p-t-Butyl-calix[4]arene Tetracarboxylic Acid. A Water Soluble Calixarene in a Cone Structure

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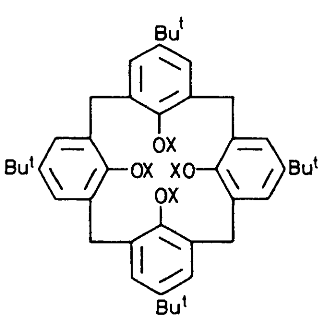
Treatment of *p*-t-butyl-calix[4]arene (**1**) with t-butyl bromoacetate in tetrahydrofuran–*N,N*-dimethylformamide gives, after hydrolysis, a tetracarboxylic acid which exists in a cone structure with an enforced hydrophobic cavity, and whose alkali and ammonium salts are soluble in water.

The design and synthesis of artificial water-soluble host compounds with a hydrophobic cavity of definite size and shape, which can be used as synthetic analogues of cyclodextrins to study the specific binding of substrates in aqueous solution, is a growing interest.[1]

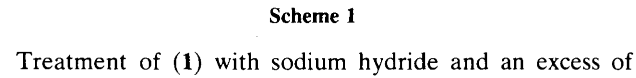
The calixarenes[2] are a class of phane-type macrocycles, derived from the condensation of phenols and formaldehyde, whose ability to form inclusion compounds with organic molecules in the solid state has been recently discovered.[3—6]

Among these compounds the *p*-t-butyl-calix[4]arene (**1**) is particularly interesting since it is able to form 1 : 1[3] or 2 : 1[6] inclusion complexes with aromatic guest molecules which occupy intramolecular cavities, whereas other calix[4]arenes give clathrates,[7] with the guests held in intermolecular voids or channels of the crystal lattice.[5,8—9] Therefore we have chosen the macrocycle (**1**) and explored several approaches for the introduction of functional groups capable of making it water soluble. We report here an account of the most relevant results obtained.

Our previous studies on the molecular inclusion properties of these macrocycles[3—6] indicated the importance of t-butyl groups in determining the intramolecular host–guest character of the inclusion complexes between (**1**) and aromatic molecules. Therefore, in this case, as for other calixarene derivatives,[10,11] we have introduced functional groups on the phenolic oxygen atoms of (**1**).



(**1**) X = H
(**2**) X = $CH_2CO_2Bu^t$
(**3**) X = CH_2CO_2H



$$(1) \xrightarrow[\text{BrCH}_2\text{CO}_2\text{Bu}^t]{\text{NaH, (THF - DMF)}} (2) \xrightarrow[\text{EtOH - H}_2\text{O}]{\text{KOH}} (3)$$

Scheme 1

Treatment of (**1**) with sodium hydride and an excess of t-butyl bromoacetate in tetrahydrofuran (THF)–*N,N*-dimethylformamide (DMF) solution gives the tetraester (**2**),

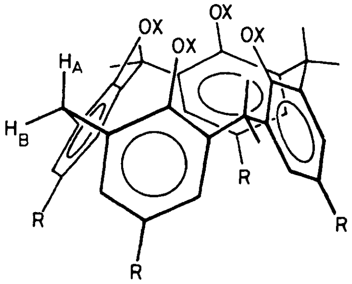


Figure 1. The cone conformation of macrocycles (**2**) and (**3**).

m.p. 258—261 °C, isolated in *ca.* 70% yield by flash chromatography on silica gel with ethyl acetate as eluant.†

Compound (**2**) has a cone conformation, with the $\mathrm{Bu^t}$ groups on one side and the ester groups on the other with respect to an ideal plane containing the bridging methylene groups of the macrocycle (Figure 1). This conclusion is consistent with the the ^{1}H and ^{13}C n.m.r. spectra which show a very simple pattern.[12] The high field doublet at δ 3.18 (J_{AB} 13 Hz) has been assigned to the equatorial proton H_B on the basis of the nuclear Overhauser effect and pyridine-induced shift experiments on (**2**), (**3**), and other simple calix[4]arene derivatives.[13]

It is noteworthy that the ester (**2**) could be obtained selectively in a perfect cone structure, preserving the shape of the hydrophobic cavity observed in the solid state for the starting macrocycle (**1**).

In fact, the derivatization of calix[4]arenes at the phenolic oxygen atoms usually leads to conformationally rigid compounds with less symmetrical structures,[2,10] although calix[4]arene derivatives in a fixed cone conformation similar to that thought to occur for compound (**2**) have been reported.[2]

Other tested procedures different from that outlined in Scheme 1 lead to *p*-t-butyl-calix[4]arene tetraesters with more distorted cone structures. Basic hydrolysis of compound (**2**) gives quantitatively the tetra-acid (**3**),† m.p. 264—267 °C (decomp.), which maintains the cone structure of the ester (**2**).

Alkali and ammonium salts of the acid (**3**) are soluble in water at pH *ca.* 7 between 5×10^{-4} and 5×10^{-3} M depending on the cation used ($\mathrm{Na^+ < K^+ < Cs^+ < NH_4^+ < Li^+}$). The tetra-acid (**3**) represents the first example of a water soluble calixarene and, more interestingly, it maintains a cone structure with the four carboxylic groups on the same side of the macrocycle. It has other interesting properties worth investigating further. For example, it will allow the study of the selective inclusion of organic guests in aqueous solution and a comparison with the results obtained in the solid state. Also, the presence of four carboxylic groups in close proximity and in a fixed spatial arrangement makes (**3**) attractive as a new type of acidic complexone with a lypophilic backbone for the extraction and separation of metal ions.

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† Satisfactory elemental analyses were obtained for compounds (**2**) and (**3**). ^{1}H N.m.r. spectrum of (**3**) (100 MHz, $\mathrm{CDCl_3}$, $\mathrm{Me_4Si}$), δ 1.10 (s, 36H), 3.23 (d, 4H, H_B, J_{AB} 13 Hz), 4.53 (d, 4H, H_A), 4.58 (s, 8H, $\mathrm{OCH_2CO}$), 6.83 (s, 8H, ArH), and 9.56 (s, 4H, OH).