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Calixarenes as enzyme models

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Calixarenes as enzyme models

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A review of the progress towards the use of calixarenes as enzyme models is presented. Double recognition of a substrate is illustrated with the crystal structure of $(H_3O^+)[La(ONC_5H_5)_2(H_2O)_6(p\text{-sulfonatocalix[4]arene})]^- \cdot 6.5H_2O$, 1. The binding of zinc to calixarenes in a second-sphere fashion is shown with the crystal structure of $Na_2[Zn(H_2O)_4(ONC_5H_5)_2][calix[4]arene] \cdot 8.5H_2O$, 4. The preparation and structures of aminomethylcalix[4]arenes are demonstrated with [*p*-(4-(2-pyridyl)piperidinomethyl)calix[4]arene], 5, and [*p*-(4-phenylpiperidinomethyl)calix[4]arene], 6.

INTRODUCTION

The requirements for the design of an enzyme model have been summarized by Dugas[1]:

(1) The model should provide a hydrophobic binding site for the substrate.
(2) The model should afford hydrogen bonding and/or electrostatic binding sites that are complimentary to those of the substrate.
(3) Appropriate catalytic groups should be attached to the model.
(4) The structure of the model should be well defined and rigid.
(5) The model should be water soluble and catalytically active under physiological conditions.

In this contribution the progress towards meeting these criteria with calix[4]arenes[2,3] is reviewed. Particular attention is paid to the development of metal ion binding sites which are also accessible to the hydrophobic pocket. It is shown that the construction of enzyme models based on calix[4]arenes is still some distance in the future, but progress is being made.

It is appropriate to focus on rim-derivatized calix[4]arenes in view of the points noted above. Work in our laboratories has concerned the water soluble *p*-sulfonatocalix[4]arene, and the discussion will treat (a) the hydrophobic pocket, (b) double-recognition of a substrate, and (c) binding of catalytically active metals at the upper rim of the cavity.

In the cone conformation,[2] the hydrophobic pocket of *p*-sulfonatocalix[4]arene is of appropriate size to accommodate small molecular or ionic guests, as is seen in Figure 1.[4] In the absence of an appropriate guest, the water-soluble calix[4]arene must take one or more water molecules into the cavity. For $Na_4[p\text{-sulfonatocalix[4]arene}] \cdot 13.5H_2O$, one water molecule is deeply imbedded in the cavity. The O(water)...centroid(aromatic) distances are 3.16, 4.19, 3.19, and 4.08 Å and the hydrogen atoms are directed towards the two closest aromatic centroids. The H...centroid distances are 2.38 and 2.50 Å, and the O...H–centroid angles are 127 and 133°. The H–O–H bond angle is 125°.[5]

Cyclodextrins have played an important role in the search for metalloenzyme models.[6,7] Tabushi[8] has noted the need for a 'double recognition' which involves both metal coordination recognition and hydrophobic recognition. Two approaches have evolved. In one, the focus has been on the catalysis, while in the other emphasis has been placed on structural models. The second-sphere coordination of transition metals by cyclodextrins has been an outgrowth of the structural model approach.[9–21]

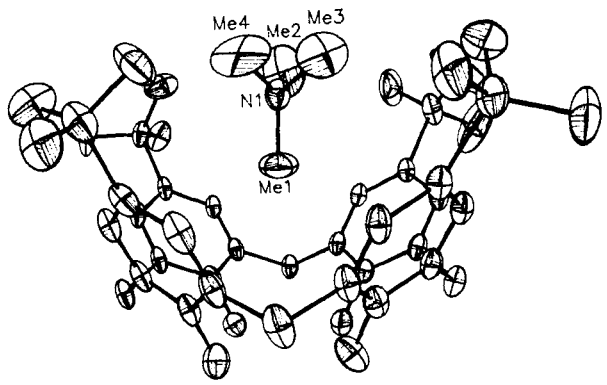
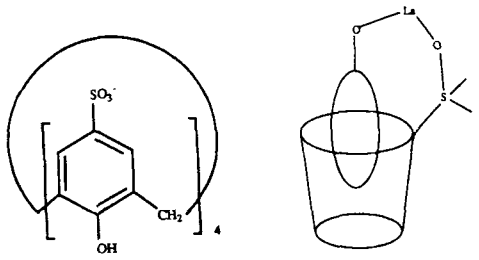


Figure 1 Structure of the complex of [*p*-sulfonatocalix[4]-arene]$^{5-}$ with NMe_4^+ illustrating the size and shape of the calix[4]arene cavity.

* To whom correspondence should be addressed.



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3

Indeed, Stoddart[9,10] has prepared complexes in which the metal is hydrogen bonded via primary-sphere ammine ligands to α-cyclodextrin, with the organic ligands held within the cavity. In this contribution we reveal a complex, $(H_3O^+)[La(ONC_5H_5)_2(H_2O)_6(p\text{-sulfonatocalix[4]arene})]^- \cdot 6.5H_2O$, **1**, in which a metal ion is directly bonded to the upper rim of a calix[4]arene (**2**) and a primary-sphere ligand is inserted in the cavity (**3**), effecting a double-recognition of the ligand. In addition, we present structural information on $Na_2[Zn(H_2O)_4(ONC_5H_5)_2][calix\text{-}[4]arene] \cdot 8.5H_2O$, **4**, in which the zinc coordination complex is bonded to the calix[4]arene by a combination of weak bonding forces. Finally, it is clear that amino-functionality will provide better metal binding than sulfonato-functionality. First efforts in this direction are illustrated by the structure of [*p*-(4-(2-pyridyl)piperidinomethyl)calix[4]arene], **5**.

RESULTS AND DISCUSSION

Structure of $(H_3O^+)[La(ONC_5H_5)_2(H_2O)_6(p\text{-sulfonatocalix[4]arene})]^- \cdot 6.5H_2O$, 1

The complex, shown in Figure 2, features a 9 coordinate lanthanum(III) ion. One of the nine ligands is [*p*-sulfonatocalix[4]arene]$^{4-}$ which is bonded to the La^{3+} ion through a sulfonate oxygen atom. A pyridine N-oxide ligand is bonded to the metal ion (La–O = 2.489(6) Å) and a portion of the hydrophobic aromatic ring is inserted into the hydrophobic calix[4]arene cavity. The depth of penetration may be measured by the distance of the centroid of the pyridine ring from the plane of the calix[4]arene $-CH_2-$ carbon atoms. The value in this complex, 4.3 Å, may be compared with 4.0 Å for $C_5H_5NH^+$ in Na_4(pyridinium)[*p*-sulfonatocalix-[4]-arene]$\cdot 8H_2O$.[22] Thus, in the metalloenzyme analogy the pyridine N-oxide is recognized by both the metal coordination and the hydrophobic complexation.

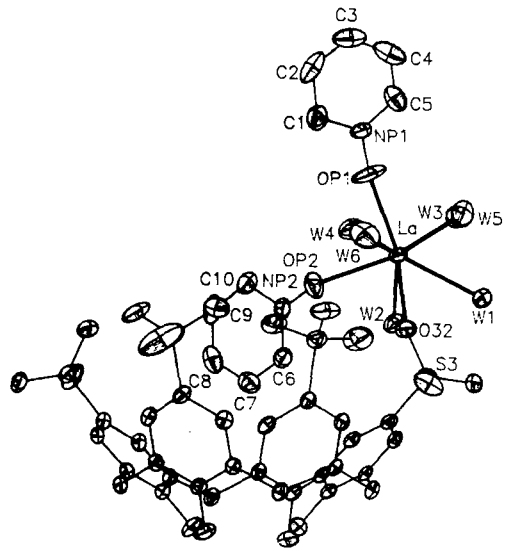

Figure 2 Coordination environment of the La^{3+} ion in $(H_3O^+)[La(ONC_5H_5)_2(H_2O)_6(p\text{-sulfonatocalix[4]arene})]^- \cdot 6.5H_2O$, **1**, illustrating double recognition of the pyridine N-oxide.

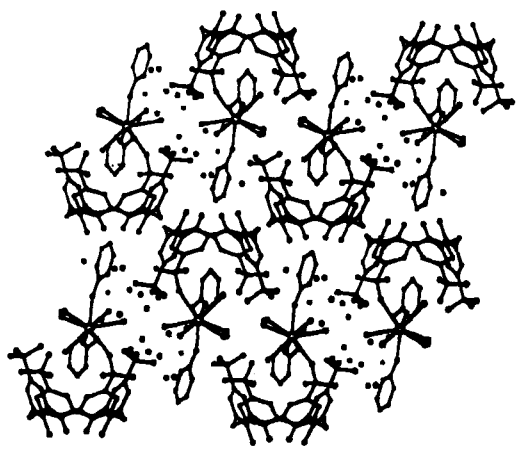

Figure 3 Crystal packing diagram for $(H_3O^+)[La(ONC_5H_5)_2(H_2O)_6(p\text{-sulfonatocalix[4]arene})]^- \cdot 6.5H_2O$, **1**, showing the bilayer arrangement of the calix[4]arenes. One metal coordinated pyridine N-oxide ligand is intercalated into the calix[4]arene bilayer.

The crystal structure is composed of alternating hydrophobic calix[4]arene bilayers and hydrophilic layers,[23,24] spanned by the metal ion complex (Fig 3). The second pyridine N-oxide ligand (La–O = 2.375(6) Å) is intercalated into the calix[4]arene bilayer.[25]

Structure of $Na_2[Zn(H_2O)_4(ONC_5H_5)_2][p\text{-sulfonatocalix[4]arene}] \cdot 8.5H_2O$, 4

The chemistry of Zn^{2+} is of interest in the context of this discussion because the metal ion is central to the functioning of such metalloproteins as carboxy-peptidase and carbonic anhydrase.[26] Indeed, the latter

contains a Zn^{2+} coordinated to the nitrogen atoms of three histidine residues, and the ion is near a hydrophobic pocket which contains eight ordered water molecules.[27] The attempted preparation of a complex of Zn^{2+} with pyridine failed, presumably due to the appreciable acidity of the $Zn(H_2O)_6^{2+}$ ion which readily protonates the pyridine base and produces an insoluble material.[28]

The second, successful attempt involving the use of pyridine N-oxide led to the crystallization of **4**. The central features of the structure are revealed in Figure 4. One pyridine N-oxide ligand of an octahedral *trans*-$[Zn(H_2O)_4(ONC_5H_5)_2]^{2+}$ ion is bound within the cavity of the negatively charged calix[4]arene. The calix[4]arene thus functions as a second-sphere ligand for the Zn^{2+} ion. A second, symmetry-related complex is found across the hydrophilic layer (Fig 5) such that the cavities of the calix[4]arenes are approximately aligned with each other. The two Zn^{2+} ions lie at either sides of the two calix[4]arenes and all four of their aqua ligands interact with two adjacent sulfonato groups on both calix[4]arenes. This means that there are eight hydrogen bonding interactions per zinc center (each hydrogen atom of each aqua ligand is involved in hydrogen bonding). The eight O...O distances range from 2.76 to 3.05 Å. This supramolecular dimer is thus held together by a combination of weak forces.[22]

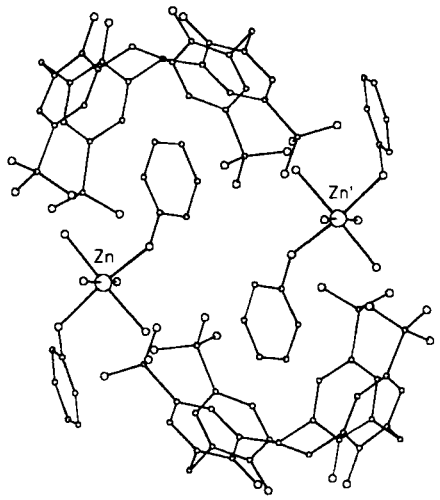

Figure 4 View of the dimeric structure of $Na_2[Zn(H_2O)_4(ONC_5H_5)_2]$p-sulfonato[calix[4]arene]·$8.5H_2O$, **4**.

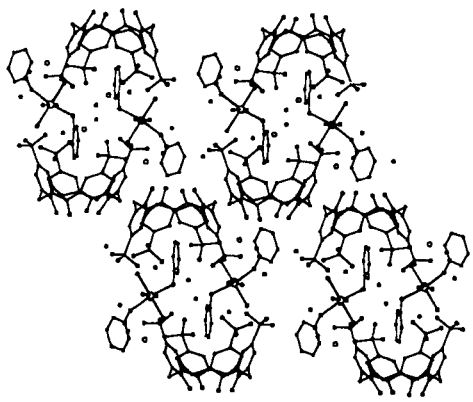

Figure 5 Crystal packing of $Na_2[Zn(H_2O)_4(ONC_5H_5)_2]$p-sulfonato[calix-[4]arene]·$8.5H_2O$, **4**, showing the bilayer arrangement. As for the structure of **1**, one of the pyridine N-oxide ligands is intercalated into the calix[4]arene bilayer.

Pyridine N-oxide ligand in 1 and 4

An additional point of interest concerns the nature of the pyridine N-oxide ligand. The mesomeric forms of pyridine N-oxide shown in Figure 6 indicate that a formal positive charge appears on nitrogen as a result of donative bond formation to oxygen. These mesomeric forms also indicate that the formal positive charge may be distributed onto the ring. On the other hand, since nitrogen acts as a σ-donor and also has a vacant p-orbital available for back-donation from oxygen, the mesomeric forms must also be considered in which the N–O bond has significant double bond character and negative charge is distributed onto the ring. In the $[Zn(H_2O)_4(ONC_5H_5)_2]^{2+}$ ion the N–O bond lengths are 1.336(8) and 1.340(8) Å. These values may be compared with other crystallographically determined values of 1.34 Å for pyridine N-oxide,[29] 1.37 Å for its hydrochloride salt[30] and 1.34 Å for a copper complex.[31] Thus, the apparent insensitivity of the N–O bond length seems to suggest that coordination of oxygen to a metal center occurs primarily by σ-donation with little contribution from π back-bonding. Indeed this must be true in the case of Zn^{2+} since it has a d^{10} electronic configuration. Furthermore, the Zn–O–N bond angles are 118.9(5) and 121.3(4)°

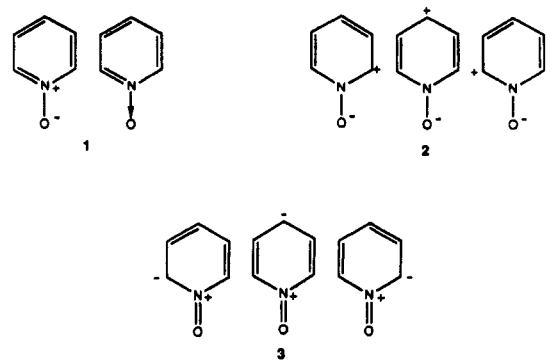

Figure 6 Mesomeric forms of pyridine N-oxide: (1) positive charge located on nitrogen with no N–O double bond character; (2) distribution of positive charge onto the ring with no N–O double bond character; (3) back-donation from oxygen to nitrogen with N–O double bond character.

suggesting that the oxygen atom is essentially sp^2 in character. Finally, the Zn–O–N–C torsion angles are very nearly 90° (84.2 and 86.5°) which implies that the p-orbitals on the nitrogen and oxygen atoms are necessarily mutually orthogonal, thus precluding significant N–O double bond character.[32]

For structure **1** the La–O distance in the case of the pyridine N-oxide ligand bound within the calix[4]arene cavity is 2.489(6) Å. This value is consistent with the range of 2.49–2.50 Å found in the complex $[La(ONC_5H_5)_8](ClO_4)_3$,[33] as is the La–O–N angle of 136.2(5)° compared with the range of 127.7–136.6°. The N–O bond distance in this case is 1.326(8) Å.[33] In contrast, the La–O distance of 2.375(6) Å in the case of the second pyridine N-oxide ligand, which is projected away from the calix[4]arene and is intercalated into the hydrophobic layer, is significantly shorter than expected. The N–O distance is shortened to 1.301(8) Å and the La–O–N bond angle is 160.0(6)°. A possible explanation is that given that the La–O–N angle has been forced open, the oxygen may then approach the lanthanum center more closely since steric interactions between the aqua ligands and the pyridine N-oxide ring have been relieved. However, it is then difficult to rationalize the small contraction of the N–O bond length. The La–O–N–C torsion angles are larger than expected if there is to be significant N–O π-bond character (75.6° for the intercalated one and 86.2° for the intracavity one).

Synthesis and structure of [*p*-(4-(2-pyridyl)piperidinomethyl)calix[4]arene], 5

Gutsche and Nam[34] reported in 1988 the acetic acid-catalyzed aminomethylation of calix[4]arene in the presence of formaldehyde and dimethylamine in THF. This Mannich reaction[35] can be used to synthesize a wide range of aminomethylcalix[4]arenes, two of which are [*p*-(4-(2-pyridyl)piperidinomethyl)-calix[4]arene], **5**, and [*p*-(4-phenylpiperidinomethyl)-calix[4]arene], **6**.

The structure of **5**, Figure 7, illustrates the flexibility about the $-CH_2-$ spacer of the extended cavity calix[4]arene. Three arms are extended upward from the cavity, while the fourth is directed away at almost 90° to the cavity. However, the complete view of the structure, Figure 8, shows that **5** exists as a supramolecular dimer situated over a crystallographic center of inversion. The dimer is held together by the insertion of one arm from each calix[4]arene into the cavity of the other. Of the remaining three arms on each calix[4]arene, two are positioned in the direction of the other calix[4]arene, forming four walls to the dimer. The remaining arm on each is directed away from the center of the structure. $(\mathbf{5})_2$ is thus held together by the hydrophobic interaction of the two intracavity pyridyl rings with the opposite cavities. As the crystal packing diagram, Figure 9, shows, the exterior arms are packed among the dimers.

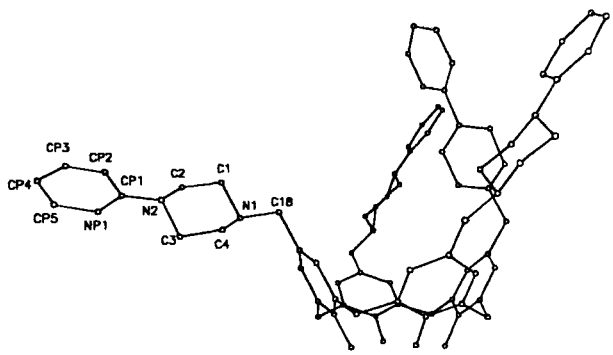

Figure 7 Structure of one molecule of [*p*-(4-(2-pyridyl)piperidinomethyl)calix[4]arene], **5**.

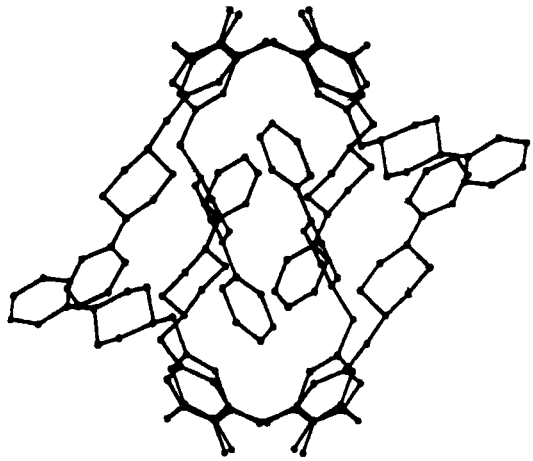

Figure 8 Dimeric structure of **5** (over a crystallographic center of inversion).

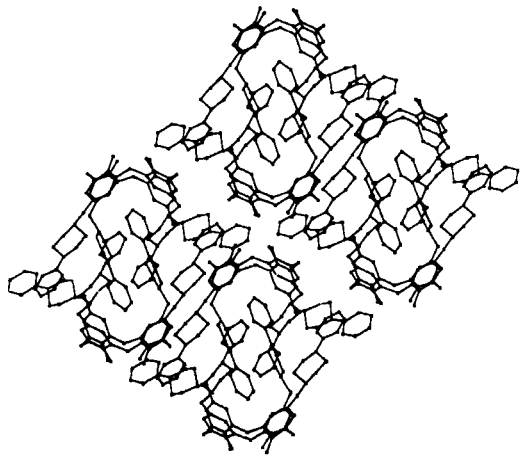

Figure 9 Packing diagram of **5** illustrating the assembly of the dimeric units in the crystal.

The aminomethylcalix[4]arene, **5**, is rich in metal ion binding sites. However, the compound has good solubility in ethyl acetate, but poor water solubility. The synthesis of water soluble aminomethylcalix[4]-amines with their metal binding sites unprotonated is in progress.

EXPERIMENTAL SECTION

Preparation of $(H_3O^+)[La(ONC_5H_5)_2(H_2O)_6(p$-sulfonatocalix[4]arene)$]^- \cdot 6.5H_2O$, 1

$Na_4[p$-sulfonatocalix[4]arene] was synthesized as in ref. 5. The preparation of **1** was accomplished by the addition of one equivalent of $La(NO_3)_3$ and eight equivalents of pyridine N-oxide to a solution of one equivalent of $Na_4[p$-sulfonatocalix[4]arene] in water. Large, pale yellow crystals of **1** grew upon slow evaporation.

Preparation of $Na_2[Zn(H_2O)_4(ONC_5H_5)_2][p$-sulfonatocalix[4]arene$] \cdot 8.5H_2O$, 4

$Na_5[p$-sulfonatocalix[4]arene] was synthesized as in ref. 5. The preparation of **4** was accomplished by the addition of one equivalent of $Zn(NO_3)_2$ and two equivalents of pyridine N-oxide to a solution of one equivalent of $Na_5[p$-sulfonatocalix[4]arene] in water. Large, colorless crystals of **4** grew upon slow evaporation.

Synthesis of [*p*-(4-(2-pyridyl)piperidinomethyl)-calix[4]arene], 5

In a 100 mL round-bottomed flask fitted with a magnetic stirrer, 1.00 g (2.36 mmol) of calix[4]arene and 1.93 g (11.8 mmol) of 1-(2-pyridyl)piperazine were dissolved in 25 mL of THF and 2.7 mL of glacial acetic acid. To the resulting colorless solution, 0.88 mL (11.8 mmol) of 37% aqueous formaldehyde solution was added and the contents were stirred in a sealed flask at room temperature. After 2 h the solution turned pale green. TLC analysis indicated the absence of calix[4]arene after 8 h. The stirring was continued for a total of 32 h after which the volatile components were removed under vacuum at 40°. The resulting pale green residue was dissolved in 25 mL of distilled water, extracted twice with 25 mL of ethyl ether, and neutralized to pH 9 with 10% K_2CO_3 solution. To the mixture, 50 mL of $CHCl_3$ was added and the contents were stirred until both phases cleared. The aqueous phase was extracted twice more with 50 mL of $CHCl_3$. The combined organic phases were washed with distilled water, dried over anhydrous Na_2SO_4, and evaporated to dryness with a rotary evaporator. The residue was dissolved in a minimum amount of boiling ethyl acetate and crystallization was effected by the addition of isopropanol followed by cooling in an ice bath. The crystalline solid was collected on a medium-mesh fritted funnel, washed with a small amount of ice-cold ethyl ether, and dried under vacuum at 40° for 48 h to afford 2.2 g (82%) of colorless plates: m.p. 118–120°; ^{1}H NMR ($CDCl_3$) δ = 9.42 (br s, 4H, OH), 8.17 (br m, 4H, Ar′ H-6), 7.43 (m, 4H, Ar′H-4), 7.04 (s, 8H, ArH), 6.59 (br m, 8H, Ar′H-3,5), 4.25 and 3.54 (br pair of d, 8H, $ArCH_2Ar$), 3.52 (br t, 8H, J = 4 Hz, CH_2N-Ar′), 3.35 (s, 8H, $ArCH_2N$), 2.51 (br t, 8H, J = 4.7 Hz, NCH_2); ^{13}C NMR ($CDCl_3$) δ = 159.6 (Ar′-2), 148.1 (Ar-OH), 148.0 (Ar′-6), 137.4 (Ar′-4), 131.4 (Ar-para), 129.9 (Ar-meta), 128.1 (Ar-ortho), 113.2 (Ar′-5), 107.0 (Ar′-3), 62.4 ($ArCH_2N$), 52.8 (CH_2N-Ar″), 45.1 (NCH_2), 31.8 ($ArCH_2Ar$). X-ray diffraction-quality crystals were obtained by carefully layering isopropanol onto a solution in ethyl acetate. Crystals formed at the interface over a 24 h period at room temperature.

Synthesis of [*p*-(4-phenylpiperidinomethyl)calix[4]-arene], 6

In a 100 mL round-bottomed flask fitted with a magnetic stirrer, 1.00 g (2.36 mmol) of calix[4]arene and 1.91 g (11.8 mmol) of 1-phenylpiperazine were dissolved in 25 mL of THF and 2.7 mL of glacial acetic acid. To the resulting colorless solution, 0.88 mL (11.8 mmol) of 37% aqueous formaldehyde solution was added and the contents were stirred in a sealed flask at room temperature. TLC analysis indicated the absence of calix[4]arene after 10 h. The stirring was continued for a total of 40 h after which the volatile components were removed under vacuum at 40°. The resulting yellow-green residue was dissolved in 50 mL of methanol, the pH was adjusted to approximately 9 with 10% K_2CO_3 solution, and the resulting suspension was stirred for 1 h. To the mixture, 100 mL of distilled water and 50 mL of $CHCl_3$ were added and the contents were stirred until both phases cleared. The aqueous phase was extracted twice more with 50 mL of $CHCl_3$. The combined organic phases were washed with distilled water, dried over anhydrous Na_2SO_4, and the volatile components were removed on a rotary evaporator. The residue was dissolved in a minimum amount of boiling ethyl acetate and crystallization was effected by the addition of hot methanol followed by cooling in an ice bath. The crystalline solid was collected on a medium-mesh fritted funnel, washed with a small amount of ice-cold ethyl ether, and dried under vacuum at 40° for 48 h to afford 2.1 g (81%) of colorless plates: m.p. 194–195°; ^{1}H NMR ($CDCl_3$) δ = 10.6 (br s, 4H,

OH), 7.23 (m, 8H, Ar'H-meta), 7.05 (s, 8H, ArH), 6.89 (m, 8H, Ar'H-ortho), 6.83 (m, 4H, Ar'H-para), 4.25 and 3.54 (br pair of d, 8H, J = 13.2 Hz, $ArCH_2Ar$), 3.34 (s, 8H, $ArCH_2N$), 3.17 (br m, 16H, CH_2N-Ar'), 2.53 (br m, 16H, NCH_2); ^{13}C NMR ($CDCl_3$) $\delta = 1.51$ (Ar'-N), 148.0 (Ar-OH), 131.7 (Ar-para), 129.7 (Ar-meta), 129.1 (Ar'-meta), 128.1 (Ar-ortho), 119.6 (Ar'-para), 116.0 (Ar'-ortho), 62.5 ($ArCH_2N$), 53.1 (CH_2-Ar'), 49.1 (NCH_2), 31.8 ($ArCH_2Ar$). X-ray diffraction-quality crystals were obtained by carefully layering methanol onto a solution of ethyl acetate. Crystals formed at the interface over a 24 h period at room temperature.

X-ray structure determination of $(H_3O^+)[La(ONC_5H_5)_2(H_2O)_6$(*p*-sulfonatocalix[4]arene)$]^- \cdot 6.5H_2O$, 1

The compound quickly decomposes via loss of H_2O, so the crystals were mounted in thin-walled capillaries with a drop of mother liquor. Details of usual procedures in our laboratory have been given previously.[36] A summary of data collection parameters and crystal data is presented in Table 1. The structure was solved using Patterson methods. All non-hydrogen atoms except for the fractional occupancy water molecules were treated with anisotropic thermal parameters. The oxonium ion was assigned for charge balance. Hydrogen atoms on the pyridine N-oxide ligands and on the calix[4]arene were placed in calculated positions and were not refined. Occupancy factors were initially assigned by observation of the thermal parameters and finally by refinement. Final fractional coordinates are presented in Table 2.

X-ray structure determination of $Na_2[Zn(H_2O)_4(ONC_5H_5)_2]$[*p*-sulfonatocalix[4]arene]$\cdot 8.5H_2O$, 4

A summary of data collection parameters and crystal data is presented in Table 1. The structure was solved in the same manner as for **1** above. All non-hydrogen atoms except for the fractional occupancy water molecules were treated with anisotropic thermal parameters. Hydrogen atoms on the pyridine N-oxide ligands and on the calix[4]arene were placed in calculated positions and were not refined. Occupancy factors were assigned by observation of the thermal parameters. Final fractional coordinates are presented in Table 3.

X-ray structure determination of [*p*-(4-(2-pyridyl)-piperidinomethyl)calix[4]arene], 5

A summary of data collection parameters and crystal data is presented in Table 1. The structure was solved using direct methods. All non-hydrogen atoms were treated with anisotropic thermal parameters. Hydrogen atoms were placed in calculated positions and were not refined. Three atoms of a badly disordered organic molecule (either isopropyl alcohol or ethyl acetate) were located in the crystal lattice and were assigned isotropic thermal parameters. Final fractional coordinates are presented in Table 4.

Table 1 Crystal data and summary of data collection

Compound	1	4	5	6
Mol. weight	1314.3	1267.4	*	*
Space group	$P\bar{1}$	$P2_1/n$	$P\bar{1}$	$P\bar{1}$
Cell constants				
a, Å	12.242(5)	11.818(1)	12.248(2)	13.684(6)
b, Å	14.750(5)	28.182(6)	16.948(3)	13.938(6)
c, Å	15.143(3)	15.247(1)	17.065(3)	19.256(8)
α, deg	96.12(2)	90	118.84(2)	78.80(2)
β, deg	102.56(2)	99.26(1)	93.34(2)	89.28(2)
γ, deg	99.50(2)	90	100.05(2)	79.70(2)
V, Å^3	2604	5012	3013	3544
Molecules/unit cell	1	4	2	2
D_c, g cm^{-3}	1.68	1.69	*	*
Radiation	Mo K_α	Mo K_α	Mo K_α	Mo K_α
Decay of standards	<2%	<2%	<2%	<2%
2θ range, deg	2–50	2–50	2–50	2–40
No. reflctns collctd	8122	7416	6182	3794
No. obsvd reflctns	6580	4450	2761	2829
No. parameters varied	748	696	769	805
R	0.048	0.055	0.086	0.130
R_w	0.057	0.064	0.095	0.140

* Molecular weight and calculated density are not listed because not all of the solvent of crystallization has been identified.

Table 2 Final fractional coordinates for 1

Atom	*x/a*	*y/b*	*z/c*
La	0.24416(4)	0.26373(3)	0.47086(3)
S(1)	−0.5508(2)	0.4565(1)	0.2412(1)
O(11)	−0.3641(4)	0.2832(3)	−0.0459(3)
O(12)	−0.6699(4)	0.4131(4)	0.2244(3)
O(13)	−0.4846(5)	0.4372(4)	0.3255(3)
O(14)	−0.5322(5)	0.5545(4)	0.2363(4)
C(11)	−0.4090(5)	0.3215(5)	0.0219(4)
C(12)	−0.3768(5)	0.4166(4)	0.0489(4)
C(13)	−0.4235(5)	0.4580(5)	0.1145(4)
C(14)	−0.4981(5)	0.4042(4)	0.1532(4)
C(15)	−0.5280(5)	0.3096(5)	0.1263(4)
C(16)	−0.4849(5)	0.2654(4)	0.606(4)
C(17)	−0.5173(5)	0.1608(4)	0.0327(4)
S(2)	−0.3345(2)	0.0137(2)	0.3164(1)
O(21)	−0.3533(5)	0.1074(4)	−0.0544(3)
O(22)A	−0.400(2)	0.071(1)	0.3581(9)
O(22)B	−0.298(3)	0.098(1)	0.375(1)
O(23)A	−0.217(1)	0.045(2)	0.369(1)
O(23)B	−0.245(2)	−0.038(2)	0.333(1)
O(24)A	−0.372(3)	−0.080(1)	0.308(1)
O(24)B	−0.438(3)	−0.046(3)	0.314(2)
C(21)	−0.3466(5)	0.0845(4)	0.0317(4)
C(22)	−0.4285(5)	0.1089(4)	0.0771(4)
C(23)	−0.4233(5)	0.0862(4)	0.1639(4)
C(24)	−0.3416(6)	0.0419(5)	0.2043(5)
C(25)	−0.2599(6)	0.0163(4)	0.1584(4)
C(26)	−0.2626(5)	0.0384(4)	0.0723(4)
C(27)	−0.1718(5)	0.0136(4)	0.0241(4)
S(3)	0.2335(2)	0.1052(1)	0.2447(1)
O(31)	−0.1314(4)	0.1858(3)	−0.0415(3)
O(32)	0.2113(4)	0.1402(4)	0.3327(3)
O(33)	0.3408(4)	0.1545(4)	0.2344(3)
O(34)	0.2221(6)	0.0061(4)	0.2312(4)
C(31)	−0.0461(5)	0.1701(4)	0.0256(4)
C(32)	−0.0613(5)	0.0842(4)	0.0577(4)
C(33)	0.0252(5)	0.0657(4)	0.1246(4)
C(34)	0.1256(5)	0.1303(4)	0.1596(4)
C(35)	0.1378(5)	0.2157(4)	0.1266(4)
C(36)	0.0533(5)	0.2368(4)	0.0613(4)
C(37)	0.0690(5)	0.3315(4)	0.0294(5)
S(4)	0.0421(2)	0.5570(1)	0.3124(1)
O(41)	−0.1446(4)	0.3609(3)	−0.0654(3)
O(42)	−0.0438(6)	0.5994(5)	0.3398(4)
O(43)	0.1432(7)	0.6216(6)	0.3140(5)
O(44)	0.0690(6)	0.4854(5)	0.3650(4)
C(41)	−0.1043(5)	0.4081(4)	0.0222(4)
C(42)	0.0022(5)	0.3966(4)	0.0708(4)
C(43)	0.0465(5)	0.4444(4)	0.1575(4)
C(44)	−0.0145(5)	0.5012(4)	0.1979(4)
C(45)	−0.1199(6)	0.5104(4)	0.1496(4)
C(46)	−0.1675(5)	0.4646(4)	0.0611(4)
C(47)	−0.2859(5)	0.4748(5)	0.0120(5)
Op(1)	0.2204(8)	0.2778(7)	0.6229(4)
Np(1)	0.2249(6)	0.2610(5)	0.7061(4)
C(1)	0.1282(8)	0.2241(7)	0.7297(7)
C(2)	0.141(1)	0.2119(7)	0.824(1)
C(3)	0.244(2)	0.2373(9)	0.8797(7)
C(4)	0.331(1)	0.2736(9)	0.8527(8)
C(5)	0.3222(8)	0.2852(7)	0.7676(7)
Op(2)	0.0333(5)	0.2194(5)	0.4132(4)
Np(2)	−0.0487(5)	0.2575(4)	0.3683(4)
C(6)	−0.0735(7)	0.2460(5)	0.2773(5)

Table 2 *continued*

Atom	*x/a*	*y/b*	*z/c*
C(7)	−0.1600(8)	0.2784(7)	0.2289(6)
C(8)	−0.2258(8)	0.3239(7)	0.2719(8)
C(9)	−0.1998(8)	0.3364(7)	0.3653(9)
C(10)	−0.1095(8)	0.3041(7)	0.4143(6)
W(1)	0.4165(4)	0.2809(4)	0.3925(3)
W(2)	0.2066(4)	0.3602(4)	0.3441(3)
W(3)	0.4092(5)	0.3994(5)	0.5448(4)
W(4)	0.1621(6)	0.4113(4)	0.5186(4)
W(5)	0.4053(6)	0.1845(5)	0.5512(5)
W(6)	0.1633(7)	0.1010(5)	0.5072(5)
W(7)	−0.3011(7)	0.3529(6)	−0.2089(5)
W(8)	0.6438(6)	0.4138(6)	0.5394(5)
W(9)	−0.0071(7)	0.0091(6)	0.3438(6)
W(10)	0.6320(8)	0.2132(8)	0.5134(8)
W(11)*	0.164(1)	−0.0446(9)	0.3598(9)
W(12)	1.394(1)	−0.002(1)	0.4263(8)
W(13)	0.891(1)	0.128(1)	0.540(1)
W(14)A	0.717(1)	0.103(1)	0.658(1)
W(14)B	0.767(2)	0.207(2)	0.641(1)
W(15)	0.863(1)	0.195(2)	0.757(1)
W(16)	1.635(1)	0.156(1)	0.7630(8)

* W(11)–W(16) are 0.50 occupancy.

Table 3 Final fractional coordinates for 4

Atom	*x/a*	*y/b*	*z/c*
Zn	0.88217(8)	0.01862(4)	0.73353(7)
Na(1)	0.5196(3)	0.1411(1)	0.7753(2)
Na(2)	0.5278(3)	0.0502(1)	0.4331(2)
S(1)	0.6234(2)	0.12628(8)	0.5676(1)
O(11)	0.8873(4)	0.2822(2)	0.4409(3)
O(12)	0.6890(4)	0.0841(2)	0.5523(4)
O(13)	0.5112(4)	0.1246(2)	0.5137(4)
O(14)	0.6228(5)	0.1330(2)	0.6620(4)
C(11)	0.8256(6)	0.2477(3)	0.4691(5)
C(12)	0.8511(6)	0.2319(3)	0.5580(5)
C(13)	0.7863(6)	0.1954(3)	0.5870(5)
C(14)	0.6963(6)	0.1749(3)	0.5306(5)
C(15)	0.6708(6)	0.1904(3)	0.4436(5)
C(16)	0.7336(6)	0.2265(3)	0.4121(5)
C(17)	0.7068(6)	0.2406(3)	0.3148(5)
S(2)	0.8203(2)	0.09593(8)	0.1328(1)
O(21)	0.9083(4)	0.2882(2)	0.2763(3)
O(22)	0.8067(6)	0.0657(2)	0.2073(5)
O(23)	0.9185(6)	0.0813(3)	0.0946(5)
O(24)	0.7172(7)	0.0972(3)	0.0692(6)
C(21)	0.8870(6)	0.2443(3)	0.2418(5)
C(22)	0.7896(6)	0.2187(3)	0.2594(5)
C(23)	0.7704(6)	0.1742(3)	0.2254(5)
C(24)	0.8438(6)	0.1533(3)	0.1733(5)
C(25)	0.9381(6)	0.1793(3)	0.1560(5)
C(26)	0.9602(6)	0.2238(3)	0.1886(5)
C(27)	1.0690(6)	0.2492(3)	0.1712(5)
S(3)	1.3774(2)	0.11537(8)	0.2432(1)
O(31)	1.1577(4)	0.2915(2)	0.3391(3)
O(32)	1.3779(5)	0.0819(2)	0.3154(4)
O(33)	1.3089(5)	0.0976(2)	0.1626(4)
O(34)	1.4923(5)	0.1296(2)	0.2319(4)
C(31)	1.2051(6)	0.2498(3)	0.3180(5)

Table 3 *continued*

Atom	*x/a*	*y/b*	*z/c*
C(32)	1.1718(6)	0.2302(3)	0.2344(5)
C(33)	1.2254(6)	0.1894(3)	0.2116(5)
C(34)	1.3092(6)	0.1677(3)	0.2724(5)
C(35)	1.3391(6)	0.1858(3)	0.3570(5)
C(36)	1.2886(6)	0.2272(3)	0.3810(5)
C(37)	1.3157(6)	0.2453(3)	0.4757(5)
S(4)	1.2153(2)	0.10000(8)	0.6635(1)
O(41)	1.1019(4)	0.2862(2)	0.4995(3)
O(42)	1.1347(7)	0.0704(2)	0.6055(4)
O(43)	1.1901(5)	0.0982(2)	0.7536(4)
O(44)	1.3338(6)	0.0897(3)	0.6593(5)
C(41)	1.1333(6)	0.2457(3)	0.5451(5)
C(42)	1.2372(6)	0.2231(3)	0.5342(5)
C(43)	1.2637(6)	0.1798(3)	0.5732(5)
C(44)	1.1911(6)	0.1584(3)	0.6252(5)
C(45)	1.0926(6)	0.1826(3)	0.6402(5)
C(46)	1.0632(6)	0.2254(3)	0.6018(5)
C(47)	0.9549(6)	0.2511(3)	0.6192(5)
Op(1)	0.8648(5)	−0.0148(2)	0.6113(4)
Np(1)	0.9285(6)	−0.0534(3)	0.6025(4)
Cp(1)	0.8851(7)	−0.0958(3)	0.6117(5)
Cp(2)	0.9476(8)	−0.1359(3)	0.6007(6)
Cp(3)	1.0559(9)	−0.1314(4)	0.5799(6)
Cp(4)	1.0983(7)	−0.0864(4)	0.5698(6)
Cp(5)	1.0356(7)	−0.0471(4)	0.5823(5)
Op(2)	0.8631(5)	0.0613(2)	0.8427(4)
Np(2)	0.9394(6)	0.0950(3)	0.8717(4)
Cp(6)	0.9157(9)	0.1403(4)	0.8458(6)
Cp(7)	0.989(1)	0.1757(4)	0.8758(8)
Cp(8)	1.089(1)	0.1650(4)	0.9342(8)
Cp(9)	1.1115(8)	0.1196(5)	0.9600(6)
Cp(10)	1.0358(8)	0.0839(4)	0.9277(6)
W(1)	1.0607(4)	0.0155(2)	0.7694(4)
W(2)	0.9039(5)	0.0818(2)	0.6599(4)
W(3)	0.7000(5)	0.0179(3)	0.7105(5)
W(4)	0.8811(6)	−0.0445(2)	0.8082(4)
W(5)	0.4970(4)	0.0430(2)	0.9171(4)
W(6)	0.3686(5)	0.0219(2)	0.5067(4)
W(7)	0.3887(5)	0.1166(3)	0.8765(5)
W(8)	0.6502(5)	0.0951(3)	0.8825(4)
W(9)	0.6338(6)	0.0597(3)	0.3126(5)
W(10)	0.4758(7)	0.0242(4)	0.7546(6)
W(11)*	0.997(2)	0.3841(6)	0.547(1)
W(12)	0.6676(9)	0.5008(4)	0.5164(7)
W(13)	0.999(1)	0.4473(6)	0.573(1)
W(14)	0.866(2)	0.4807(9)	0.542(2)
W(15)	0.858(3)	0.504(1)	0.433(2)

* W(11)–W(15) are 0.50 occupancy.

Table 4 Final fractional coordinates for **5**

Atom	*x/a*	*y/b*	*z/c*
O(11)	−0.8395(7)	−0.9119(6)	0.1136(7)
C(11)	−0.730(1)	−0.854(1)	0.135(1)
C(12)	−0.702(1)	−0.774(1)	0.213(1)
C(13)	−0.589(1)	−0.717(1)	0.234(1)
C(14)	−0.515(1)	−0.753(1)	0.172(1)
C(15)	−0.546(1)	−0.835(1)	0.094(1)
C(16)	−0.660(1)	−0.8918(9)	0.0725(9)
C(17)	−0.690(1)	−0.982(1)	−0.018(1)

Table 4 *continued*

Atom	*x/a*	*y/b*	*z/c*
C(18)	−0.393(1)	−0.692(1)	0.197(1)
N(1)	−0.3307(9)	−0.6935(8)	0.2710(8)
N(2)	−0.129(1)	−0.7041(9)	0.3578(9)
Np(1)	−0.025(1)	−0.795(1)	0.384(1)
C(1)	−0.223(1)	−0.618(1)	0.310(1)
C(2)	−0.156(1)	−0.616(1)	0.386(1)
C(3)	−0.234(1)	−0.783(1)	0.315(1)
C(4)	−0.299(1)	−0.780(1)	0.240(1)
Cp(1)	−0.044(1)	−0.713(1)	0.404(1)
Cp(2)	0.030(1)	−0.635(1)	0.466(1)
Cp(3)	0.116(2)	−0.642(2)	0.510(2)
Cp(4)	0.139(2)	−0.722(2)	0.497(2)
Cp(5)	0.067(2)	−0.801(2)	0.431(2)
O(21)	−0.9197(7)	−0.9737(6)	−0.0548(7)
C(21)	−0.846(1)	−0.9682(9)	−0.113(1)
C(22)	−0.735(1)	−0.9777(9)	−0.098(1)
C(23)	−0.667(1)	−0.9754(9)	−0.159(1)
C(24)	−0.701(1)	−0.969(1)	−0.233(1)
C(25)	−0.813(1)	−0.9579(9)	−0.244(1)
C(26)	−0.884(1)	−0.9585(9)	−0.183(1)
C(27)	−0.999(1)	−0.941(1)	−0.194(1)
C(28)	−0.627(1)	−0.978(1)	−0.305(1)
N(3)	−0.6462(9)	−0.9237(9)	−0.3470(9)
N(4)	−0.578(1)	−0.801(1)	−0.413(1)
Np(2)	−0.556(1)	−0.651(1)	−0.389(1)
C(5)	−0.606(1)	−0.825(1)	−0.286(1)
C(6)	−0.626(2)	−0.770(1)	−0.331(1)
C(7)	−0.612(1)	−0.901(1)	−0.475(1)
C(8)	−0.590(1)	−0.951(1)	−0.425(1)
Cp(6)	−0.554(1)	−0.740(1)	−0.448(1)
Cp(7)	−0.525(1)	−0.770(1)	−0.532(1)
Cp(8)	−0.497(2)	−0.706(2)	−0.560(1)
Cp(9)	−0.499(2)	−0.618(2)	−0.504(2)
Cp(10)	−0.529(2)	−0.593(2)	−0.423(2)
O(31)	−1.0000(7)	−0.8726(6)	−0.0197(6)
C(31)	−1.000(1)	−0.810(1)	−0.049(1)
C(32)	−1.000(1)	−0.8419(9)	−0.1328(9)
C(33)	−0.971(1)	−0.777(1)	−0.161(1)
C(34)	−0.974(1)	−0.685(1)	−0.106(1)
C(35)	−1.000(1)	−0.657(1)	−0.023(1)
C(36)	−1.000(1)	−0.718(1)	0.009(1)
C(37)	−1.000(1)	−0.683(1)	0.0993(9)
C(38)	−0.948(1)	−0.618(1)	−0.143(1)
N(5)	−0.820(2)	−0.575(1)	−0.127(1)
N(6)	−0.614(1)	−0.463(1)	−0.0864(9)
Np(3)	−0.468(1)	−0.332(1)	0.011(1)
C(9)	−0.777(1)	−0.512(1)	−0.034(1)
C(10)	−0.659(2)	−0.461(2)	−0.017(1)
C(11)	−0.659(2)	−0.534(1)	−0.179(1)
C(12)	−0.775(2)	−0.578(2)	−0.189(1)
Cp(11)	−0.498(2)	−0.409(1)	−0.070(1)
Cp(12)	−0.431(1)	−0.437(1)	−0.134(1)
Cp(13)	−0.325(1)	−0.383(1)	−0.114(1)
Cp(14)	−0.288(2)	−0.305(1)	−0.034(1)
Cp(15)	−0.358(2)	−0.280(1)	0.027(1)
O(41)	−0.9734(7)	−0.7991(6)	0.1479(7)
C(41)	−0.931(1)	−0.702(1)	0.197(1)
C(42)	−0.981(1)	−0.646(1)	0.1792(9)
C(43)	−0.941(1)	−0.551	0.232(1)
C(44)	−0.851(1)	−0.513(1)	0.304(1)
C(45)	−0.801(1)	−0.572(1)	0.321(1)
C(46)	−0.837(1)	−0.668(1)	0.267(1)

Table 4 *continued*

Atom	*x/a*	*y/b*	*z/c*
C(47)	−0.780(1)	−0.732(1)	0.281(1)
C(48)	−0.812(1)	−0.409(1)	0.372(1)
N(7)	−0.814(1)	−0.3551(8)	0.3237(8)
N(8)	−0.727(1)	−0.218(1)	0.277(1)
Np(4)	−0.727(1)	−0.73(1)	0.298(1)
C(13)	−0.727(1)	−0.368(1)	0.266(1)
C(14)	−0.733(1)	−0.315(1)	0.217(1)
C(15)	−0.799(1)	−0.199(1)	0.347(1)
C(16)	−0.790(1)	−0.255(1)	0.392(1)
Cp(16)	−0.712(1)	−0.159(1)	0.243(1)
Cp(17)	−0.682(1)	−0.186(1)	0.159(1)
Cp(18)	−0.665(1)	−0.120(2)	0.132(1)
Cp(19)	−0.677(2)	−0.030(2)	0.190(2)
Cp(20)	−0.708(2)	−0.011(2)	0.269(2)
Os(1)	1.086(4)	0.000(4)	0.435(4)
Cs(1)	1.033(3)	0.078(3)	0.559(2)
Cs(2)	1.072(5)	−0.024(5)	0.513(5)

X-ray structure determination of [*p*-(4-phenylpiperidinomethyl)calix[4]arene], 6

A summary of data collection parameters and crystal data is presented in Table 1. The structure was solved using direct methods. All non-hydrogen atoms were treated with anisotropic thermal parameters. At this point in the refinement badly disordered organic fragments and/or water molecules in the crystal lattice prevent final refinement of the structure. However, the identity of the calix[4]arene has been confirmed.

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