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Synthesis of a Fully OH-depleted *p-tert*-Butyl-Calix[6]arene.

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Abstract : The reaction of $ClP(O)(OEt)_2$ with the *p-tert*-butyl-calix[6]arene provided its fully phosphorylated analog **2** *plus* a penta- esterified species **3** bearing one bridging phosphoester. Reaction of **2** with K/NH_3 afforded the corresponding [1^6] metacyclophane **1**.

In the field of supramolecular chemistry, the cyclic phenolic oligomers or calixarenes show, since the pionnering work of Gutsche[1] an increasing interest. Mixing complexation abilities for neutral or ionic guests and a good functionalization flexibility with a high thermal stability, they became in few years a promising chemical platform for the building of a new family of synthetic receptors[2]. The main chemical work on those structures has been dedicated to the substitution of the *p-tert*-butyl groups by hydrogen, halogens, sulfonic acid, nitro groups, chloromethyl or aldehyde groups (upper rim), or, at the lower rim, by the functionalization of the OH groups through esterification or etherification reactions[3].

Some research teams have been interested by the direct substitution of OH by NH_2[4], SH[5], or H. In this sense, Biali and coworkers[6], by an adaptation of the Kenner and Williams method[7] for synthesizing benzene rings from phenols, developped a procedure allowing the access to apolar benzylic macrocyclic systems. It involves the activation of the phenolic OH group into its di(ethyl) aryl phosphoester, followed by a reductive cleavage step by means of potassium in liquid ammonia. By this way, the *p-tert*-butyl-calix[4] and [8]arenes gave in good yields the corresponding [1^4] and [1^8] metacyclophanes. More recently, Reinhoudt and coworkers[8] employed this procedure for the *p-tert*-butylcalix[6]arene, without preparing of its fully OH-depleted analog **1**.

We tried unsuccessfully to obtain **1** by different methods involving reduction of the activated Caryl-O bond, notably the hexa-tosylate with hydrazine/Pd/C[9] or the hexaphosphoester **2** with titanium metal[10]. We found preliminary that the hexa-ester **2** was co-synthesized with a bridged penta-ester analog **3** which is actually under X-ray crystallographic analysis and will be the object of a future report.

Some recent publications describe the controled formation of bridged or unbridged phosphoesters of calix[4], [6] and [8]arenes[11]. Roundhill and coworkers[11e] prepared mono- and bis- adjacent bridged phosphoesters of the *p-tert*-butyl-calix[6]arene; however, this study was not helpful to elucidate the structure of **3**.

We describe here the synthesis of the two phosphoesters **2** and **3**[12], and the preparation of the [1^6]-*p-tert*-butyl-metacyclophane **1**[13] by means of reduction of **2** with K/NH_3 mixture, in a 33% yield procedure (fig.I). The *p-tert*-butyl-calix[6]arene **4**[14] was treated by a large excess of $ClP(=O)(OEt)_2$ and aqueous NaOH in PTC conditions, affording two major compounds, the hexaester **2** and a compound **3** we analyzed as a hexa-esterified species bearing one bridging phosphoester unit, in 20% and 17% yields respectively. Replacing aqueous NaOH by solid NaOH[8] changed those values to 35% and 12%. Treating **3** in the same PTC conditions did not afford any **2**, allowing us to certify that **3** and **2** are co-products in this reaction. Separation of **2** and **3** was achieved by silica gel column chromatography using a gradient of EtOH in CH_3COOEt.

The conversion of **2** into **1** was performed by reducing the Caryl-O-bond with potassium metal in liquid ammonia at -70°C, following the previously, but slightly modified, described procedure[6a]. **1** was isolated from a multitude of compounds by precipitation in EtOH, with a moderate yield of 33%.The same procedure applied on **3** did not afford **1** but a mixture of polar compounds which are actually under investigations.

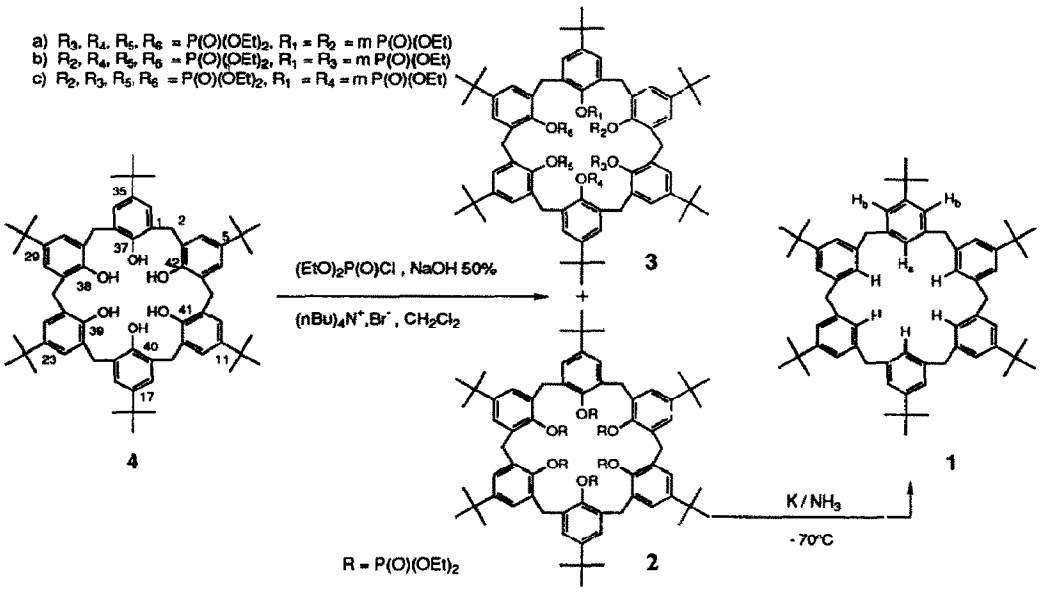

Fig. 1 : Synthesis of the p-tert- Butyl [1[6]] metacyclophane **1**

^{1}H-NMR was not sufficient enough, even under variable temperature, to give clearly the structure of **2**. At 225 K, the structure begins to rigidify, but the resonance signals are still too much overlaped to be analyzed; at room temperature, **2** can be described with broad signals at the related aromatic and alkyl positions.

In the case of **3**, the room temperature ^{1}H-NMR spectrum is perfectly well defined in the aromatic region: ten resonance signals (proton ratio: 1, 1, 1, 2, 1, 2, 1, 1, 1, 1) are located as doublets (J = 2.2 Hz) at 6.22, 6.27, 6.76, 7.15, 7.21, 7.24, 7.37, 7.60, 7.63 and 7.69 ppm respectively. Attempts to attribute directly those peaks were unsuccessful. In fact, three bridging positions can be considered (**3 a, b and c**), in each of which many conformations can be proposed. The preliminary results of X-ray crystal analysis of **3** are in agreement with the hypothesis of a 38, 39 - bridge, equivalent to the molecular structure **3a**[15].

^{1}H-NMR spectroscopy of **1** shows the high equivalence in the Ar-CH_2-Ar and aromatic protons families, characterized by three singlets at 3.81, 6.65 (Ha) and 6.96 (Hb) ppm respectively, in agreement with the fact that the removal of the hydroxyl hydrogen bonds may result in an increase of the conformational flexibility of this new molecular system. ^{13}C-NMR and DEPT experiment confirm the structure of **1**.

Beyond the disappearance of the O-P(=O) $(OEt)_2$ bands, we notice that infra-red spectrum of **1** shows bands at 690 and 787 cm^{-1}, characteristic of 1,3,5-trisubstituted benzene rings.

The electronic spectrum of **1** displays a broad absorption pattern at 270 nm, with a shoulder at 285 nm. The value of the measured ε_{270} (1480 mol^{-1} l cm^{-1}) is surprising if compared to diphenylmethane (ε_{262} = 5000 mol^{-1} l cm^{-1}), but is reliable with the absorption characteristic of six 1,3,5-trisubstituted benzene.

Finally, the mass measurement of **1** gives the value of the molecular peak at 900.1 for $[M+Na]^+$.

Studies of conformational and chemical properties of **1**, **2** and **3** are presently under investigation, as well as the search of new synthetic pathways to change **4** into **1** and in a general manner, any calixarene into their corresponding [1^n] metacyclophanes.

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12. Melting points (°C,uncorrected) were determined on a Electrothermal 9100 Capillary apparatus. ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker AM 300 (300 MHz) and a Bruker AC 200 (50.3 MHz) respectively (TMS as internal standard, chemical shifts in ppm). Mass spectra were obtained by electrospray technique (HP 5989/MS Engine, Service Central d'Analyse, CNRS, Solaize). Infra-red was performed on a Mattson 5000 FT apparatus (ν in cm^{-1}) and UV spectra were recorded on a Perkin-Elmer Lambda 2 UV/VIS apparatus (λ max in nm, ε in mol^{-1} l cm^{-1}). Elemental analyses were performed at the Service Central de Microanalyse, Ecole Supérieure de Chimie, Montpellier. Macherey-Nagel TLC plates were used for chromatography analysis (SiO_2, Polygram SIL G/UV254, ref.805021) and column purifications were run on silica gel (Merck 7734, 70-230 mesh). All commercialy available products were used without further purification unless specified otherwise.
Calixarenes 2 and 3a: a solution of 50% NaOH (50ml) was added dropwise to a stirred solution of **4** (1g, 1.03 mmole), diethylchlorophosphate (7.15 ml) and tetrabutylammonium bromide (0.1 g) in CH_2Cl_2 (100 ml). After 6 h under reflux, the solution was cooled, the organic phase was separated, washed with brine, dried over Na_2SO_4 then evaporated to a brown syrup. The later was dissolved in Et_2O (40 ml), washed with water (5 x 100ml) to remove $(EtO)_2P(O)OH$ and unreacted (EtO) P(O)Cl, then evaporated to give a white foam. Crystallization in n-heptane gave a white powder (1.35 g) containing **2** and **3a** which were chromatographed over silica gel. Pure CH_3COOEt afforded **3a** (0.29 g, 17%). **2** was obtained with a 30% EtOH : CH_3COOEt eluant (0.36 g, 20%).
2: mp 275-276. ^{1}H-NMR ($CDCl_3$): d 0.9-1.5 (br.m, 90 H, $C(CH_3)_3$ and CH_3-CH_2-O); 3.51-4.8 (br s, 36 H, Ar-CH_2-Ar and CH_3-CH_2-O); 7.13-7.69 (br m, 12 H, ArH). ^{13}C-NMR ($CDCl_3$): d 16.02 (CH_3-

CH_2-0); 31.51 ($C(\underline{C}H_3)_3$); 33.8 (Ar-$\underline{C}H_2$-Ar); 34.15 ($\underline{C}(CH_3)_3$), 64.61, 64.49 ($\underline{C}H_2$-0); 128.39 (Ar $\underline{C}$-H); 131.64, 144.98, 147.1 (Ar $\underline{C}$). IR: 964, 1030, 1175, 1265 (Phosphoester). M.S: m/z = 1812.6 ($[M+Na]^+$ calc.1812.6). Elemental anal. calc. for C_{90} H_{138} O_{24} P_6 (1789.8): C 60.39, H 7.77, O 21.45, found: C 60.20, H 7.85, O 21.66. UV ($CHCl_3$): 275.5 (2675), 270.0 (2475).

3: mp 218-219. ^{1}H-NMR ($CDCl_3$): d 0.9-1.67 (br m, 81 H, $C(C\underline{H}_3)_3$ and $C\underline{H}_3$-CH_2-O); 3.35-5.36 (br m, 30 H, Ar-$C\underline{H}_2$-Ar and CH_3-$C\underline{H}_2$-O); 7.15-7.24 (d, 4 H, Ar$\underline{H}$); 6.22, 6.27, 6.76, 7.21, 7.37, 7.6, 7.63, 7.69 (8 d, $J_{H\text{-}H}$ 2.2 Hz, 8 H, Ar$\underline{H}$). ^{13}C-NMR ($CDCl_3$): d 15.8, 16.03, 16.16, 16.21, 16.40 ($\underline{C}H_3$-CH_2-O); 24.72, 30.33 (Ar-$\underline{C}H_2$-Ar); 31.09, 31.29, 31.41 ($C(\underline{C}H_3)_3$); 32.32, 32.87, 33.68 (Ar-$\underline{C}H_2$); 34.15, 34.29 ($C(CH_3)_3$); 64.22, 64.6, 64.85, 64.96 (CH_3-$\underline{C}H_2$-O); 124.11, 125.09, 125.54, 126.03, 127.50, 128.15, 128.96 (Ar $\underline{C}$-H); 126.57, 128.45, 129.25, 130.98, 131.40, 131.84, 132.27, 132.62, 133.00, 133.5, 133.91(Ar-$\underline{C}$);144.26, 144.38, 144.54, 145.15, 146.87, 147.21, 147.48, 148.10, 148.33 (Ar $\underline{C}$). IR: 964, 1030, 1180, 1273 (Phosphoester). M.S: m/z = 1629.6 ($[M+Na]^+$ calc. 1629.6). Elemental anal. calc.for C_{84} H_{123} O_{20} P_5 (1607.66): C 62.75, H 7.77, O 19.90, found: C 62.67, H 7.74, O 19.69. UV ($CHCl_3$) : 276-2 (2770); 271.0 (2508).

13 ***Metacyclophane 1***: in a cold finger equiped with a magnetic stirring bar, 40 ml of liquid NH_3 were trapped under N_2. Potassium metal (3.2 g) was added carefully in small bits over 1 h until complete dissolution. A solution of **2** (0.4 g, 0.22 mmol) in dry Et_2O (5 ml) was mixed to the stirred blue solution, followed by potassium metal (0.5 g). After 20 min, NH_4Cl (5 g) was carefully added in small portions until the blue colour was discharged and the ammonia solution became white. Et_2O (30 ml) was added and the mixture was left to warm up until all the ammonia had evaporated. The residue was treated with hot Et_2O (40 ml). Filtration, evaporation of the solvent and cristallization of the residue in ethanol afforded pure compound **1** (65 mg, 33%).

1 : mp 213. ^{1}H-NMR ($CDCl_3$): d 1.16 (s, 60 H, $C(C\underline{H}_3)_3$ and H_2O); 3.81 (s, 12 H, Ar-$C\underline{H}_2$-Ar); 6.65 (s, 6H, Ar-$\underline{H}$a); 6.96 (s, 12 H, Ar $\underline{H}$b). ^{13}C-NMR ($CDCl_3$): d 31.4 ($C(\underline{C}H_3)_3$); 34.54 ($\underline{C}(CH_3)_3$); 42.16 (Ar-$\underline{C}H_2$-Ar); 123.16 ($\underline{C}$-Hb); 126.7 ($\underline{C}$-Ha); 140.57 ($\underline{C}_{Ar}$-CH_2); 141.11 ($\underline{C}_{Ar}$-tBu). IR: 690 and 787 (1,3,5, trisubstitued benzene), 1000, 1090,1257 (ring hydrogen rocking vibration). Elemental anal. calc. for $C_{66}H_{84}$, 4 H_2O (949.43): C 83.49, H 9.77, found: C 83.82, H 9.84. M.S: m/z = 877.9 (M^+ calc. 877.4) and 900.1 ($[M+Na]^+$ calc. 900.1). UV ($CHCl_3$) : 270.1 (1480), 285 (s, 140).

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