# Multiple Reductive Cleavage of Calixarene Diethyl Phosphate Esters: a Route to [1$^n$]metacyclophanes

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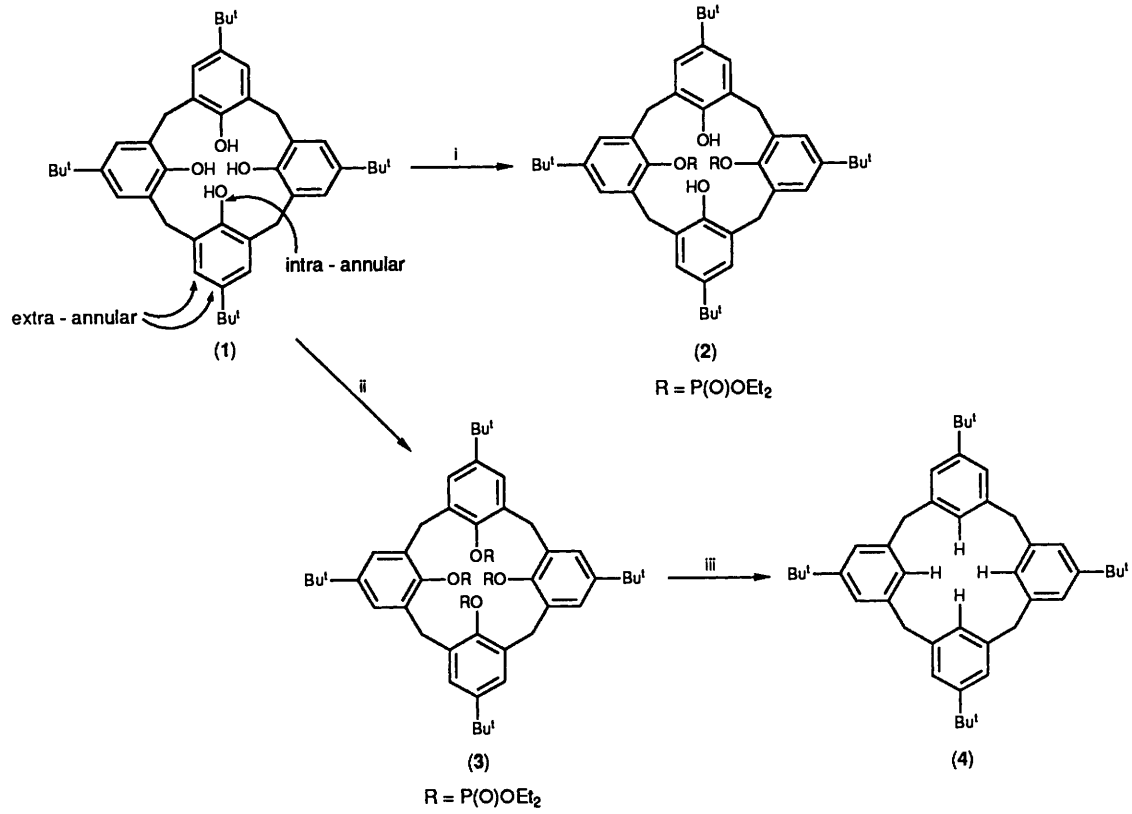
The OH groups of *p*-t-butylcalix[*n*]arene (*n* = 4 and 8) were converted into diethyl phosphate esters and reductively cleaved by treatment with K/$NH_3$ to yield tetra-*p*-t-butyl[1$^4$]- and octa-*p*-t-butyl[1$^8$]metacyclophanes (**4**) and (**7**).

Calixarenes are cyclic phenol–formaldehyde condensation products which are presently being extensively investigated as host molecules and enzyme mimics.[1,2] Most investigated is the synthetically readily available *p*-t-butyl[4]calixarene (**1**).[3] This compound exists in solution[4] as well as in the crystal[5] in a 'cone' conformation, in which the OH groups are engaged in a cyclic hydrogen bond. This intramolecular hydrogen bond is believed to stabilize the cone conformation as well as to determine its rigidity.

Calixarenes have been chemically modified in order to alter or improve their binding capabilities and solubilities. Most modifications have been carried out by removal of the *p*-t-Bu$^t$ group and introduction of a functional group at that position [an extra-annular modification, *cf.* (**1**)].[6] A drawback of this approach, is that the functional groups in the *para* position are not pointing inwards towards the cavity and, therefore, the newly introduced substituents cannot co-operatively behave as binding groups. Another synthetic approach involves conversion of the phenolic OH into another functional group. However, since only a limited number of reactions are capable of substituting phenolic OH groups under mild conditions,[7] most intra-annular [*cf.* (**1**)] modifications of calixarenes have been based on derivatization of the OH group into ether or ester derivatives.[8] Although functionalized alkyl groups can be introduced by this route, the weakness of this approach is that the conformational flexibility of the alkyl chains reduces the preorganization[9] of the binding groups. To the best of our knowledge, *direct replacement* of the OH groups of a calixarene has never been reported. In this communication we report the total replacement of the calixarene phenolic OH groups, and describe a family of cyclophanes which have the potential of being converted into calixarenes with binding groups different from OH at intra-annular positions.

In their study of the reduction of phenols to aromatic hydrocarbons, Kenner and Williams showed that phenolic OH groups can be replaced by hydrogen *via* a two-step process involving the conversion of the OH into a phosphate ester, and the cleavage of the resulting ester by treatment with an alkali




**Scheme.** *Reagents and conditions:* i, $HPO(OEt)_2$, $Et_3N$, $CCl_4$; ii, $(EtO)_2POCl$, 50% aqueous NaOH/PTC; iii, $K/NH_3$.

metal dissolved in liquid ammonia.[10] We reasoned that if this synthetic protocol could be applied to the corresponding *p*-t-butylcalixarenes it will allow an entry into *p*-t-butyl[1$^n$]metacyclophane systems.

Reaction of (**1**) under standard reaction conditions for the formation of aryl diethyl phosphate ester [$HPO(OEt)_2/Et_3N/CCl_4$, 0 °C][10] resulted in formation of the 1,3-diphosphate product (**2**) (Scheme).[11] Reaction of either (**1**) or (**2**) under more drastic conditions [$(EtO)_2POCl$, 50% aqueous NaOH/$CH_2Cl_2$, phase transfer catalysis (PTC)] resulted in the formation of the tetra(diethyl phosphate) ester (**3**) in good yield. Both (**2**) and (**3**) exist on the NMR time scale in a fixed cone conformation as evidenced by the number of signals in the $^1H$ and $^{13}C$ spectra, and the anisochronicity of the benzylic methylene protons, which appear as a single AB quartet in the $^1H$ NMR spectrum.

Addition of a solution of (**3**) in dry ether to an excess of K dissolved in liquid $NH_3$ resulted in a high yield (91%) conversion of (**3**) into (**4**),[12] in addition to small amounts of regenerated calixarene (**1**). The high yield transformation (**3**)→(**4**) is most notable since it involves the four-fold cleavage of the C(aromatic)–O(phosphate) bonds. Reaction of (**3**) under $S_RN1$ conditions[13] (K, $KNH_2/NH_3$) resulted also in the exclusive formation of (**4**): in contrast with simple aryl diethyl phosphate esters,[7b] no aniline product could be detected. The OH depletion scheme was also applied to *p*-t-butylcalix[8]arene (**5**).[14] Reaction of (**5**) with $(EtO)_2POCl$ (50% aqueous NaOH/$CH_2Cl_2$, PTC) resulted in the formation of the octa(diethyl phosphate) ester (**6**). Eight-fold reductive cleavage of (**6**) with $K/NH_3$ resulted in the formation of the *p*-t-butyl[1$^8$]cyclophane (**7**).[12]

The $^1H$ NMR spectra (200 MHz, r.t., $CDCl_3$) of (**4**) and (**7**) display a single singlet for the Bu$^t$ protons and one doublet and one triplet for the aromatic protons at the extra-annular and intra-annular positions, respectively. In contrast with their calixarene parent compounds, the metacyclophanes (**4**) and (**7**) display a single signal (singlet) for the methylene protons, in agreement with a conformational flexible species in solution. This is in agreement with the expectations, since the removal of the cyclic hydrogen bond present in (**1**) and (**5**) should result in an increase of the conformational mobility of the systems. Lowering the temperature of samples of either (**4**) or (**7**) to 190 K ($CD_2Cl_2/CDCl_3$) resulted in no appreciable broadening of the signals. An alternative explanation for the isochronicity of the methylene protons could be that in the preferred conformation the phenyl rings are alternately disposed ('up' and 'down') with regards to the mean macrocyclic plane resulting in $D_2d$ and $D_4d$ skeleton symmetries. In order to clarify this

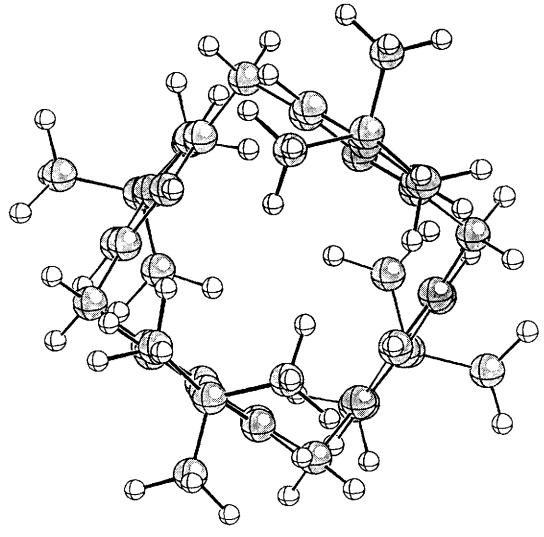
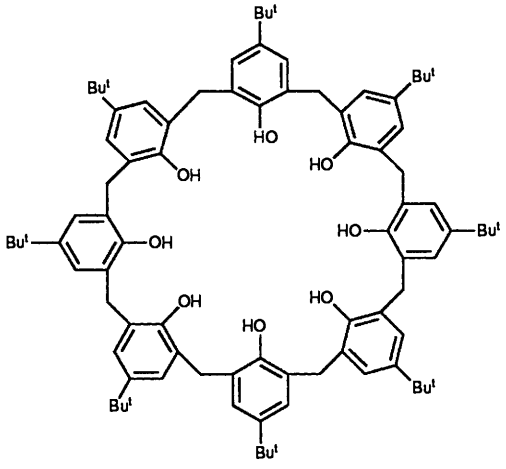


**Figure.** Ball-and-stick representation of the calculated [MM2(85)] low-energy conformation of compound (**4**). The conformation (1,3-alternate) is viewed along the $S_4$ alternating axis.

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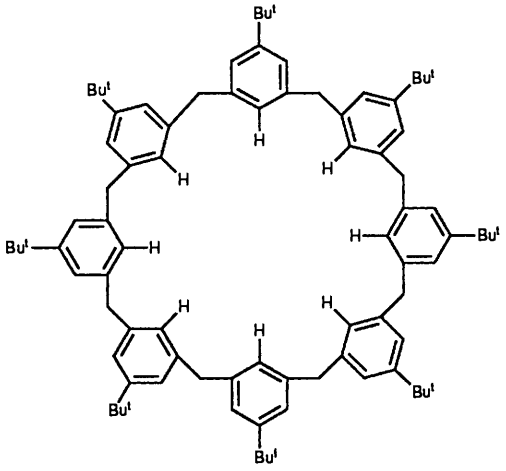


(7)

question we decided to resort to molecular mechanics (MM) calculations, choosing the cyclophane (**4**) which is within our computational capabilities.

MM Calculations were carried out using Allinger's MM2(85) program.[15] The conformations considered were the four forms designated by Gutsche 'cone', 'partial cone', '1,3-alternate', and '1,2-alternate'.[2] The calculated relative strain energies of these conformations are 0.6, 1.1, 0, and 3.1 kcal mol$^{-1}$, respectively, indicating that in contrast with the parent compound (**1**), the preferred conformation of (**4**) is the '1,3-alternate'. The calculated low-energy conformation of (**4**) is shown in the Figure. It should be noted that although the calculated conformation has $S_4$ symmetry, the effective dynamic symmetry of the conformation under fast Bu$^t$ rotation is $D_2$d.

In the cyclophanes (**4**) and (**7**) the p-*t*-Bu$^t$ groups can serve as protective groups, since they can, in principle, shield and avoid reactions at the extra-annular positions.[16] The cyclophanes (**4**) and (**7**) should, in principle, be capable of undergoing substitution selectively at the intra-annular positions since these positions are exposed for functionalization. Electrophilic substitution on (**4**) and (**7**) should afford a synthetic route for calix[*n*]arenes having binding groups different from OH directly attached to the intra-annular positions. Work is under way to carry out these transformations and will be reported in due course.

## Experimental

*Compound* (**3**).—A solution of 50% NaOH (50 ml) was added dropwise to a stirred solution of (**1**) (1 g, 1.54 mmol), diethyl chlorophosphate (5 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 separated and washed (brine), dried ($Na_2SO_4$), and evaporated. The residue was dissolved in a small amount of hot dimethoxyethane, cooled, and filtered. Evaporation of the filtrate afforded pure (**3**) as a white powder (1.05 g, 57%). Further purification of the product was achieved by crystallization from ether–methanol; it had m.p. 242 °C.

*Compound* (**4**).—A three-necked flask (250 ml) equipped with a magnetic stirrer, a cold finger condenser, and a dropping funnel and cooled to −78 °C by a solid $CO_2$–acetone cooling mixture was charged with ammonia (50 ml). Potassium metal (4 g) was added carefully in 0.2 g pieces during 1 h to give complete dissolution of the metal. A solution of compound (**3**) (0.5 g, 0.42 mmol) in dry ether (6 ml) was added dropwise to the stirred blue solution followed by potassium metal (0.5 g). After 15 min, $NH_4Cl$ (6.2 g) were carefully added in small portions until the blue colour was discharged and the ammonia solution became white. Ether (50 ml) was added and the mixture was left to warm up until all the $NH_3$ had evaporated. The residue was treated with hot ether (100 ml). Filtration and evaporation of the ether gave compound (**4**) (0.22 g, 91%). Further purification of the product by column chromatography [$SiO_2$, eluant: 5% ethyl acetate 95% light petroleum (b.p. 40–60 °C)] afforded pure compound (**4**) as a white powder (0.17 g, 69%), m.p. 215 °C.

## Acknowledgements

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