Pergamon

Tetrahedron Letters 42 (2001) 9139–9142

TETRAHEDRON LETTERS

Shaping calixarene frameworks. Synthesis and structure of a calix[8]arene containing three bridging phosphate units

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Received 12 September 2001; accepted 10 October 2001

Abstract—The reaction of *p-tert*-butylcalix[8]arene with PCl_5, followed by hydrolysis and subsequent esterification with triethyl orthoformate afforded a triphosphate involving all phenolic oxygen atoms of the calixarene framework. As revealed by an X-ray diffraction study, the presence of two μ_3-(*O*,*O*,*O*) and one μ_2-(*O*,*O*) bridging phosphoryl groups results in an unusual lengthening of the calix[8]arene loop (longest O···O separation: 13.9 Å) © 2001 Elsevier Science Ltd. All rights reserved.

As part of an ongoing programme aimed at the preparation of phosphorus-functionalized polyphenol derivatives we have been exploring the reaction of PCl_5 with various generic calix[n]arenes. Most of these reactions resulted in the formation of chlorophosphonium compounds that could be readily converted into the corresponding phosphates.[1,2] Recent work of our group includes the synthesis of calix[n]arene phosphates ($n=4$, 6) having phosphoryl units that act either as μ_2 or μ_3-bridges between phenolic oxygen atoms of the macrocyclic framework or simply behave as pendant–$P(O)(OR)_2$ moieties. Our previous work in this area has also led to some chiral derivatives that have been resolved.[3] We now report on the synthesis and molecular structure of the first calix[8]arene that contains three bridging phosphoryl groups. Some calix[8]arenes bearing phosphate substituents have been described recently, but in all these compounds the phosphorus atom is tethered to two phenolic oxygen atoms at most.[4] The chemistry of the more common calix[4]arene phosphates has been reviewed in several recent papers.[5]

Treatment of *p-tert*-butylcalix[8]arene (**1**) with 5 equiv. of PCl_5 in CH_2Cl_2 and subsequent hydrolysis gave compound **3** which was obtained in 18% yield after column chromatography (Scheme 1[6]). Compound **3**[7] was authenticated by mass spectrometry, elemental analysis as well as ^1H and ^{31}P NMR spectroscopy. The ^{31}P NMR spectrum of **3** displays three distinctive peaks that may be assigned,[1,2] respectively to two triply bridging phosphoryl units ($\delta=-21.2$ and -22.0 ppm) and a pendant $P(O)(OH)_2$ function ($\delta=-5.4$ ppm). The relative arrangement of the three phosphate groups was determined via derivatization. Thus, reaction of **3** with triethyl orthoformate in refluxing DMF resulted in formation of a ca. 1:1 mixture of the two stereoisomeric triphosphates **4** and **5** (86% yield) which were separated chromatographically. It is noteworthy that during this esterification, bridge formation also took place. In the ^1H NMR spectrum, the $ArCH_2Ar$ protons give rise to a complex pattern due to 4 non equivalent methylene groups that overlap with the CH_2CH_3 signal.[7] The ^{31}P NMR spectra of **4** and **5** are quite similar,[7] both showing three phosphate signals, one at ca. −12 ppm ($\delta=-11.5$ ppm for **4**; −12.4 ppm for **5**) and two others near −21 ppm ($\delta=-20.5$ and −22.5 for **4**; −21.1 and −21.4 ppm). The former peaks may unambiguously be assigned to μ_2 bridging phosphate groups, while those at near −21 ppm correspond to μ_3 bridges.

The molecular structure of isomer **4** was determined by an X-ray diffraction study (Figs. 1 and 2).[8]

The μ_2-phosphate group (P(2)) spans the aromatic units 1 and 5, while the μ_3 bridging phosphates (P(1) and P(3)) are, respectively linked to the aromatic units [2,3,4] and [6,7,8].[9] The polyphenol core consists of two diverging bowls having each a μ_3-phosphorus atom in the bottom. The P(1) and P(2) phosphate fragments lie

Keywords: calix[8]arene; phosphates; X-ray.

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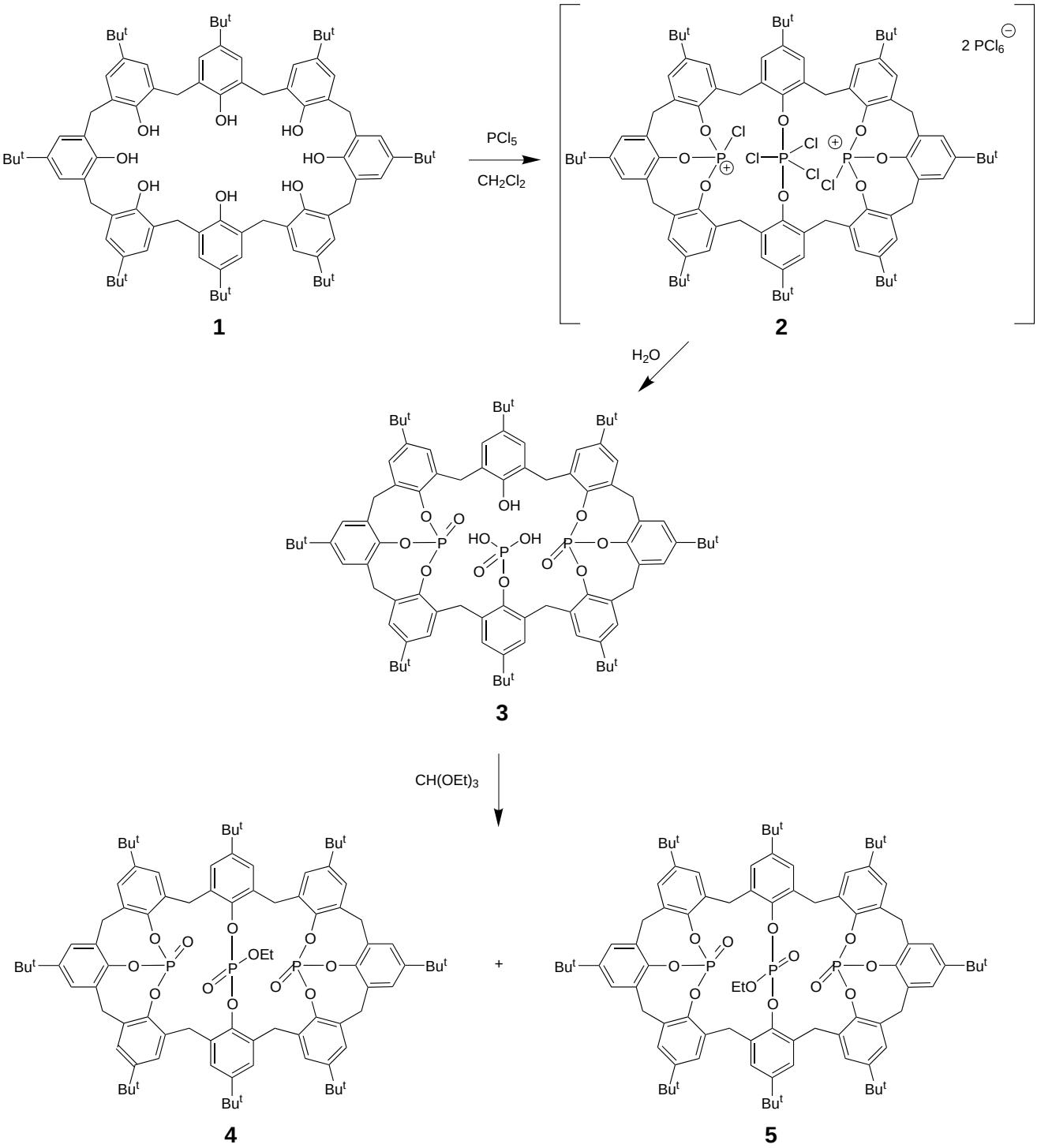
PII: S0040-4039(01)01959-1



Scheme 1.

on opposite sides of the calixarene reference plane and will therefore be designated as being in an ANTI relationship. The same holds for phosphates P(1) and P(3). Note, in this nomenclature, *capital letters* refer to the relative position of bridging units with respect to a particular plane (the calix reference plane), while the choice of P(1) is arbitrary. Furthermore, the P=O bond of the central phosphate group (P(2)) is pointing towards the calixarene side that bears the $P(1)O_4$ unit (again taken as reference). This particular orientation will be termed *syn* (small letters).[12] We note that the presence of three bridges across the calix[8]arene core strongly distorts its shape, making the macrocycle roughly ellipsoidal. The longest O···O separation between phenolic oxygen atoms is 13.9(1) Å (O(3)-O(12)), while that between O(5) and O(7) is 2.42(1) Å (Fig. 2).[14]

As mentioned above the ^{31}P spectra of phosphates **4** and **5** are almost identical and hence we assign to **5** the

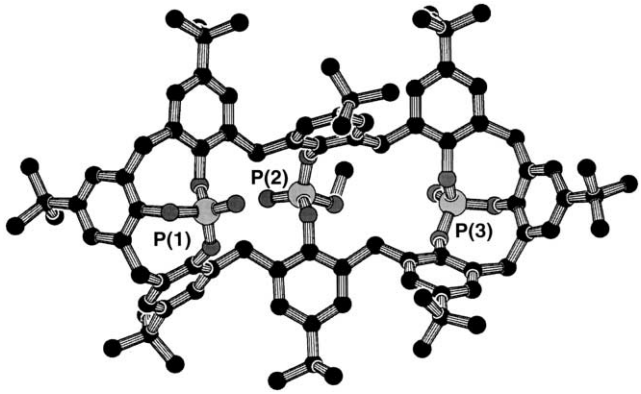


Figure 1. Molecular structure of **4** (top view).

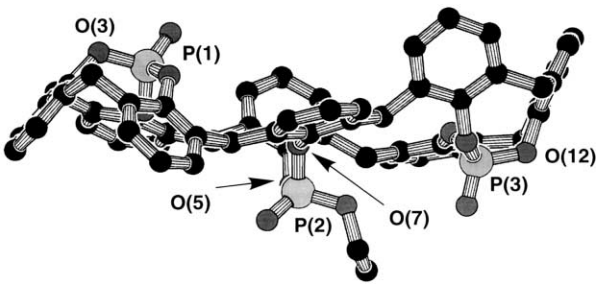


Figure 2. Molecular structure of **4** (side view). In this view the ^{t}Bu groups have been omitted for clarity.

drawn structure. This conclusion is corroborated by the fact that the OCH_2CH_3 signal of **5** is considerably highfield-shifted with respect to that of **4**, in keeping with an ethyl group located inside a polyaromatic cavity.[16] Thus, applying the nomenclature defined above, the triphosphates **4** and **5** adopt, respectively *syn-ANTI-ANTI* and *anti-ANTI-ANTI* configurations.[17]

In conclusion, this study describes the first calix[8]arene derivative containing three bridging phosphate units. Compound **4** constitutes the most elongated calix[8]arene reported to date.

Acknowledgements

We thank Dr. B. Costisella (University Dortmund) and Dr. M. Gruner (Technical University Dresden) for the NMR measurements. S. Ozegowski is grateful to the Deutsche Forschungsgemeinschaft for financial support.

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6. Compound **2** of this scheme has not been isolated; its structure has been assigned retrosynthetically, but formation of other structures cannot be excluded.
7. Preparation of **3**, **4** and **5**: A dichloromethane solution (450 ml) containing **1** (7.787 g, 6.0 mmol) and PCl_5 (4.120 g, 30.0 mmol) was refluxed for 1.5 h. The solution was evaporated to dryness. The residue was treated with conc. HCl (300 ml) and dioxane (50 ml), and the resulting solution was boiled for 3 h. The insoluble solid was filtered off, washed with hexane, then purified by column chromatography (silica, $CHCl_3$/MeOH, 100:1), and finally recrystallized from $CHCl_3$/MeOH. Yield for **3**: 1.600 g (18%); mp 463–465°C (dec.); ^{1}H NMR ($CDCl_3$, 500 MHz): 7.24–7.10 (16 H, arom. H), 4.68 (d, 4H, $ArCH_2Ar$, $^2J=14.1$ Hz), 4.45 (br d, 4H, $ArCH_2Ar$), 4.24 (d, 4H, $ArCH_2Ar$, $^2J=16.6$ Hz), 3.67 (d, $ArCH_2Ar$, $^2J=14.1$ Hz), 1.28 (s, 18H, Bu^t), 1.25 (s, 18H, Bu^t), 1.19 (s, 18H, Bu^t), 1.05 (broad signal, 18H, Bu^t); ^{31}P NMR ($CDCl_3$): −5.4, −21.2; −22.0 ppm; MS(FAB): 1465 [(M+1)$^+$]; $C_{88}H_{107}O_{13}P_3$ (1465.75): calcd C, 72.11; H, 7.36%. Found C, 71.74; H, 7.08%.
A solution of **3** (0.500 g, 0.34 mmol) in a 1:1 (v/v) $HC(OEt)_3$–DMF mixture (140 ml) was refluxed for 20 h. The solvent was evaporated and the resulting residue was purified on column chromatography (silica, acetone/heptene 1:3) affording first **4** (0.158 g, 32%), then **5** (0.270 g, 54%). Compound **4** was recrystallized from ethanol/water; mp 375–380°C (dec); $C_{90}H_{109}O_{12}P_3\cdot H_2O$ (1475.78+18.01): calcd C, 72.37; H, 7.49%. Found C, 72.41; H, 7.36%; ^{1}H NMR ($CDCl_3$, 500 MHz): 7.28–7.15 (14 H, arom. H) and 6.68 (s, 2H, arom. H), 4.72 (d, 2H, $ArCH_2Ar$, $^2J=13.8$), 4.71 (d, 2H, $ArCH_2Ar$, $^2J=14.0$), 4.57–4.44 (m, 6H, $ArCH_2Ar$), 4.42 (m, 2H, CH_2CH_3), 4.20 (br signal, 2H, ArCH), 3.69 (m, 4H, ArCH), 1.47 (t, 3H, CH_2CH_3, $^3J=7.1$ Hz), 1.30 (s, 9H, Bu^t), 1.27 (s, 9H, Bu^t), 1.27 (s, 18H, Bu^t), 1.20 (s, 18H, Bu^t), 0.95 (s, 18H, Bu^t) ppm. ^{31}P NMR ($CDCl_3$): −11.5, −20.5, −22.5 ppm; MS(FAB): 1475 [M$^+$]. Compound **5** was recrystallized from $CDCl_3$/hexane, mp 375–380°C (dec.); $C_{90}H_{109}O_{12}P_3$ (1475.78): calcd C, 73.25; H, 7.44%. Found C, 73.30; H, 7.50%; ^{31}P NMR ($CDCl_3$): −12.4, −21.1, −21.4 ppm. The mixture could also be separated by HPLC (Lichrospher. Si 60, $CDCl_3$/hexane 6:4); flow rate: 1.0 ml/min; retention time: 2.6 min. (**4**); 5.0 min. (**5**).
8. *Crystal data* for **4**·(5 $CDCl_3$): $C_{95}H_{114}Cl_{15}O_{12}P_3$, $M=2072.68$, triclinic, $a=12.1644(2)$, $b=20.1950(4)$, $c=21.6568(6)$ Å, $\alpha=81.477(5)$, $\beta=89.497(5)$, $\gamma=82.375(5)$°, $U=5214.6(2)$ Å^3, $T=173$ K, space group $P\bar{1}$, $Z=2$, $D_{calcd}=1.32$ g cm^{-1}, μ (Mo Kα) $=0.497$ mm^{-1}. Data were collected on a Nonius KappaCCD diffractometer, 23415 reflections measured, 7874 with $I>3\sigma(I)$. The structure was solved by direct methods and refined anisotropically on F^2 using the OpenMoleN package (OpenMoleN,

Interactive Structure Solution, Nonius B. V., Delft, 1997). Hydrogen atoms were included using a riding model or rigid methyl groups. Final results: $R(F)=0.089$, $wR(F)=0.100$, 1118 parameters. Further details of the structural investigations of **4**·(5 $CHCl_3$) are available on request from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (Deposit number CCDC 166047).

9. Earlier this compound was erroneously formulated as having the P(2)-bridge crossing proximal phenol units.[10,11]
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12. A similar nomenclature was used for trifunctional calix[4]arene derivatives.[13]
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14. For comparison, the corresponding distances in *p-tert*-butylcalix[8]arene·pyridine are 9.65 and 4.39 Å, respectively.[15]
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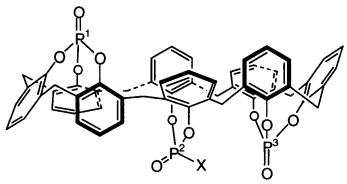
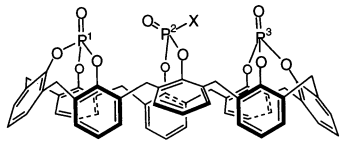
16. ^1H NMR ($CDCl_3$) for the OCH_2CH_3 group: $\delta=1.47$ ppm (**4**); –0.28 ppm (**5**).
17. The following four main conformations may be considered: (arbitrarily P^1 belongs to the phosphate group that lies on the left side of the drawing).

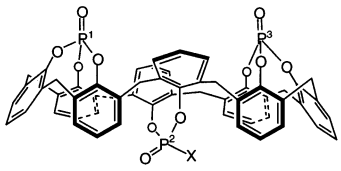
    The corresponding three *anti* structures (i.e. with the P^2=O phosphoryl bond oriented to the calix fragment bearing P^3) have not been drawn. Alternatively, **4** could also be designated as having an *anti-SYN-ANTI* structure (the reference P(1) atom being in this case located at the right side of the drawing). The latter nomenclature is equivalent to that used in this paper.



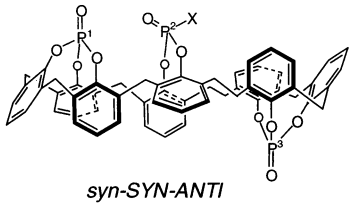
syn-ANTI-ANTI



syn-SYN-SYN



syn-ANTI-SYN



syn-SYN-ANTI