to the limited information available on the regio- and stereoselective substitution of the larger calixarenes. In addition, the large number of conformations available for calix[8]arenes precludes the long-range ordering required for crystalline forms, thus making the amount of structural information on the eight-membered macrocycles particularly sparse.[4]

A strategy devised to limit the conformational flexibility of calix[8]arenes involves the introduction of intramolecular bridges.[5] To this effect, the use of cesium carbonate has allowed the regioselective introduction of covalent bridges to the 1 and 5 phenolic positions of *p*-*tert*-butylcalix[8]arene **1**, which results in intramolecularly bridged calix[8]crowns.[6] Despite these advances, the introduction of nitrogen-containing spanning elements remains largely unexplored, and the few cases reported are limited by the low yields of 1,4-disubstituted calix[8]arenes obtained.[7] The presence of nitrogen donors as bridging elements in *p*-*tert*-butylcalix[8]arene derivatives could lead to the development of new types of receptors, with the potential to bind different types of metals within the calixarene cavity. To extend the chemistry of nitrogen-containing calix[8]arenes, we herein report the regioselective preparation of a 1,5-disubstituted *p*-*tert*-butylcalix[8]arene by introduction of a 2,6-dimethylpyridyl group. The complexing properties of the intramolecularly bridged calix[8]arene derivative toward cesium ions are also reported, along with the solid-state structure of a dicesium complex.

Following previous reports on the regioselective disubstitution at the 1 and 5 phenolic positions of **1**, we employed 2 equiv of cesium carbonate in anhydrous DMF for the reaction of **1** with 1 equiv of 2,6-bis(chloromethyl)pyridine (see Scheme 1). After 18 h at 70 °C the solvent was evaporated under reduced pressure, and with the purpose of isolating cesium complexes of the calixarene derivatives obtained, we avoided the neutralization step with aqueous HCl reported in related work.[5g] Instead, we extracted the solid with a 10:1 mixture of CH_2Cl_2/CH_3CN, and after filtration slow evaporation of the solvents resulted in colorless microcrystals. Purification of the product by column chromatography was thus avoided, and the solid obtained was characterized by FAB mass spectrometry. A peak consistent with the introduction of a 2,6-dimethylpyridyl group to **1** was detected at $m/z = 1401$ [**2**+H]$^+$, as well as the expected peak corresponding to a cesium

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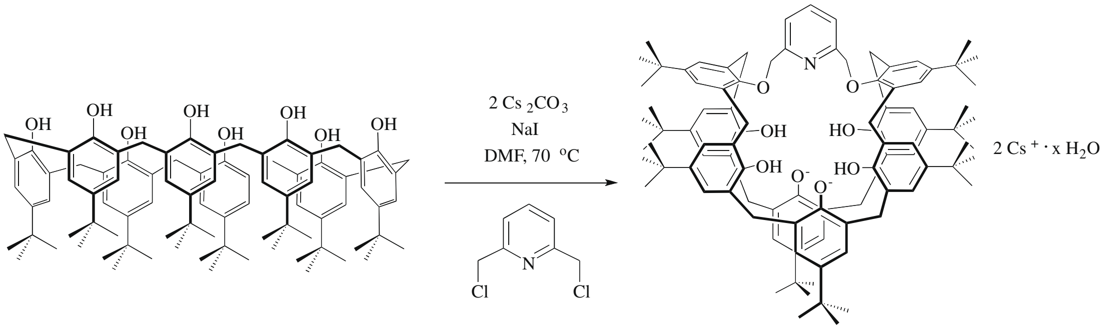

1

$\mathbf{2}\cdot Cs_2(H_2O)_x$

Scheme 1. Preparation of cesium complexes of **2**.

complex of the calix[8]arene derivative at *m/z* = 1533 [**2**+Cs]$^+$. Although this evidence appears to indicate that the product is a calixarene–monocesium complex, combustion analysis agrees with the presence of two cesium ions, with an empirical formula [$\mathbf{2}\cdot Cs_2O$].[8]

In previous reports, the template effect of cesium results in the predominant formation of 1,5-bridged products, except in the introduction of the nitrogen-containing diazobenzene bridge to **1**.[7c] Restriction of the conformational mobility of the macrocycle by an alkali cation allows the determination of the substitution pattern by ^{1}H NMR spectroscopy. In the case of [$\mathbf{2}\cdot Cs_2O$], spectra acquired at 22 °C in $CDCl_3$ or $(CD_3)_2SO$ feature broad resonances attributed to a fluxional behavior in solution, perhaps involving an exchange of the coordination environments of the cesium ions within the calixarene cavity. In contrast, the spectra acquired in toluene-d_7 point to a C_{2v} symmetric calix[8]arene based on the resonances corresponding to the *tert*-butyl groups: the singlets at δ 1.06, 1.32, and 1.41 ppm are consistent with substitution at the 1 and 5 phenolic positions, although further analysis is precluded by the low solubility of [$\mathbf{2}\cdot Cs_2O$] in toluene, even at elevated temperatures.

Fortunately [$\mathbf{2}\cdot Cs_2O$] is more soluble in CD_2Cl_2 than in toluene-D_7, and the ^{1}H NMR signals are relatively sharp, and also consistent with 1,5-disubstitution. Thus, the familiar 2:1:1 pattern of *tert*-butyl groups for a 1,5-bridged calix[8]arene becomes apparent. In addition to the resonances corresponding to the *tert*-butyl groups, two sets of AX coupled systems (δ 3.28 and 3.99, J = 12 Hz; 3.47 and 4.68 J = 14 Hz) are also consistent with $ArCH_2Ar$ groups in a 1,5-substituted calix[8]arene. A broad singlet at δ 3.81 was assigned to acetonitrile exchanging between cesium ions (see below).

When the reaction was serendipitously carried out in DMF that was not freshly distilled, a compound with a slightly different composition was obtained.

This was immediately apparent upon analysis of the ^{1}H NMR spectrum of the product in $CDCl_3$, which displays slightly broadened but clearly distinct signals characteristic of 1,5-disubstitution. Mass spectrometry data of this second product are similar to those of [$\mathbf{2}\cdot Cs_2O$], with the exception of a new peak at *m/z* = 1665, which was assigned to the [(**2**-H)+2Cs]$^+$ ion.

Combustion analysis yields the empirical formula [$\mathbf{2}\cdot Cs_2O(H_2O)$], which is consistent with the dicesium-containing ions observed by mass spectrometry. Addition of D_2O to $CDCl_3$ solutions of [$\mathbf{2}\cdot Cs_2O$] resulted in spectra very similar to those of [$\mathbf{2}\cdot Cs_2O(H_2O)$], indicating that the drastic difference in the ^{1}H NMR spectra is due to water molecules as ligands. The structure that we propose for the complexes corresponds to a doubly deprotonated macrocycle coordinated to two cesium ions, with water molecules completing the coordination sphere of the metal centers [$(\mathbf{2}\text{-}2H)\cdot Cs_2(H_2O)_x$] ($x$ = 1 or 2).

Relative to related calix[8]arene-monocesium complexes,[4h] in which the cesium ion is hosted in the center of the basket-shaped cavity, the arrangement of the two cations in our complexes needs to be addressed. The solid-state structure of [$\mathbf{2}\cdot Cs_2O(H_2O)$] consists of a calix[8]arene with the 2,6-dimethylpyridyl group bridging the 1 and 5 phenolic positions (O2 and O6 in Fig. 1), and two cesium cations hosted within the macrocyclic cavity.[9] The hydrogen atoms of the calixarene OH groups were located on the difference Fourier map, except for those corresponding to O4 and O8 (3 and 7 positions with respect to the pyridyl substituent). This characterizes the calix[8]arene as a dianionic ligand, while the exogenous donors

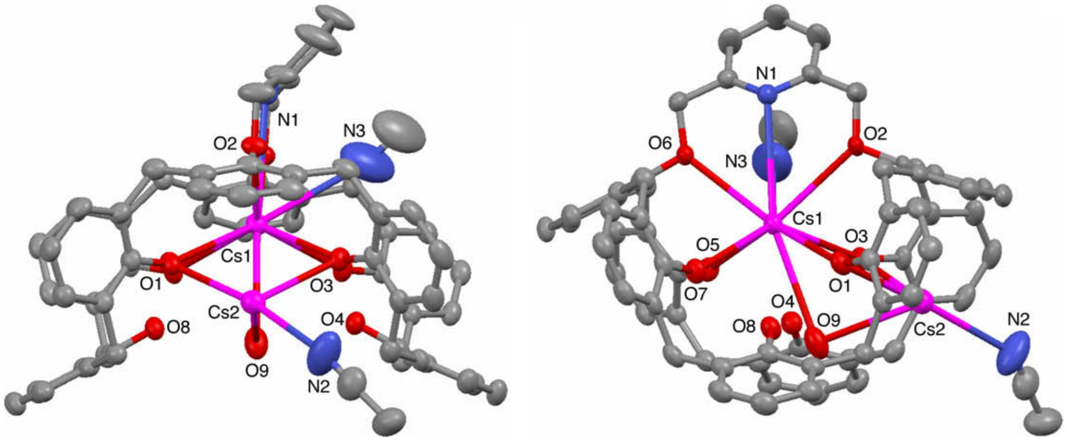

Figure 1. ORTEP diagram of [$(\mathbf{2}\text{-}2H)\cdot Cs_2(H_2O)_2$] from two perspectives at the 50% probability level. Hydrogen atoms, solvent molecules, and *tert*-butyl groups are omitted for clarity.

correspond to H_2O molecules, so that the formula is more accurately expressed as $[(\mathbf{2}\text{-}2H){\cdot}Cs_2(H_2O)_2]$. Single crystals degrade rapidly once dry, and were thus mounted for diffraction directly from the mother liquor. The presence of molecules of the solvents CH_2Cl_2 and CH_3CN as a requisite is evident from the crystal formula C99.60 H124.20 Cl1.19 Cs2 N3 O9.41, 2(C H2 Cl2), C1.83 H2.83 Cl.

Cs1 sits deep within the cavity, thus maximizing the Cs–O contacts, with Cs1–O bonds to six phenolic groups of the calixarene framework (O1–O3, and O5–O7). Interestingly, Cs1 does not interact with the formally anionic O4 and O8, rendering those phenolic positions ideally suited for further substitution.[10]

The Cs1–O bond lengths range from 2.991(3) to 3.373(4) Å, with an average of 3.171 Å, which is within the range of reported Cs–O bonds.[11] The coordination geometry around Cs1 is a distorted, tricapped trigonal prism defined by O1–O3 and O5–O7 triangles. O9 corresponds to a water molecule, which bridges the two cesium ions, and caps the face defined by O1, O3, O5, and O7. In addition, the Cs1–N1 bond [3.456(3) Å] to the pyridyl nitrogen caps the face defined by O2, O3, O5, and O6, while the Cs1–N3 bond [3.37(4) Å] to an acetonitrile molecule caps the O2–O6 edge of the trigonal prism.

Cs2 interacts with the phenolic O1 [3.104(3) Å] and O3 [3.175(4) Å] atoms, while not interacting with the anionic O4 and O8. In addition to the bridging O9 [3.033(3) Å], Cs2 interacts with a molecule of water disordered over 3 positions (O10–O12), placed outside the calixarene cavity. Additionally, the aromatic π-cloud of the pyridyl-bound O2 phenol group coordinates in a η^6—fashion to Cs2, with a Cs2-ring centroid distance of 3.33 Å.

In addition, there is a Cs2–N2 interaction to an acetonitrile molecule, characterized by a bond length of 3.212(6) Å. The coordinated molecules of CH_3CN give rise to broad resonances in the NMR spectra of the cesium complexes of dianionic **2**, probably due to fast exchange between the cations. Based on variable temperature ^1H NMR data acquired on samples of $[(\mathbf{2}\text{-}2H){\cdot}Cs_2(H_2O)_2]$ down to −80 °C in CD_2Cl_2 (Fig. 2), the C_2 symmetry of the 1,5-disubstituted calix[8]arene is maintained on the NMR timescale. Thus, a fast process that exchanges the cesium ion sites must occur in solution.

In conclusion, we have developed a regioselective and high yield method for the introduction of a 2,6-dimethylpyridyl group to the 1 and 5 phenolic positions of **1**. The heteroatom-bridged calix[8]arene derivative **2** can host two cesium cations within its cavity.[12] Efforts to obtain complexes with different metals are currently underway.

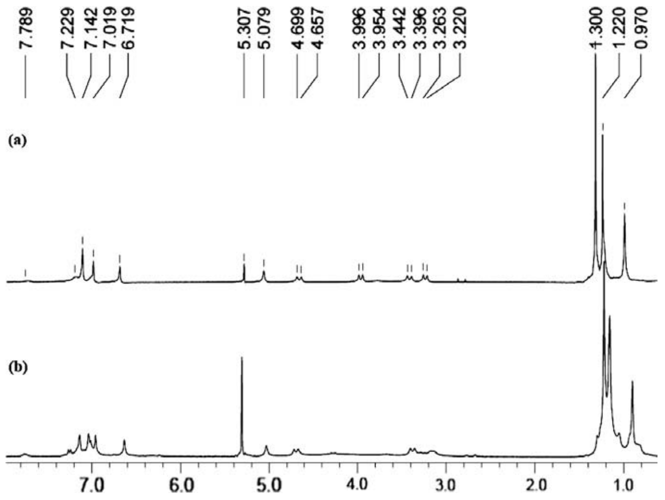

Figure 2. ^1H NMR spectra of $[(\mathbf{2}\text{-}2H){\cdot}Cs_2(H_2O)_2]$ at (a) ambient temperature, and (b) −80 °C in CD_2Cl_2.

Acknowledgments

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8. *Synthesis of* $[\mathbf{2}{\cdot}Cs_2O]$: To a suspension of **1** (1.00 g, 0.77 mmol) in 40 mL anhydrous DMF was added anhydrous Cs_2CO_3 (0.50 g, 1.54 mmol) under a nitrogen atmosphere while stirring. When both reagents had dissolved, solid 2,6-bis(chloromethyl)pyridine (0.14 g, 0.77 mmol), and NaI (15 mg, 0.10 mmol) were added, and the mixture was heated to 70 °C for 18 h. After cooling to room temperature, volatiles were removed under vacuum, the solid was extracted with 3 × 30 mL of 10:1 CH_2Cl_2/CH_3CN, and the solution was filtered through Celite. Slow evaporation yielded colorless microcrystals of $[\mathbf{2}{\cdot}Cs_2O]$; concentration of the mother liquor and afforded more crystals for a yield of 0.88 g (68%); mp (dec.) 325–326 °C; ^1H NMR (CD_2Cl_2, 300 MHz): 0.99 (s, 18H), 1.25 (s, 18H), 1.33 (s, 36H) 3.28 (d, J = 12 Hz, 4H), 3.47 (d, J = 14 Hz, 4H), 3.81 (s, 4H), 3.99 (d, J = 12 Hz, 4H), 4.68 (d, J = 14 Hz, 4H), 4.70 (s, 4H), 6.73 (s, 4H), 7.05 (s, 8H), 7.17 (m, 6H), 7.74 (m, 1H); ^{13}C NMR (CD_2Cl_2, 75 MHz): 30.87, 31.26, 31.72, 31.80, 33.85, 34.10, 34.48, 35.76, 77.18, 120.99, 125.17, 125.59, 125.78, 127.04, 128.10, 129.05, 129.19, 130.09, 135.05, 137.97, 138.12, 141.89, 147.49, 151.21, 151.67, 156.94; IR (KBr): 3386, 3044, 2958, 2907, 2868, 1664, 1596, 1480, 1363, 1294, 1256, 1204, 1117, 876, 820, 800, 731; $C_{95}H_{117}Cs_2NO_9$ (1682.76, $\mathbf{2}{\cdot}Cs_2O$): Calcd C, 67.81; H, 7.01; N, 0.83. Found: C, 67.46; H, 7.03; N, 1.16.

9. *Crystal data* [($\mathbf{2}$-2H)·$Cs_2(H_2O)_{1.41}(CH_3CN)_{2.83}(CH_2Cl_2)_{2.77}$]: $C_{103.42}H_{131.01}Cl_{5.53}Cs_2N_{3.83}O_{9.41}$, $M = 2040.07$, monoclinic, space group $P2_1/n$, $a = 18.839(3)$, $b = 32.253(5)$, $c = 19.718(3)$ Å, $\beta = 117.116(2)°$, $V = 10665(3)$ Å^3, $T = 173(2)$ K, $Z = 4$, $D_c = 1.271$ g cm^{-3}, μ (Mo Kα) = 0.876 mm^{-1}, $F(000) = 4230$. A prismatic crystal (0.26 × 0.22 × 0.18 mm) was mounted on a glass capillary and used for data collection on a Bruker SMART diffractometer equipped with an Apex CCD area detector. Frames were collected by omega scans, and integrated with the Bruker SAINT software package using the appropriate unit cell. The structure was solved with SHELXS-97, and refined by full-matrix least-squares on F^2 with SHELXL-97.[13] The final refinement was based on 19631 unique reflections and 1625 parameters: $R = 0.049$, $R_w = 0.123$, $\delta\rho_{max} = 1.384$ and $\delta\rho_{min} = -0.896$ e Å^{-3}. CCDC 720098 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
10. In FAB MS a peak corresponding to the introduction of a second 2,6-dimethylpyridil group was observed at $m/z = 1636$, which corresponds to its monocesium complex. We are currently exploring the feasibility of its preparation.
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12. Compound **2** was isolated by treatment of its Cs^+ complexes with diluted HCl solution, followed by H_2O and drying.
13. SHELXTL 6.10; Bruker Analytical Instrumentation: Madison, Wisconsin, 2000.