Selective Phosphorylation of *p-tert*-Butylcalix[6]arene

Rob G. Janssen,[a] **Willem Verboom,**[a] **Sybolt Harkema,**[b] **Gerrit J. van Hummel,**[b] **David N. Reinhoudt,***[a] **Andrea Pochini,**[c] **Rocco Ungaro,**[c] **Pilar Prados**[d] **and Javier de Mendoza**[d]

[a] *Laboratory of Organic Chemistry, University of Twente, 7500 AE Enschede, The Netherlands*
[b] *Laboratory of Chemical Physics, University of Twente, 7500 AE Enschede, The Netherlands*
[c] *Istituto di Chimica Organica dell'Università, Viale delle Scienze, I-43100 Parma, Italy*
[d] *Departamento de Química, Universidad Autónoma de Madrid, Cantoblanco, 28049-Madrid, Spain*

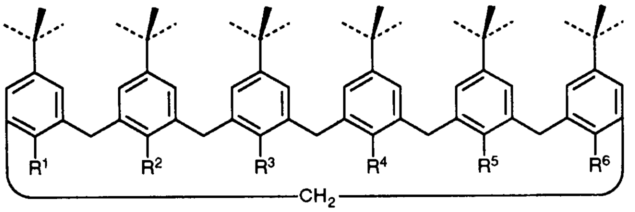
The synthesis of selectively phosphorylated and thiophosphorylated *p-tert*-butylcalix[6] arenes is described; the solid-state structure of the 1,4-bis(thiophosphorylated) *p-tert*-butylcalix[6]arene is elucidated by X-ray crystallography.

In addition to calix[4]arenes, the calix[6]arenes may become a versatile class of molecular building blocks for the construction of synthetic receptors. However, calix[6]arenes have an increased flexibility compared with calix[4]arenes, because of the two additional aryl moieties. So far, hexafunctionalized calix[6]arenes have been used for the complexation of neutral molecules[1] and cations.[2] In order to make calix[6]arenes available as molecular building blocks, we have investigated possible synthetic routes towards selectively functionalized calix[6]arenes, as well as the conformational preferences of

Table 1 Isolated yields of partially phosphorylated *p-tert*-butylcalix[6]arenes[a]

Equiv.			Yield of products (%)			
Calix[6]arene **1**	Et_3N	$POCl(OEt)_2$	Mono- **2**	1,3-Di- **3**	1,4-Di- **4**	1,2,4-Tri- **5**
1	28	7			28	41
1	28	6			20	56
1	4	4		31	27	
1	3	4		19	28	21
1	3	4	21	25	22	
1	3	2	37			

[a] Yields after column chromatography.



1; $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = OH$
2; $R^1 = OP(=O)(OEt)_2$, $R^2 = R^3 = R^4 = R^5 = R^6 = OH$
3; $R^1 = R^3 = OP(=O)(OEt)_2$, $R^2 = R^4 = R^5 = R^6 = OH$
4; $R^1 = R^4 = OP(=O)(OEt)_2$, $R^2 = R^3 = R^5 = R^6 = OH$
5; $R^1 = R^2 = R^4 = OP(=O)(OEt)_2$, $R^3 = R^5 = R^6 = OH$
6; $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = OP(=O)(OEt)_2$
7; $R^1 = R^4 = OP(=S)(OEt)_2$, $R^2 = R^3 = R^5 = R^6 = OH$
8; $R^1 = R^2 = R^3 = R^4 = R^5 = OP(=S)(OEt)_2$, $R^6 = OH$
9; $R^1 = R^2 = R^4 = H$, $R^3 = R^5 = R^6 = OH$
10; $R^1 = R^2 = R^3 = R^4 = R^5 = H$, $R^6 = OH$

these molecules. Recently, Gutsche and coworkers[3] and our groups[4] described the selective benzylation, aroylation and alkylation, respectively, of *p-tert*-butylcalix[6]arene **1**, and only a few other selectively functionalized calix[6]arenes have been reported.[5,6] In this paper we present our preliminary results on the selective phosphorylation and thiophosphorylation of *p-tert*-butylcalix[6]arene **1**. Previously, we[7] and others[6,8] reported the (selective) phosphorylation of calix[4]arenes.

Phosphorylation of *p-tert*-butylcalix[6]arene **1** was performed with diethoxyphosphoryl chloride in the presence of varying amounts of triethylamine as a base in refluxing chloroform. In all cases mixtures were obtained, which were analysed by HPLC, and separated by flash column chromatography (silica gel, EtOAc–hexane 1:3), to give monophosphorylated **2**, 1,3-diphosphorylated **3**,† 1,4-diphosphorylated **4** and 1,2,4-triphosphorylated **5**‡ as new partially functionalized calix[6]arenes. Dependent on the reaction conditions, these compounds§ were isolated in optimal yields of 37, 31, 28 and 56%, respectively (Table 1).

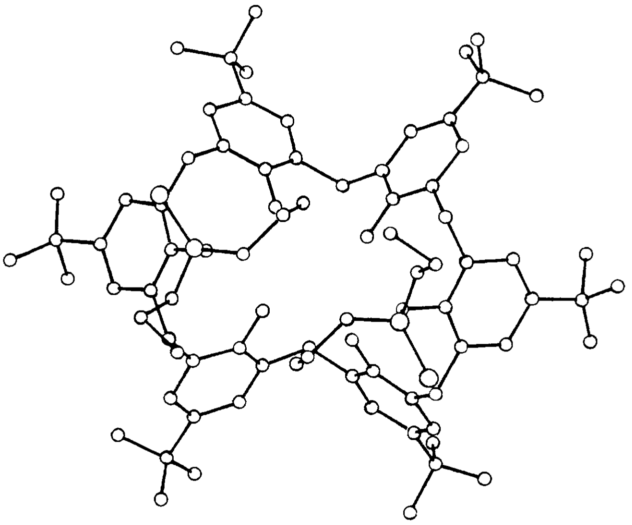


Fig. 1 Solid-state structure of compound **7**

Phosphorylation of **1** with an excess of diethoxyphosphoryl chloride and 50% aqueous NaOH under phase-transfer conditions in refluxing dichloromethane for 6 h, gave the hexaphosphorylated derivative **6** in 20% yield. Reaction of **1** with a large excess of the less reactive diethoxythiophosphoryl chloride under the same reaction conditions, afforded selectively the 1,4-bis(thiophosphorylated) **7** in 60–70% yield. Treatment of **1** with diethoxyphosphoryl chloride under anhydrous phase transfer conditions with solid NaOH as a base in dichloromethane at room temp. for 24 h, gave an increased yield of 36% of hexaphosphorylated **6**. A different substitution pattern was obtained when **1** was treated with diethoxythiophosphoryl chloride under the same conditions—in this case, pentakis(thiophosphorylated) **8** was obtained in 37% yield.

The structures of the compounds **2**–**4**, **6** and **7** could be deduced from their ^1H NMR spectra together with their fast atom bombardment (FAB) mass spectra. The structures of the 1,2,4-triphosphorylated **5** and pentakis(thiophosphorylated) **8** were determined indirectly. They were converted quantitatively into the dephosphorylated and dethiophosphorylated compounds **9** and **10**, respectively, upon treatment with a solution of potassium metal in liquid ammonia at −80 °C. To the best of our knowledge the formation of **10** is the first example of a reductive dethiophosphorylation. ^1H NMR spectroscopy proved the substitution pattern.

Substitution of the lower rim of *p-tert*-butylcalix[6]arene **1** with phosphate or thiophosphate groups leads to a restriction of the conformational freedom of the calix[6]arene skeleton. This is illustrated by the ^1H NMR spectrum of monophosphorylated **2** which exhibits one sharp ABq system at δ 4.70 and 3.57, and two broad ABq systems (δ 3.4–3.9) for the methylene protons. The differences of coalescence of the ABq systems indicate local differences of conformational flexibility of the core of the calix[6]arene skeleton. The ^1H NMR spectrum of 1,4-diphosphorylated **4** exhibits one broad ABq system (δ 4.6–4.4 and 3.7–3.3) and one broad singlet, which

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† The phenolic hydroxy groups, which are attached to carbon atoms 37–42, are numbered from 1–6 to give better insight into the substitution pattern of the different derivatives.

‡ According ref. 6, a high yield of the 1,3,5-triphosphorylated derivative should be obtained. Unfortunately, we were not able to trace or isolate this compound.

§ All new compounds were characterized by elemental analysis, ^1H NMR and ^{13}C NMR spectroscopy and FAB mass spectrometry.

coincides with the upfield doublet of the ABq system.¶ The signal of the *tert*-butyl groups of the phosphorylated aryl moieties is broad, while that of the *tert*-butyl group of the unsubstituted aryl moieties is sharp. According to these spectral data, which correspond to those reported by Gutsche for aroylated calix[6]arenes[3] a 1,2,3-alternate conformation could be proposed for 1,4-diphosphorylated **4**. However, the ^1H NMR spectrum of 1,4-bis(thiophosphorylated) **7** exhibits only sharp signals *e.g.* two ABq systems at δ 4.57, 3.49 and 3.94, 3.40 (rato 2 : 1) and two signals for the *tert*-butyl groups (ratio 2 : 1), which points to a cone like conformation.

Conclusive evidence for the conformation of **7** was obtained from its X-ray structure‖ (Fig. 1). In the solid state **7** adopts a pinched cone conformation with a C_2 axis of symmetry. Obviously, the replacement of the phosphate groups in **4** for thiophosphate groups in **7**, has a significant influence on the flexibility of the calix[6]arene core, and consequently on the conformation.

These selectively phosphorylated and thiophosphorylated calix[6]arenes can be used as the starting materials for other, selectively alkylated calix[6]arenes,[4] because after functionalization of the remaining free OH groups, the phosphates can easily be hydrolysed. A study to the conformational properties, as well the application of these compounds is currently under investigation.

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¶ According to variable temperature ^1H NMR spectra.

‖ *Crystal data*: $C_{74}H_{102}O_{10}P_2S_2 \cdot xC_6H_{14}$, monoclinic, space group $I2/a$; a = 16.311(5), b = 30.313(8), c = 17.203(6) Å, β = 113.62(7)°; V = 7793 Å^3; Z = 4; D_c = 1.09 g cm^{-3}. Reflections measured in the ω/2θ scan mode at 141(5) K, graphite monochromated Mo-Kα radiation [scan with (ω) (1.3 + 0.35 tanθ)°; 3 < θ < 20°]. A total of 1259 reflections with $F_o^2 > 3\sigma(F_o^2)$ was used in the refinement. The asymmetric unit contains one half of a calixarene and a hexane molecule, the other halves being generated by a twofold rotation axis. The hexane molecule is disordered. The number of parameters refined was 277 (scale factor, extinction parameter, positional parameters of the heavy atoms, thermal parameters refined anisotropically for S, P, the atoms of the ethoxy group and the terminal C-atoms of the *tert*-butyl groups; isotropically for the other atoms; H-atoms treated as riding atoms). Final R-factors were R = 7.3%, R_w = 7.4%.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.