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Organization of lower rim *O*-alkylated *p*-phosphonic acid calix[4]arenes

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Abstract

Lower rim *O*-methyl, -*n*-butyl, and *n*-octadecyl calix[4]arenes bearing *p*-phosphonic acid groups on the upper rim have been prepared in high yield, compounds **12–14**. Where possible the compounds have been characterized in the solid state using X-ray diffraction, or as the precursor phosphate esters or a cesium salt. The cone conformation ethyl phosphate ester for the octadecyl compound crystallizes in a bi-layer 39.1 Å thick which approaches the 40 Å of biological membranes. The 1,3-alternate cone conformation of the cesium salt of the *O*-methyl phosphonic acid has a metal ion coordinated to two methoxy groups, four O-P (two from neighboring calixarenes), and two η^3 -C₃ moieties from two 1,3-disposed aromatic rings. MALDI-TOF spectra of compounds **12–14** show successive peaks corresponding to 15, 33 and 16 calixarene units, which is consistent with the intra-molecular H-bonding capabilities of the di-protic phosphonic acid groups where the calixarenes are arranged into layers, including bilayers.

Keywords

calixarenes; self-assembly; phosphonic acid *O*-alkylated calix[4]arene; supramolecular chemistry; mass-spectrometry; nanostructures

Introduction

Nature uses self-organized complementary architectures to form new functional structures held together *via* inherently weak non-covalent interactions. These include the DNA double helix, which spontaneously dimerizes from self-complementary nucleic acid strands¹ and the collagen triple helix, which trimerizes from self-complementary polypeptide strands.² Synthetic systems can be programmed to self-assemble into a variety of arrays including nano-scale molecular containers, which can be used, for example, as nano-reaction vessels or selective carriers of guest molecules.³

Calixarenes are a class of cavitands which are popular with researchers due to the ease with which their basic skeletal framework can be functionalized with self-complementary components.⁴ This functionalization can occur at the so called ‘upper or lower rim’ and can be used to finely tune the coordination and host-guest properties of the calixarene. The addition of sulfonic acid groups to the upper rim imparts water solubility on the calixarenes⁵ which can

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Supplementary Supporting Information Crystallographic information file (cif). This material is available free of charge *via* the Internet at <http://pubs.acs.org>.

bind a wide variety of metal cations,⁶ leading to extraordinary self assembled architectures, for example taking on cuboctahedral and icosahedral geometries.⁷ The addition of phosphonate ester groups to the upper rim of alkylated calixarenes is less well studied presumably due to a more challenging synthetic procedure⁸ relative to the one pot synthesis of *p*-sulfonic acid calixarenes.⁵ Nevertheless the potential applications of the corresponding phosphonic acids has led to their investigation as amphiphilic receptor molecules for the detection of proteins and the recognition of amino alcohols and atrazine in aqueous media, amongst others.⁹

Recently we reported a series of new water-soluble calixarenes, which incorporate phosphonic acid groups on the upper rim with the lower rim devoid of substitution,¹⁰ with a similar synthesis of the *p*-phosphonic acid calix[4]arene, and some lower rim alkyl substituted analogues (including methyl and *n*-propyl), being simultaneously reported by Dziemidowicz *et al.*¹¹ These *p*-phosphonic acid calix[*n*]arenes (*n* = 4, 5, 6 and 8) form supramolecular arrays both in solution and the gas phase which relates in part to the H-bonding capability of the phosphonic acid group.¹⁰ In the present paper we report the synthesis of *p*-phosphonic acid calix[4]arene substituted with a variety of alkyl group substitutions on the lower rim, namely methyl, *n*-butyl and *n*-octadecyl, in an attempt to decouple the effect of the H-bonding of the phosphonic acid groups with that of the lower rim OH groups, although they tend to favour cyclic intramolecular H-bonding. To this end we report their properties in solution and the gas phase along with their packing in the solid state. We also report the structure of a cesium salt for the methyl *O*-substituted compound, as the starting point in developing the metal ion complexation of *p*-phosphonic acid calixarenes in general, now that robust syntheses have been established for the compounds.

Results and Discussion

The synthesis of alkylated *p*-phosphonic acid calix[4]arenes, **12-14**, followed an adoption of the general synthesis of alkylated *p*-phosphonate ester calix[4]arenes,⁸ utilizing a nickel catalyzed Arbuzov reaction on the fully brominated or iodinated calixarene precursors, **5-7**. The alkylated *p*-phosphonate ester calix[4]arenes, **8-11**, were subsequently de-esterified using bromotrimethylsilane (BTMS) to yield the alkylated *p*-phosphonic acid calix[4]arenes, **12-14**, in 92-96% yield (Scheme 1). The recently reported methyl analogue was similarly prepared using the methyl phosphonated ester and different solvents and reagents.¹¹ It is noteworthy that bromination of the octadecyl derivative, **4**, using *N*-bromosuccinimide (NBS) failed to give the desired product in contrast to the methyl and butyl derivatives, **2** and **3** respectively. However, iodination of **4** using silver trifluoroacetate and iodine yielded the fully iodinated calixarene, **7**, which was subsequently phosphorylated to give **11**.

Single-crystal X-ray diffraction was used to authenticate structure on calixarenes **8-12**, as complexes **8a-12a** respectively. Crystalline complexes of **8a-11a** were prepared by slow evaporation of a saturated solution of the calixarene from the respective solvent to yield complex **8a** as **8**·2H₂O, complex **9a** as **9**·C₇H₈·H₂O, complex **10a** as **10**·H₂O and complex **11a** as **11**·H₂O. Crystals of complex **12a** were prepared by slow evaporation of a saturated solution of calixarene **12** with 4 mol equiv of CsNO₃ in 6 *M* HNO₃, with composition **12a** as **12**⁺·Cs⁺·H₂O. Only complexes **11a** and **12a** will be described in detail herein.

Complex **11a** crystallizes in the triclinic space group *P*-1 (No. 2), *Z* = 2, with the asymmetric unit comprising one calixarene and one water molecule. The calixarene molecule adopts the usual cone conformation for calix[4]arene and the calixarenes line up in a head-to-head and tail-to-tail alternating manner creating a pseudo bi-layer arrangement (Figure 1). This packing arrangement is reminiscent of the packing seen for tetra-*O*-octadecylcalix[4]arene, either as a benzene or toluene solvate whereby the alkyl groups pack into bundles rather than interdigitating with other alkyl groups.¹² In the case of tetra-*O*-octadecylcalix[4]arene the

aromatic solvent molecules occupy the interstitial space between the layers of calixarenes whereas in the present case the ethoxy groups of the phosphonate esters protrude into the interstitial space. The water molecule is located at the outer extremity of the calixarene cavity and is associated by hydrogen bonding with two adjacent phosphonate groups on the same calixarene, which is reflected in the P=O...O distances at 2.693 and 2.892 Å (Figure 2A). The orientation of the cavity relative to the alkyl chains can be quantified by the angle θ , between the normal to the plane of the four oxygen centers and the vector of the direction of the alkyl chains being 161°. This shows the flexibility of the calixarene as the angle θ observed in the tetra-*O*-octadecylcalix[4]arene solvates ranges from 159 to 170° (Figure 2B).¹² There is no disorder of the alkyl chains or the phosphonate ester groups.

The calixarene adopts a pinched cone conformation whereby two phenyl rings 1,3-relative to each other are either splayed apart or approach each other with dihedral angles of 30.9, 48.9 and 88.2, 90.2° respectively. The phosphonate ester groups on the two phenyl rings that approach each other have a possible close contact with a P=O...CH₃ distance of 3.204 Å. The alkyl chains of the calixarenes are efficiently packed into an hexagonal close packed arrangement at their van der Waals limit. This is analogous to the hexagonal close packing seen for tetra-*O*-octadecylcalix[4]arene and is attributed to the long chain length controlling the overall packing efficiency.¹² The calixarenes between the same layers have numerous close contacts near the van der Waals limit whereas the calixarenes between different layers have no obvious close contacts near the van der Waals limit. The thickness of the bi-layer for complex **11a** is 39.1 Å, which is close to the thickness of biological membranes at around 40 Å. In contrast the thickness of the bi-layer seen for tetra-*O*-octadecylcalix[4]arene is around 33 Å.¹² The thicker bi-layer herein has implications in the development of new synthetic transmembrane ion channel mimics, for which calixarenes represent an excellent model skeleton, but up until now have not formed appropriately thick bi-layers to span the cell membrane.¹³

Complex **12a** crystallizes in the orthorhombic space group *Pbca* (No. 61), *Z* = 8, with the asymmetric unit comprised of one deprotonated calixarene molecule, one water molecule and one cesium cation. The calixarene molecule adopts the 1,3 cone conformation instead of the usual cone conformation as a result of the conformational flexibility of calixarene due to the ability of the methoxy groups to pass through the annulus of the calixarene. The 1,3 cone conformation relates to optimizing the interaction of the large cation with the calixarene.

The cesium cation resides in the cavity formed by two phenyl groups 1,3-relative to each other being coordinated through the oxygen atoms of the phosphonic acid and methoxy moieties, and has polyhapto coordination with two aromatic rings of the calixarene (Figure 3). This kind of polyhapto coordination has been observed before for the 1:1 cesium complex of *p*-*tert*-butylcalix[4]arene whereby there is delocalization of the negative charge over the aromatic rings.¹⁴ In the present case the negative charge is delocalized over the aromatic rings and phosphonic acid groups but cannot be associated with one particular group. This is a common occurrence in the metal complexes of *p*-sulfonato-calixarenes where X-ray diffraction data is unable to unambiguously determine the number of negative charges on the sulfonate moieties.¹⁵ The coordination distances of cesium are P-O...Cs 3.119 and 3.299 Å, H₃CO...Cs 3.168 and 3.223 Å and C_{Ar}...Cs 3.419 to 3.738 Å. The two remaining phosphonic acid groups form a second cavity that is occupied by a water molecule which is associated with one of the phosphonic acid groups with a P-O...O distance of 2.505 Å.

The overall packing arrangement takes on a bi-layer appearance with the bi-layer coordinated through P-O...Cs interactions (Figure 4). The two phosphonic acid groups associated with the water-occupied cavity coordinate with cesium cations coordinated within the cavity of neighboring calixarenes of a different layer, with P-O...Cs distances of 3.271 and 3.406 Å.

It is noteworthy that the present complex, **12a**, was formed using a 4 molar excess of CsNO₃ relative to the calixarene, and attempts at trying to bind a second cesium cation in the water occupied cavity of the calixarene using a 20 molar excess of CsNO₃ furnished crystals with the same unit cell as complex **12a**. Thus the second cavity is likely to be too small for binding cesium ions.

Previously *p*-phosphonic acid calix[*n*]arenes (*n* = 4, 5, 6 and 8) have been shown to form stable nano-arrays (nano-particles) or nano-rafts (*n* = 4) in the gas phase using MALDI-TOF-MS with around 20 calixarene units (18-30 kDa) per nano-array.¹⁰ As for the *p*-phosphonic acid calixarenes, nano-arrays are also observed in the gas phase for the alkylated *p*-phosphonic acid calix[4]arenes with successive peaks out to 15, 33 and 16 calixarene units for the methyl, butyl and octadecyl derivatives, **12-14**, respectively (Figure 5). The packing of the calixarenes within the nano-arrays for *p*-phosphonic acid calix[4,5]arenes have been proposed to be a bi-layer arrangement.¹⁰ It is reasonable to postulate that the packing within the alkylated *p*-phosphonic acid calix[4]arene nano-arrays is similar with respect to the intramolecular interplay of the polar head groups on the upper rim. The alky groups are then likely to be directed to each other in the bi-layers, including where they are interdigitated as in the structure of octadecyl derivative, as the di-ethyl ester (see above).

The nano-particles of *p*-phosphonic acid calix[4,6]arene are remarkably stable in a solution of d₆-DMSO for 36 and 24 hours respectively whereby they slowly dissociate into their solvated monomeric units.¹⁰ This behaviour is in stark contrast to that observed for tetra-urea-calix[4]arene dimers, which 'denature' within seconds upon addition of a few mol% of DMSO.¹⁶ The addition of *n*-butyl groups to the lower rim of *p*-phosphonic acid calix[4]arene, **13**, stabilize self-assembled nano-particles for up to 96 hours in DMSO, as observed in the ¹H and ³¹P NMR (Figure 6) with freshly prepared solutions of **13** in d₆-DMSO showing a broad singlet and two doublets in the aromatic region for the two equivalent aromatic protons. The doublets are attributed to the splitting by the single phosphorus environment within the conformationally locked self assembled nano-particles and these slowly decrease in intensity as the broad singlet of the more flexible solvated monomers increases in intensity over 96 hours. This dissociation can also be followed by ³¹P NMR whereby two sharp singlets decrease in intensity over time as a broad singlet increases in intensity (Figure 6).

Addition of *n*-butyl groups to the lower rim of *p*-phosphonic acid calix[4]arene increases the stability of the nano-particles in DMSO from 36 to 96 hours relative to the phosphonic acid calix[4]arene devoid of lower rim alkyl groups. This can be attributed to the interplay of the hydrophobic butyl groups adding to the overall stability of nano-particles, adding to the stabilisation associated with the upper rim hydrogen bonded network involving the phosphonic acid groups. This is consistent with MALDI-TOF-MS studies where the size of the self assembled nano-particles accessible in the gas phase for the same conditions increases from 20 to 33 monomeric units upon incorporating lower rim butyl groups.

Conclusion

We have synthesized three new alkylated *p*-phosphonic acid calix[4]arenes with methyl, butyl and octadecyl groups attached to the lower rim. Like their non-alkylated *p*-phosphonic acid analogues, they show nano-particle formation in the gas phase with between 15 and 33 calixarene units per particle, and in solution, with nano-particles of the *n*-butyl derivative being stable for up to 96 hr in DMSO. The ethyl phosphate ester for the *n*-octadecyl derivative forms a crystalline interdigitated bi-layer, which is close to the 40 Å found in biological membranes, and this leads to the possibility of using long chain phosphonated calixarenes as phospholipid bi-layer mimics, either their phosphonic acid or the mono-alkyl phosphate ester, which is an area we are pursuing. The 1:1 complex of Cs⁺ of the O-methyl derivative, as the exclusive

product, suggests that the O-alkyl *p*-phosphonic acid calixarenes in general have potential in forming metal complexes with a variety bonding modes, in the present study as a coordination polymer.

Experimental Section

Materials and Methods

All starting materials and solvents were obtained from commercial suppliers and used without further purification except otherwise noted. Acetonitrile was dried over 4 Å molecular sieves for 24 hours and NiCl₂·6H₂O was dried at 180 °C in vacuo for 8 hours before use. All moisture-sensitive reactions were performed under a positive pressure of nitrogen. Chromatographic purification was performed using 200-400 mesh silica gel. TLC analysis was performed on silica gel plates (absorbent thickness 250 µm) containing a fluorescent indicator. Melting points were determined using sealed and evacuated capillary tubes on an Electrothermal 9100 melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin Elmer Spectrum One spectrometer. ¹H NMR (600, 500 and 200 MHz), ¹³C NMR (151 and 126 MHz) and ³¹P NMR (243 and 202 MHz) were recorded on Bruker spectrometers and internally referenced to the solvent signal or phosphoric acid for ³¹P NMR. No NMR spectra could be obtained for compound **14** due to its insolubility in all common NMR solvents. Only the ¹H NMR spectrum of compound **12** is reported due to the conformational flexibility of the calixarene giving complicated ¹³C and ³¹P NMR spectra. Elemental analysis was performed at The Campbell Microanalytical Laboratory, Otago, New Zealand and FAB-MS was performed on a HP5896 mass spectrometer. MALDI-TOF-MS experiments were recorded on an Applied Biosystems Voyager DE-STR in linear negative mode with delayed extraction. The accelerating and grid voltages were set at 25 kV and 98%. The delay time was set at 500 ns with the low mass gate of 500 Da. Each spectrum was an average of 1000 laser shots. A peptide calibration standard from 1000 to 6000 Da was used as the external mass calibrant. Compounds **12** and **13** were dissolved in methanol to a final concentration of 1 mM and mixed with 2,5-DHB (15 mg/ml in 50% (v/v) methanol) by ratio of 1:1 (v/v) and spotted on the MALDI plate using the dried droplet method. Compound **14** was dissolved in either 1-butanol or 1-hexanol providing a saturated solution with a final concentration slightly smaller than 1 mM. A 0.3 µl drop of this solution was applied to a MALDI plate with hydrophobic surface and dried in air. A 0.3 µl drop of the DHB matrix solution was added to the top of the first layer and allowed to air dry.

Compounds **1-3**,¹⁷ **5-6**,¹⁷ **4**¹², **8**¹⁸ and **10**¹⁹ were prepared as described previously in the literature. Compound **8** was isolated as an oil, which crystallized over the course of 1 year to yield crystals of **8a** and compound **10** was recrystallized from toluene to yield crystals of **10a**.

5,11,17,23-Tetraiodo-25,26,27,28-tetraoctadecoxycalix[4]arene (7)—A suspension of 7.40 g (33.49 mmol) of CF₃CO₂Ag and 6.00 g (4.19 mmol) of **4** was refluxed in 200 mL of chloroform for 4 h. After this time 10.63 g (41.86 mmol) of I₂ was added and the purple solution refluxed for a further 2 h. After cooling to RT the reaction mixture was filtered over Celite and washed with a saturated solution of Na₂S₂O₅ (2 × 30 mL) and then water (3 × 30 mL). The organic layer was dried over MgSO₄, filtered and evaporated under reduced pressure to leave an orange oil. Recrystallisation from chloroform/methanol yielded 7.56 g (93%) of **7** as a white solid. m.p. 78-79 °C; ¹H NMR (CDCl₃, 25 °C, 600 MHz) δ6.99 (s, 8H, ArH), 4.28 (d, 4H, ArCHHAr, *J* = 13.2 Hz), 3.83 (t, 8H, OCH₂, *J* = 7.5 Hz), 3.05 (d, 4H, ArCHHAr, *J* = 13.2 Hz), 1.84 (quintet, 8H, OCH₂CH₂, *J* = 7.5 Hz), 1.38-1.21(m, 120H, C₁₅H₃₀CH₃), 0.88 (t, 12H, CH₃, *J* = 7.5 Hz); ¹³C NMR (CDCl₃, 25 °C, 151 MHz) δ156.55, 137.23, 136.99, 86.22, 75.69, 32.10, 30.54, 30.28, 30.11, 30.05, 29.99, 29.98, 29.97 x2, 29.95, 29.94, 29.92, 29.91, 29.85,

29.54, 26.41, 22.85, 14.27; MS (FAB) m/z calcd for $(C_{100}H_{164}I_4O_4)^+$ 1937, found 1937; Anal. Calcd for $C_{100}H_{164}I_4O_4$: C 61.98, H 8.53, found: C 62.07, H 8.61.

5,11,17,23-Tetra(dimethoxyphosphoryl)-25,26,27,28-tetrabutoxycalix[4]arene

(9)—A solution of 0.50 g (0.52 mmol) of **6** and 67 mg (0.52 mmol) of $NiCl_2$ in 10 mL of benzonitrile was treated dropwise with 0.61 mL (5.18 mmol) of $P(OMe)_3$ under nitrogen at 180 °C. The solution was stirred for 0.5 h and the volatiles removed under reduced pressure to leave an orange residue. The residue was dissolved in 30 mL of toluene, washed with 5% ammonia solution (5×10 mL), dried over $MgSO_4$ and evaporated under reduced pressure to yield an orange oil. The oil was purified using chromatography involving silica gel to yield 0.35 g (75%) of **9** as a white solid. Recrystallization from toluene yielded X-ray quality single crystals, **9a**, which were also submitted for microanalysis. R_f 0.17 (1:19 methanol-dichloromethane); m.p. 192–193 °C; IR (KBr) 2958 (m), 2873 (m), 1639 (w), 1593 (m), 1463 (m), 1274 (s), 1022 (s), 829 (m), 776 (m), 564 (m) cm^{-1} ; 1H NMR ($CDCl_3$, 25 °C, 500 MHz) δ 7.23 (d, 8H, ArH, $J_{P-H} = 13.5$ Hz), 4.48 (d, 4H, ArCHHAr, $J = 13.5$ Hz), 3.96 (t, 8H, OCH_2 , $J = 7.5$ Hz), 3.55 (d, 24H, $POCH_3$, $J_{P-H} = 11.5$ Hz), 3.30 (d, 4H, ArCHHAr, $J = 13.5$ Hz), 1.96 (quintet, 8H, OCH_2CH_2 , $J = 7.5$ Hz), 1.46 (sextet, 8H, CH_2CH_3 , $J = 7.5$ Hz), 1.02 (t, 12H, CH_2CH_3 , $J = 7.5$ Hz); ^{13}C NMR ($CDCl_3$, 25 °C, 126 MHz) δ 159.94 (d, $^4J_{P-C} = 3.5$ Hz), 135.08 (d, $^3J_{P-C} = 15.9$ Hz), 132.54 (d, $^2J_{P-C} = 10.6$ Hz), 120.68 (d, $^1J_{P-C} = 191.0$ Hz), 75.78, 52.72 (d, $^2J_{P-C} = 5.5$ Hz), 32.37, 30.71, 19.38, 14.18; ^{31}P NMR ($CDCl_3$, 25 °C, 202 MHz) δ 22.03; HRMS (FAB) m/z calcd for $(C_{52}H_{76}O_{16}P_4 + H)^+$ 1081.4162, found 1081.4143; Anal. Calcd for $C_{52}H_{76}O_{16}P_4$: C 57.77, H 7.09, found: C 57.54, H 7.39.

Using the procedure described above for the preparation of **9**, phosphonate ester **11** was prepared.

5,11,17,23-Tetra(diethoxyphosphoryl)-25,26,27,28-tetraoctadecoxycalix[4]arene

(11)—Starting from 4.00 g (2.07 mmol) of **7**, 0.27 g (2.07 mmol) of $NiCl_2$, 3.54 mL (20.65 mmol) of $P(OEt)_3$ and 20 mL of benzonitrile, 2.91 g (71%) of **11** was obtained as a white solid. Recrystallization from ethyl acetate/dichloromethane yielded X-ray quality single crystals, **11a**, which were also submitted for microanalysis. R_f 0.36 (1:19 methanol-dichloromethane); m.p. 86–88 °C; IR (KBr) 2930 (s), 2850 (s), 1640 (w), 1593 (w), 1467 (m), 1273 (m), 1021 (s), 968 (m), 795 (w), 568 (m) cm^{-1} ; 1H NMR ($CDCl_3$, 25 °C, 600 MHz) δ 7.25 (d, 8H, ArH, $J_{P-H} = 13.2$ Hz), 4.46 (d, 4H, ArCHHAr, $J = 13.2$ Hz), 4.02–3.92 (m, 8H, $POCHHCH_3$), 3.95 (t, 8H, OCH_2 , $J = 7.2$ Hz), 3.92–3.84 (m, 8H, $POCHHCH_3$), 3.30 (d, 4H, ArCHHAr, $J = 13.2$ Hz), 1.95 (quintet, 8H, OCH_2CH_2 , $J = 7.2$ Hz), 1.40–1.23 (m, 120H, $C_{15}H_{30}CH_3$), 1.21 (t, 24H, $POCH_2CH_3$, $J = 7.2$ Hz), 0.87 (t, 12H, CH_2CH_3 , $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$, 25 °C, 151 MHz) δ 159.90 (d, $^4J_{P-C} = 3.3$ Hz), 134.84 (d, $^3J_{P-C} = 15.9$ Hz), 132.42 (d, $^2J_{P-C} = 10.6$ Hz), 122.24 (d, $^1J_{P-C} = 191.9$ Hz), 75.98, 62.28 (d, $^2J_{P-C} = 5.1$ Hz), 32.08, 31.05, 30.38, 30.12, 30.10, 30.00, 29.98 x2, 29.96, 29.94, 29.92, 29.90, 29.89, 29.83, 29.52, 26.36, 22.83, 16.43 (d, $^3J_{P-C} = 6.0$ Hz), 14.25; ^{31}P NMR ($CDCl_3$, 25 °C, 202 MHz) δ 19.66; MS (FAB) m/z calcd for $(C_{116}H_{204}O_{16}P_4 + H)^+$ 1978, found 1978; Anal. Calcd for $C_{116}H_{204}O_{16}P_4$: C 70.41, H 10.39, found: C 70.46, H 10.28.

5,11,17,23-Tetra(dihydroxyphosphoryl)-25,26,27,28-tetramethoxycalix[4]arene

(12)—2.10 mL (15.93 mmol) of Bromotrimethylsilane was added to 1.02 g (1.00 mmol) of **8** in 50 mL of dry acetonitrile and the solution was refluxed for 16 hours. The volatiles were removed under reduced pressure and the resulting residue was triturated with 30 mL of acetonitrile and 1 mL of water. The precipitate formed was filtered off and washed with acetonitrile (3×10 mL) to yield 0.77 g (96%) of **12** as a white solid. Recrystallization from methanol/chloroform yielded a white solid suitable for microanalysis. Recrystallization from methanol / 6N HNO_3 / $CsNO_3$ yielded X-ray quality single crystals, **12a**. m.p. 258–260 °C; IR (KBr) 3411 (br), 2933 (m), 2828 (m), 2345 (br), 1638 (w), 1592 (w), 1473 (m), 1270 (m), 1124

(s), 1005 (s), 967 (s), 513 (m) cm^{-1} ; ^1H NMR (DMSO- d_6 , 25 $^\circ\text{C}$, 600 MHz) δ 7.61–6.51 (m, 8H, ArH), 5.88 (br s, POH, shifts downfield with increasing $[\text{H}]^+$), 4.32–2.75 (m, 20H, $\text{ArCH}_2\text{Ar}/\text{CH}_3$); HRMS (FAB) m/z calcd for $(\text{C}_{32}\text{H}_{36}\text{O}_{16}\text{P}_4 + \text{H})^+$ 801.1032, found 801.1078; Anal. Calcd for $\text{C}_{32}\text{H}_{36}\text{O}_{16}\text{P}_4$: C 48.01, H 4.53, found: C 47.76, H 4.73.

Using the procedure described above for the preparation of **12**, phosphonic acids **13** and **14** were prepared

5,11,17,23-Tetra(dihydroxyphosphoryl)-25,26,27,28-tetrabutoxycalix[4]arene (13)—Starting from 0.76 g (0.64 mmol) of **10**, 1.35 mL (10.22 mmol) of bromotrimethylsilane and 50 mL of dry acetonitrile, 0.57 g (92%) of **13** was obtained as a white solid after recrystallization from ethanol/acetone. m.p. 257–258 $^\circ\text{C}$; IR (KBr) 3411 (br), 2959 (m), 2931 (m), 2872 (m), 2325 (br), 1637 (w), 1593 (w), 1459 (m), 1272 (m), 1125 (s), 981 (s), 550 (m) cm^{-1} ; ^1H NMR (DMSO- d_6 , 25 $^\circ\text{C}$, 600 MHz) δ 6.98 (br s, 8H, ArH), 5.83 (br s, POH, shifts downfield with increasing $[\text{H}]^+$), 4.36 (d, 4H, ArCHHAr , $J = 13.8$ Hz), 3.89 (t, 8H, OCH_2 , $J = 7.2$ Hz), 3.30 (d, 4H, ArCHHAr , $J = 13.8$ Hz), 1.83 (quintet, 8H, OCH_2CH_2 , $J = 7.2$ Hz), 1.43 (sextet, 8H, CH_2CH_3 , $J = 7.2$ Hz), 0.96 (t, 12H, CH_2CH_3 , $J = 7.5$ Hz); ^{13}C NMR (DMSO- d_6 , 25 $^\circ\text{C}$, 151 MHz) δ 158.70, 134.22 (d, $^3J_{\text{P-C}} = 13.9$ Hz), 130.74 (d, $^2J_{\text{P-C}} = 9.8$ Hz), 126.48 (d, $^1J_{\text{P-C}} = 185.5$ Hz), 74.55, 31.77, 30.17, 18.82, 13.84; ^{31}P NMR (DMSO- d_6 , 25 $^\circ\text{C}$, 243 MHz) δ 17.08; HRMS (FAB) m/z calcd for $(\text{C}_{44}\text{H}_{60}\text{O}_{16}\text{P}_4 + \text{H})^+$ 969.2910, found 969.2861; Anal. Calcd for $\text{C}_{44}\text{H}_{60}\text{O}_{16}\text{P}_4$: C 54.55, H 6.24, found: C 54.54, H 6.49.

5,11,17,23-Tetra(dihydroxyphosphoryl)-25,26,27,28-tetraoctadecoxycalix[4]arene (14)—Starting from 0.50 g (0.25 mmol) of **11**, 0.53 mL (4.05 mmol) of bromotrimethylsilane and 30 mL of dry acetonitrile, 0.42 g (95%) of **14** was obtained as a white solid after trituration with acetonitrile. m.p. >280 $^\circ\text{C}$ (dec.); IR (KBr) 3429 (br), 2918 (s), 2850 (s), 2298 (br), 1634 (w), 1595 (w), 1467 (m), 1273 (m), 1128 (m), 994 (m), 553 (w) cm^{-1} ; MS (MALDI-TOF) m/z calcd for $(\text{C}_{100}\text{H}_{172}\text{O}_{16}\text{P}_4 + \text{H})^+$ 1754.17, found 1754.44; Anal. Calcd for $\text{C}_{100}\text{H}_{172}\text{O}_{16}\text{P}_4$: C 68.42, H 9.93, found: C 68.23, H 10.17.

X-ray Crystallography

The X-ray diffracted intensities were measured from single crystals at about 100 K on an Oxford Diffraction Xcalibur or at about 153 or 173 K on a Bruker ASX SMART CCD diffractometer using monochromatized Mo- K_α ($\lambda = 0.71073$ Å). Data were corrected for Lorentz and polarization effects and absorption correction applied using multiple symmetry equivalent reflections. The structures were solved by direct method and refined on F^2 using the SHELX-97 crystallographic package²⁰ and X-seed interface.²¹ A full matrix least-squares refinement procedure was used, minimizing $w(F_o^2 - F_c^2)$, with $w = [\sigma^2(F_o^2) + (AP)^2 + BP]^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$. Agreement factors ($R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $wR2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$ and $\text{GOF} = \{\Sigma[w(F_o^2 - F_c^2)^2]/(n-p)\}^{1/2}$ are cited, where n is the number of reflections and p the total number of parameters refined). Non-hydrogen atoms were refined anisotropically. The positions of hydrogen atoms partly were localized from difference Fourier map, partly calculated from geometrical consideration and their atomic parameters were constrained to the bonded atoms during the refinement. CCDC deposition numbers 717633 - 717637.

Crystal/refinement details for 8a— $\text{C}_{48}\text{H}_{72}\text{O}_{18}\text{P}_4$, $M = 1060.94$, $F(000) = 2256$ e, monoclinic, $P2_1/n$, $Z = 4$, $T = 100(2)$ K, $a = 13.0809(7)$, $b = 25.891(2)$, $c = 15.9698(8)$ Å, $\beta = 102.257(5)^\circ$, $V = 5285.3(6)$ Å³, $D_c = 1.333$ g cm⁻³, $\sin\theta/\lambda_{\text{max}} = 0.5946$, $N(\text{unique}) = 9241$ (merged from 55971, $R_{\text{int}} = 0.1064$, $R_{\text{sig}} = .0862$), $N_o(I > 2\sigma(I)) = 5685$, $R = 0.0838$, $wR2 = 0.2126$ ($A, B = 0.13, 6.5$), $\text{GOF} = 1.004$, $|\Delta\rho_{\text{max}}| = 1.15(9)$ e Å⁻³.

Crystal/refinement details for 9a— $C_{59}H_{86}O_{17}P_4$, $M = 1191.16$, $F(000) = 2544$ e, monoclinic, $C2/c$ (No. 15), $Z = 4$, $T = 173(2)$ K, $a = 12.315(3)$, $b = 26.087(5)$, $c = 20.789(4)$ Å, $\beta = 97.05(3)^\circ$, $V = 6628(2)$ Å³, $D_c = 1.194$ gcm⁻³, $\mu_{Mo} = 0.176$ mm⁻¹, $\sin\theta/\lambda_{max} = 0.6455$, $N(\text{unique}) = 7247$ (merged from 22645, $R_{int} = 0.0673$, $R_{sig} = 0.1123$), N_o ($I > 2\sigma(I)$) = 3466, $R = 0.1047$, $wR2 = 0.2705$ ($A, B = 0.125, 27.5$), $GOF = 1.011$, $|\Delta\rho_{max}| = 0.9(1)$ e Å⁻³.

Crystal/refinement details for 10a— $C_{60}H_{94}O_{17}P_4$, $M = 1211.23$, $F(000) = 2600$ e, monoclinic, $P2_1/c$ (No. 14), $Z = 4$, $T = 153(2)$ K, $a = 13.247(4)$, $b = 31.900(10)$, $c = 15.996(5)$ Å, $\beta = 106.740(5)^\circ$, $V = 6473(3)$ Å³, $D_c = 1.243$ gcm⁻³, $\mu_{Mo} = 0.182$ mm⁻¹, $\sin\theta/\lambda_{max} = 0.5977$, $N(\text{unique}) = 10734$ (merged from 38060, $R_{int} = 0.1683$, $R_{sig} = 0.1997$), N_o ($I > 2\sigma(I)$) = 5353, $R = 0.1100$, $wR2 = 0.2217$ ($A, B = 0.13, 4.0$), $GOF = 1.003$, $|\Delta\rho_{max}| = 0.6(1)$ e Å⁻³.

Crystal/refinement details for 11a— $C_{116}H_{206}O_{17}P_4$, $M = 1996.69$, $F(000) = 2196$ e, triclinic, $P-1$ (No. 2), $Z = 2$, $T = 100(2)$ K, $a = 12.105(4)$, $b = 12.533(3)$, $c = 39.051(5)$ Å, $\alpha = 97.47(2)^\circ$, $\beta = 90.39(2)^\circ$, $\gamma = 94.84(2)^\circ$, $V = 5852(3)$ Å³, $D_c = 1.133$ gcm⁻³, $\mu_{Mo} = 0.125$ mm⁻¹, $\sin\theta/\lambda_{max} = 0.5946$, $N(\text{unique}) = 9230$ (merged from 30697, $R_{int} = 0.1352$, $R_{sig} = 0.1801$), N_o ($I > 2\sigma(I)$) = 5276, $R = 0.1954$, $wR2 = 0.4051$ ($A, B = 0.115, 121.08$), $GOF = 1.041$, $|\Delta\rho_{max}| = 0.9(1)$ e Å⁻³.

Crystal/refinement details for 12a— $C_{32}H_{37}CsO_{17}P_4$, $M = 950.41$, $F(000) = 3840$ e, orthorhombic, $Pbca$ (No. 61), $Z = 8$, $T = 173(2)$ K, $a = 10.335(2)$, $b = 20.680(4)$, $c = 34.728(6)$ Å, $V = 7422(2)$ Å³, $D_c = 1.701$ gcm⁻³, $\mu_{Mo} = 1.246$ mm⁻¹, $\sin\theta/\lambda_{max} = 0.6410$, $N(\text{unique}) = 8091$ (merged from 28249, $R_{int} = 0.0851$, $R_{sig} = 0.0948$), N_o ($I > 2\sigma(I)$) = 4763, $R = 0.0692$, $wR2 = 0.1603$ ($A, B = 0.09, 12.0$), $GOF = 1.020$, $|\Delta\rho_{max}| = 1.2(1)$ e Å⁻³.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Projection down *a* axis for complex **11a** showing the bi-layer arrangement of calixarenes. The water molecules and hydrogen's have been omitted for clarity. The following color scheme is used for all figures, light and dark blue for carbon atoms, green for phosphorus atoms, and red for oxygen atoms.

Figure 2. Projections of the calixarene **11a** in the cone conformation. (A) Showing the associated water molecule between two adjacent phosphonate esters. (B) Showing the flexibility of the calixarene in being rotated through the angle θ relative to the direction of the alkyl chains.

Figure 3.

Projection of the calixarene in the 1,3-cone conformation showing the cesium cation coordinated through Cs...O and Cs...C_{Ar} interactions, as η^3 -contacts. The water molecule and hydrogen atoms have been omitted for clarity.

Figure 4. Projection down *c* axis showing the overall packing of complex **12a** as a bi-layer coordination polymer. The water molecules, hydrogen atoms and η^3 -contacts have been omitted for clarity.

Figure 5. MALDI-TOF spectra showing nano-particles of the *p*-phosphonic acid calixarenes in the gas phase for (A) methyl derivative **12**, (B) *n*-butyl derivative **13**, (C) *n*-octadecyl derivative **14**.

Figure 6. ^1H NMR (left) and ^{31}P NMR (right) expansions between 7.8 - 6.0 and 20.0 - 2.0 ppm respectively for the *n*-butyl derivative of *p*-phosphonic acid calix[4]arene, **13**, in d_6 -DMSO. (A) 0 hr, (B) 6 hr, (C) 24 hr, (D) 48 hr, (E) 72 hr, (F) 96 hr.

Scheme 1.

Synthetic protocol for alkylated *p*-phosphonic acid calix[4]arenes. (i) RI or RBr / NaH / DMF (ii) NBS / MEK (iii) CF₃CO₂Ag / I₂ / CHCl₃ (iv) P(OR') / NiCl₂ / PhCN (v) BTMS / MeCN. Me = methyl, Et = ethyl, Bu = *n*-butyl, Ph = phenyl, BTMS = bromotrimethylsilane, DMF = dimethylformamide, MEK = methyl ethyl ketone, NBS = *N*-bromosuccinimide. R = Me, *n*-Bu, *n*-C₁₈H₃₇ and R' = Me, Et.