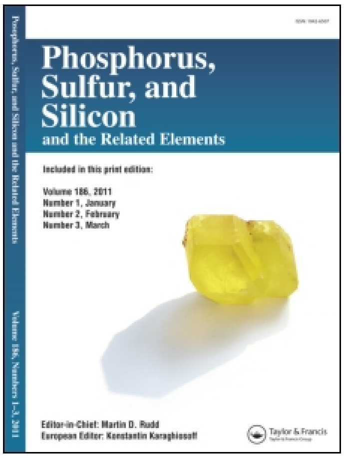

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INTRODUCTION OF BRIDGING ETHYL PHOSPHATE SUBSTITUENTS ONTO THE LOWER RIM OF CALIX[6]ARENES

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The compounds 5, 11, 17, 23, 29, 35-hexa-*tert*-butyl-37, 38, 39, 40-tetrahydroxy-μ-41, 42-ethyl phosphate calix[6]arene and 5, 11, 17, 23, 29, 35-hexa-*tert*-butyl-37, 40-dihydroxy-μ-38, 39-ethyl phosphate-μ-41, 42-ethyl phosphate calix[6]arene have been prepared. In each case the ethyl phosphate group spans two adjacent positions on the lower rim of the calix[6]arene.

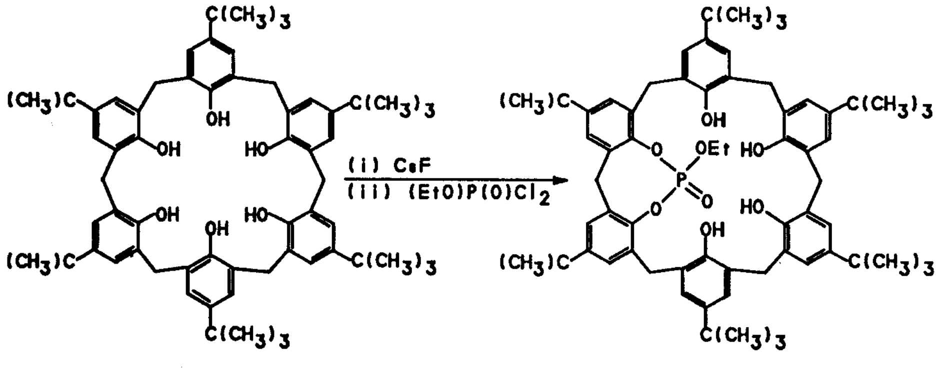
Key words: Calix[6]arenes; ethyl phosphate; lower rim.

INTRODUCTION

Calixarenes containing either 4-, 6-, or 8-phenolic residues can be readily prepared by reacting *p-tert*-butylphenol with formaldehyde.[1] By carrying out this condensation reaction under controlled conditions, it is possible to selectively synthesize each individual cyclic oligomer with 4-, 6-, or 8-phenolic residues. In the presence of base, the phenolic protons of the calixarene can be removed, and metal ions complexed to the phenolic oxygens on the lower rim.[2–8] As a means to control both the number and the type of donor atoms at this lower rim, a range of different functional groups can be appended onto the calixarene skeleton. Recently this list of groups has been expanded to include hypervalent phosphorus substituents on the lower rim.[9,10] If these phosphorus containing calixarenes are to become useful as encapsulating agents, it is important that the number of donor atoms on the lower rim can be controlled. This control can be achieved if substituents can be introduced onto the lower rim in a manner where they can be selectively introduced onto single oxygens, or pairwise onto adjacent oxygens of the lower rim.

RESULTS AND DISCUSSION

When *p-tert*-butylcalix[6]arene is treated with cesium fluoride then with ethyl dichlorophosphate, an ethyl phosphate substituent is introduced onto the lower rim of the calix[6]arene. This new compound **I** has a single ethyl phosphate spanning two adjacent phenolic oxygens of the calix[6]arene (equation 1). Compound **I** is characterized by the presence of a single phosphorus resonance in the $^{31}P\{^1H\}$ NMR spectrum at δ − 10.9. The ^1H NMR spectrum of **I** shows three sets of inequivalent hydrogens due to the *tert*-butyl methyl groups at δ 1.13, δ 1.21 and δ 1.30. Integration confirms that each resonance corresponds to 18 hydrogens. The three sets of inequivalent *tert*-butyl groups are those attached to the pairs of equivalent carbons at positions 5, 11; 17, 35; and 23, 29. The numbering scheme for calix[6]arenes is shown in Figure 1. The ethyl group on the phosphate is identified in the ^1H NMR spectrum by a methyl triplet at δ 1.24 ($^3J(HH)$ = 7.0 Hz) and a



(1)

I

methylene quartet at δ 3.81 (^3J(HH) = 7.0 Hz). The six methylene groups in the cyclic calix[6]arene core are observed at δ 3.62 and δ 4.43 as multiplets, with each set integrating to 6 hydrogens. We assign these two sets to groups of hydrogens attached to the triads of carbons 2, 8 and 14; 20, 26 and 32. These "equivalent" sets are chosen because the methylenes 2, 8 and 14 have only protons attached to each adjacent phenoxide, whereas the methylenes 20, 26 and 32 have at least one phosphate group attached to an adjacent phenoxide. Although the methylene group at carbon-8 is chemically inequivalent from those at carbons-2 and -14, and the methylene group at carbon-26 is chemically inequivalent from those at carbons 20 and -32, they are so closely similar in chemical shift that we are unable to resolve them.

The $^{13}C\{^1H\}$ NMR spectrum shows resonances due to the methyl carbons of the three inequivalent *tert*-butyl groups at δ 31.26 and δ 31,57 and δ 31.62, along with resonances due to the methine carbons of these *tert*-butyl groups at δ 32.82, δ 33.25 and δ 35.41. The ethyl phosphate substituent is identified by $^{13}C\{^1H\}$ NMR resonances for the ethoxy group at δ 33.47 ($OCH_2\mathit{C}H_3$) and δ 66.11 ($O\mathit{C}H_2CH_3$). The eighteen expected aromatic carbons in the calix[6]arene ring are observed over the chemical shift range of δ 125–150.

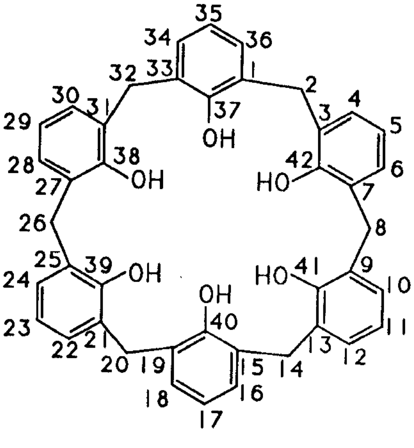


FIGURE 1 Numbering scheme for calix[6]arenes.

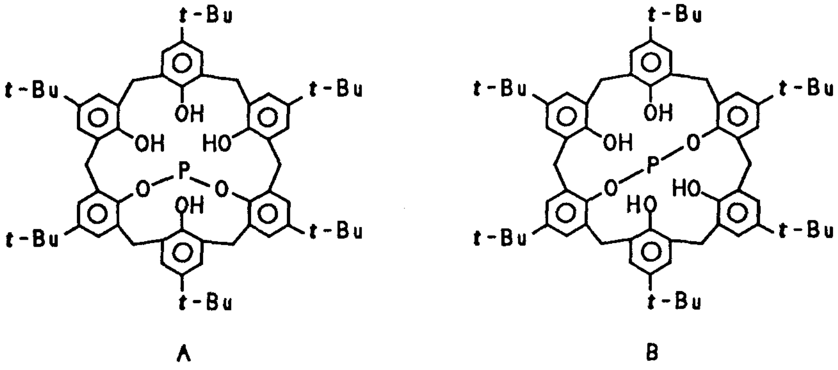
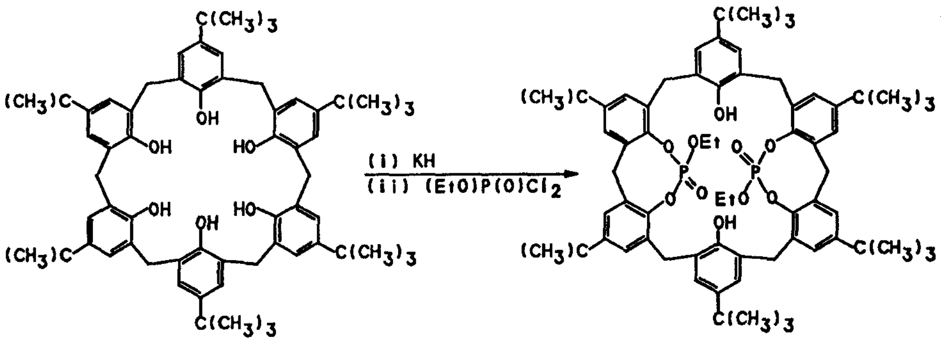


FIGURE 2 Alternate structures for the mono ethyl phosphate.

In making the assignment of the structure of **I** we have considered the two alternate structures shown in Figure 2. The structure A can be eliminated because the six *tert*-butyl groups will be present as four groups of resonances in a ratio of 1:2:2:1, and structure B can be eliminated because the six *tert*-butyl groups will now be present as two groups in a ratio of 1:2.

When the reaction between *p*-*tert*-butyl calix[6]arene and ethyl dichlorophosphate is carried out in the presence of potassium hydride, a stronger base than cesium fluoride, a second ethyl phosphate substituent can be introduced onto the lower rim of the calixarene. The product **II** has ethyl phosphate groups bridging across lower rim oxygens that are across from each other (equation 2). Compound **II** is characterized by the presence of a single phosphorus resonance in the $^{31}P\{^1H\}$ NMR spectrum at δ -11.8 for the two equivalent phosphate groups. The ^1H NMR spectrum shows two inequivalent sets of hydrogens due to *tert*-butyl methyl groups in a 2:1 ratio at δ 1.03 and δ 1.38 respectively. The ethyl phosphate group is identified in the ^1H NMR spectrum by resonances due to the methyl and methylene groups at δ 1.56 and δ 3.45 respectively. The methylene groups in the cyclic calix[6]arene core are observed as a single multiplet at δ 4.64. These NMR spectral data identify the compound as the symmetrically disubstituted isomer, and the presence of a single resonance in the $^{31}P\{^1H\}$ NMR spectrum verifies the presence of this single isomer **II**.



(2)

II

The $^{13}C\{^1H\}$ NMR spectrum shows resonances due to the methyl carbons of the two inequivalent *tert*-butyl groups at δ 31.77 and δ 32.32, along with resonances to the methine carbons of these *tert*-butyl groups at δ 34.45 and δ 34.72. The ethyl phosphate substituents are identified by $^{13}C\{^1H\}$ NMR resonances for the ethoxy groups at δ 34.01 (OCH_2CH_3) and δ 61.05 (OCH_2CH_3). The aromatic carbons in the calix[6]arene ring are observed over the chemical shift range of δ 125–155.

In making the assignment of the structure of **II** we have considered the three alternate structures shown in Figure 3. The structure A can be eliminated because the six *tert*-butyl groups will be present as three groups in a 1 : 1 : 1 ratio. Structure B can be eliminated because the six *tert*-butyl groups will be present as four groups in a 1 : 1 : 2 : 2 ratio. Our NMR data do not rule out structure C. One possible reason for eliminating structure C is based on the grounds that the conversion of **I** into **II** would require the unlikely step of cleaving a P—O bond in a 1,2-alternate structure, and converting it into a structure with the two P—O bonds in a 1,3-alternate structure. Although we have no direct evidence that compound **I** is formed on the reaction pathway to **II**, this possibility is supported by the observation that small quantities of **I** are always present in the synthesis of **II**. Furthermore, the formation of **I** having the phosphate group spanning adjacent oxygens on the lower rim of the calixarene makes it unlikely that the predominant structure for compound **II** will be isomer C. Our spectral data do not distinguish between the different conformers that can be present in calixarenes.[1] The calix[6]arenes are known to interconvert quite rapidly, and compounds **I** and **II** are likely present in solution as a mixture of conformers.[11]

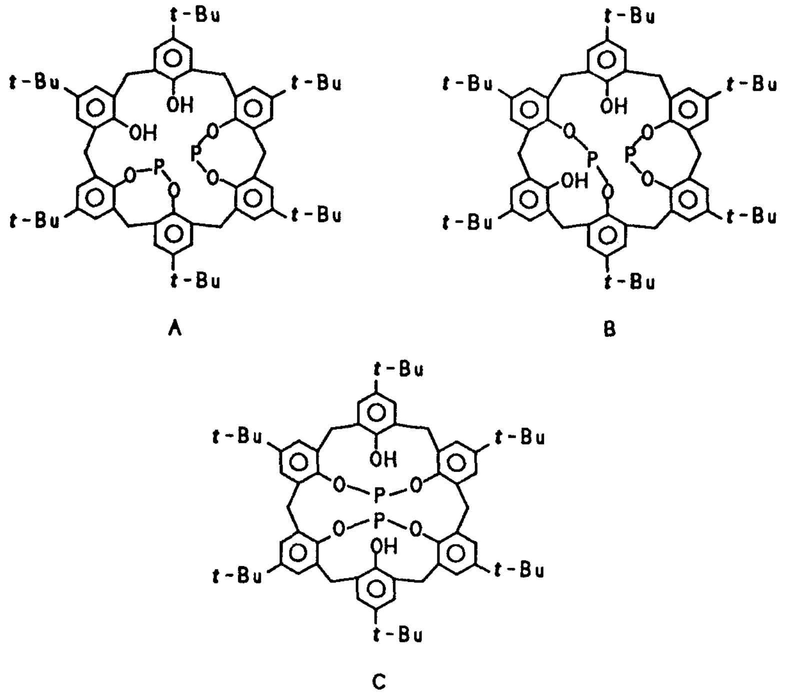


FIGURE 3 Alternate structures for the mono ethyl phosphate.

In no case do we observe the formation of a compound having three ethyl phosphates spanning pairs of phenolic oxygens on the lower rim of the calix[6]arene. The formation of this symmetrical isomer **II** with the ethyl phosphate groups spanning the 38, 39 and 41, 42 positions explains why our attempts to introduce three bridging ethyl phosphate groups onto the lower rim of the calix[6]arene have been unsuccessful. Such a compound would require that the ethyl phosphate groups span the 38, 39; 40, 41 and 42, 37 pairs of phenolic oxygens. The intermediate formation of the symmetrical isomer with ethyl phosphates spanning the 38, 39 and 41, 42 positions precludes the formation of the isomer with the three symmetrical ethyl phosphate groups, and the distance across the two remaining phenolic groups is likely too distant in a calix[6]arene to be spanned by an ethyl phosphate bridge.

The synthesis of these two new compounds shows that bridging phosphates can be used to connect adjacent pairs of hydroxyl groups on the lower rim of a calix[6]arene. The reaction can be used to incorporate either one or two such groups on this rim, thereby allowing the number of substituted phosphate moieties to be selected.

EXPERIMENTAL

^{1}H, ^{13}C{^{1}H} and ^{31}P{^{1}H} NMR spectra were measured on Bruker AC200 or GE Omega 400 spectrometers with the compounds dissolved in $CDCl_3$. Mass spectra were measured on a Kratos Concept 1H instrument using the FAB technique with samples dissolved in m-nitrobenzyl alcohol as the matrix. Microanalyses were carried out by Galbraith Inc., Knoxville, Tenn. The ^{1}H and ^{13}C NMR spectra were referenced to TMS, and the ^{31}P NMR spectra to 85% H_3PO_4. The *p-tert*-butylcalix[6]arene was prepared according to the literature procedure. Ethyl dichlorophosphate was purchased from Aldrich, and distilled immediately prior to use. Potassium hydride was obtained from Aldrich as a 35% dispersion in mineral oil, and washed two times with pentane prior to use. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Acetonitrile was distilled and stored over potassium carbonate. Chromatographic separations were carried out on a 41 mm I.D. flash column using silica gel 60 (SiO_2) 230–400 mesh. Synthetic procedures were carried out under a nitrogen atmosphere.

Preparation of 5, 11, 17, 23, 29, 35-hexa-tert-butyl-37, 38, 39, 40-tetrahydroxy-μ-41, 42-ethyl phosphate calix[6]arene (**I**). To a solution of *p-tert*-butylcalix[6]arene (1.46 g, 1.50 mmol) in acetonitrile (300 mL) was added cesium fluoride (1.41 g, 9.26 mmol). The suspension was stirred at ambient temperature for 45 min, then heated to reflux temperature. A solution of ethyl dichlorophosphate (0.56 mL, 4.80 mmol) in tetrahydrofuran (50 mL) was added dropwise over 24 hr at reflux temperature. The solution was cooled, and the solvent removed under reduced pressure. The resulting residue was dissolved in dichloromethane (200 mL), and the solution washed with brine (2 × 100 mL portions). The dichloromethane layer was separated and dried over magnesium sulfate. The solution was filtered, and the solvent removed under reduced pressure. The resulting residue was purified by flash chromatography using chloroform as the eluant. Removal of the solvent on a rotary evaporator, followed by drying *in vacuo* gave the pure compounds. Yield 0.239 g (15%). Anal. Calcd for $C_{68}H_{87}O_8P \cdot CH_3OH$: C, 75.7; H, 8.37%. Found: C, 75.6; H, 8.46%. FAB-MS (*m/z*) 1063. ^{31}P NMR: δ -10.9s. ^{1}H NMR: δ 1.13 s (18H, CH_3), δ 1.21 s (18H, CH_3), δ 1.24 t (^3J(HH) = 7.0 Hz; 3H, OCH_2CH_3), δ 1.30 s (18H, CH_3), δ 3.62 *m* (6H, CH_2), δ 3.81 quartet (^3J(HH) = 7.0 Hz; 2H, OCH_2CH_3), δ 4.43 m (6H, CH_2), δ 6.85 br (2H, CH), δ 7.04 br (2H, CH), δ 7.07 br (2H, CH), δ 7.11 br (2H, CH), δ 7.16 br (2H, CH), δ 7.17 br (2H, CH), δ 8.38 br (2H, CH), δ 9.75 br (2H, CH). ^{13}C{^{1}H} NMR: δ 29.47 (CH_2), δ 29.71 (CH_2), δ 29.93 (CH_2), δ 30.14 (CH_2), δ 31.26 (CH_3), δ 31.57 (CH_3), δ 31.62 (CH_3), δ 32.82 ($C(CH_3)$), δ 33.25 ($C(CH_3)$), δ 35.41 ($C(CH_3)_3$), δ 33.47 (OCH_2CH_3), δ 66.11 (OCH_2CH_3), δ 124.97, 125.30, 125.63, 125.99, 126.52, 127.01, 127.35, 131.55, 131.63, 132.01, 132.11, 134.66, 143.26, 143.75, 143.84, 148.34, 148.68, 149.58 (all CH and C, Aromatic).

Preparation of 5, 11, 17, 23, 29, 35-hexa-tert-butyl-, 37, 40-dihydroxy-μ-38, 39-ethyl phosphate-μ-41, 42-ethyl phosphate calix[6]arene (**II**). A suspension of *p-tert*-butyl calix[6]arene (2.03 g, 2.09 nmol) in tetrahydrofuran (10 mL) was added to a suspension of an excess of potassium hydride in tetrahydrofuran (5 mL). The solution was stirred for 30 min. The supernatant was transferred to a 500 mL, 3-necked flask, which was equipped with a pressure equalized dropping funnel and a condenser. To this solution was added tetrahydrofuran (100 mL), and the mixture was then heated to reflux. To this refluxing solution was added dropwise a solution of ethyl dichlorophosphate (0.80 mL, 6.74 mmol) in tetrahydrofuran (20 mL). After 24 hr the solution was allowed to cool, and the solvent removed under reduced pressure. The resulting tan solid was triturated with methanol, then submitted to flash chromatography using chloroform as eluant. Yield 0.212 g (9%). FAB-MS (*m/z*) 1153. ^{31}P NMR: δ-11.8. ^{1}H NMR: δ 1.03 s (36H, $\mathrm{C}\mathit{H}_3$), δ 1.38 s (18H, $\mathrm{C}\mathit{H}_3$), δ 1.56 t (^{3}J(HH) = 7 Hz; 6H, $\mathrm{OCH_2C}\mathit{H}_3$), δ 3.45 m (4H, $\mathrm{OC}\mathit{H}_2\mathrm{CH_3}$), δ 4.64 m (12H, $\mathrm{C}\mathit{H}_2$), δ 6.86 br (4H, $\mathrm{C}\mathit{H}$), δ 6.97 br (4H, $\mathrm{C}\mathit{H}_2$), δ 7.17 s (4H, $\mathrm{C}\mathit{H}$), δ 7.80 s (2H, $\mathrm{C}\mathit{H}$). ^{13}C{^{1}H} NMR: δ 31.21 ($\mathit{C}\mathrm{H_2}$), δ 32.17 ($\mathit{C}\mathrm{H_2}$), δ 31.77 ($\mathit{C}\mathrm{H_3}$), δ 32.32 ($\mathit{C}\mathrm{H_3}$), δ 34.45 ($\mathit{C}\mathrm{(CH_3)}$), δ 34.72 ($\mathit{C}\mathrm{(CH_3)}$), δ 34.01 ($\mathrm{OCH_2}\mathit{C}\mathrm{H_3}$), δ 61.05 ($\mathrm{O}\mathit{C}\mathrm{H_2CH_3}$), δ 125.73, δ 125.85, δ 129.17, δ 133.02, δ 133.28, δ 135.75, δ 146.56, δ 151.23, δ 152.66 (all *C*H and *C*, Aromatic).

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