Large Macrocyclic Rings with Complex Architectures: Polyspirodienone Calix[6]arene Derivatives

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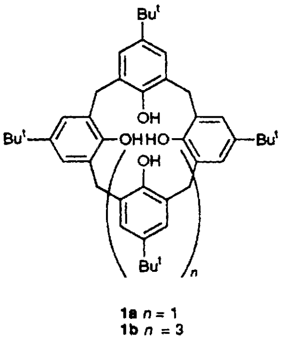
Mild oxidation of *p-tert*-butylcalix[6]arene yields tris(spirodienone) systems with alternant and non-alternant cyclic dispositions of the ether and carbonyl groups.

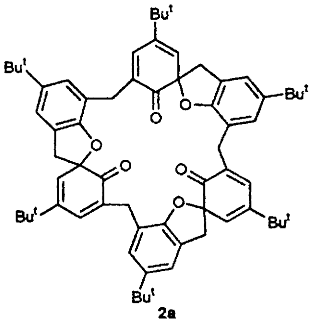
Calixarene is the common name given to a family of macrocycles composed of a cyclic arrangement of phenol and methylene units.[1] The modification of the phenolic OH functionalities by other binding groups remains one of the main synthetic goals in calixarene chemistry.[1,2] We have shown previously that the combination tetraalkylammonium tribromide–base oxidizes *p-tert*-butylcalix[4]arene **1a**[3,4] into monospirodienone[5] or bis(spirodienone) derivatives.[6,7] These spirodienone derivatives are of interest since they are useful synthetic intermediates for the preparation of calixarenes selectively functionalized in intraannular or extraannular positions,[6,8] and *per se*, as novel ligands containing both carbonyl and ether binding groups.

In principle, an analogous oxidation of *p-tert*-butylcalix[6]arene **1b**[3] to its tris(spirodienone) derivatives should yield systems with larger cavities. The presence of an odd number of stereocentres precludes the existence of *meso*-forms and therefore all tris(spirodienone) derivatives possible must be chiral. For these derivatives ten isomeric forms (five pairs of enantiomers) exist, arising from the different possible configurations (*R* or *S*) of the spiro carbons and the two possible senses of direction[6] of the spirodienone moieties.

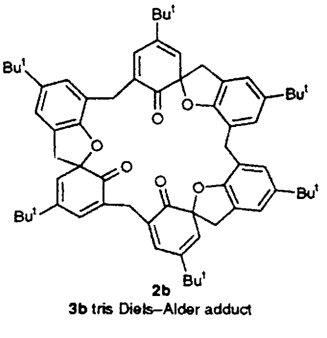
Reaction of a CH_2Cl_2 solution of **1b**[3] with excess of phenyltrimethylammonium tribromide–aq. NaOH resulted in the formation of a mixture of spirodienone derivatives of **1b** from which the two main tris(spirodienone) products **2a** (29%) and **2b** (15%) were separated by column chromatography. Both yellow compounds displayed peaks in the chemical ionization mass spectrum at *m/z* 967.7 (MH^+). The NMR spectra of both compounds are in agreement with tris(spirodienone) structures possessing C_1 symmetry. For example, three carbonyl signals (δ 196.93, 198.12, 198.76), and three signals characteristic of the spiro carbons (δ 82.49, 82.94, 82.99) were observed in the ^{13}C NMR spectrum ($CDCl_3$, room temp.) of **2a**. Since our attempts to purify the compounds by crystallization proved unsuccessful,† we treated each compound with excess of benzyne (generated from benzenediazonium-2-carboxylate hydrochloride)[9] yielding the corresponding tris Diels–Alder adducts **3a** (mp 292–294 °C, CIMS *m/z* 1195.5) and **3b** (mp 328–330 °C; CIMS *m/z* 1195.8). In both cases a major product was obtained, indicating that the reaction proceeds with high diastereofacial selectivity. By analogy with the bis(spirodienones) derived from **1a**, we assume that the benzyne adds in an all-*exo* fashion.[6] The structural assignment of the products was based on NMR spectroscopy using a combination of 2D NMR techniques (DQF COSY, TOCSY, NOESY and ROESY).[10] Based on the observed coupling pattern, the long range correlations, and the NOEs observed, **2a** and **3a** are assigned to structures with an alternant array of carbonyl and ether groups. Since **2a** has C_1 symmetry, the configurations of the spiro carbons must necessarily be different (*RRS*, or its enantiomeric arrangement *SSR*) in order to accommodate that symmetry. Based on the NOE observed between two aromatic protons, structures with a non-alternant array of



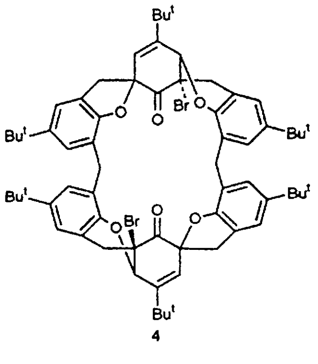
1a $n = 1$
1b $n = 3$



2a
3a tris Diels–Alder adduct



2b
3b tris Diels–Alder adduct



4

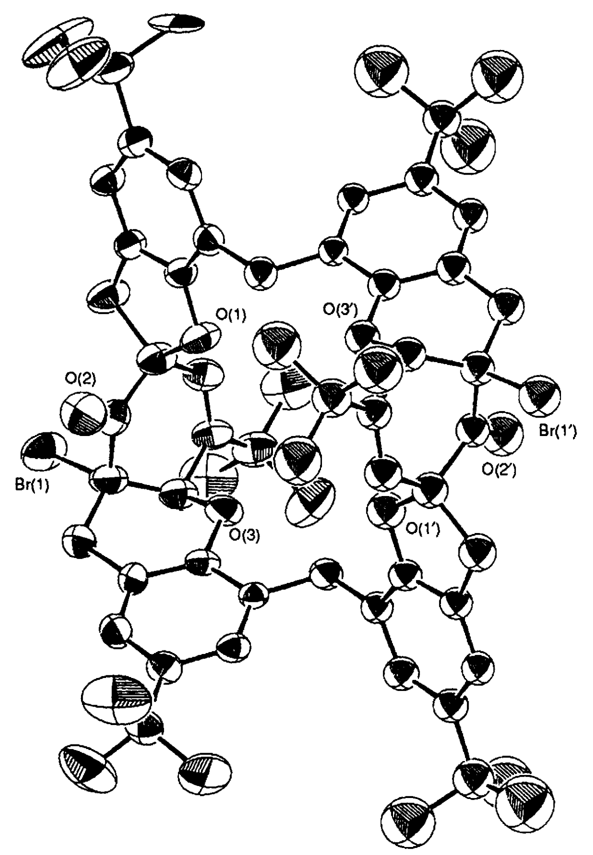


Fig. 1 Molecular structure of **4**. The molecule is located on a crystallographic inversion centre. The acetonitrile molecules have been omitted for clarity. The O···O non bonding distances (*d*/Å) are: O(1) O(2): 2.749(6), O(1) O(3): 3.593(5), O(2) O(3): 3.601(6), O(1) O(1'): 5.699(7), O(2) O(2'): 5.07(1), O(3) O(3'): 6.474(7).

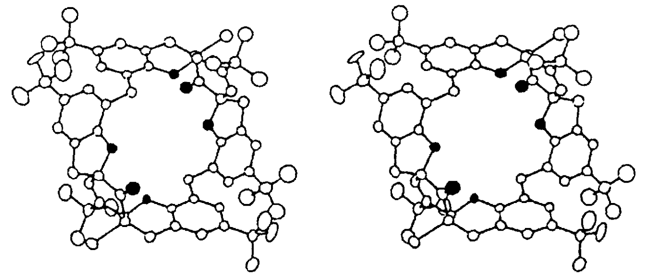


Fig. 2 Stereoview of the molecular structure of **4**. Oxygen atoms are denoted by black spheres.

carbonyl and ether groups are assigned to **2b** and **3b**. Inspection of Dreiding models indicates that the combination of configurations *RRR*/*SSS* is the one which better rationalizes the observed NOEs.

In addition to these compounds, a colourless product **4**, mp 296–299 °C (decomp.) was obtained in small yield (*ca.* 3%). Compound **4** did not react with benzyne indicating that no spirodienone moieties are present. The ^{13}C NMR spectrum of **4** (100 MHz, $CDCl_3$, room temp.) displays a single carbonyl signal at δ 200.5, two signals at δ 83.12 and 75.64, and 14 signals in the δ 118.12–156.04 region, in agreement with a structure of either C_2 or C_i symmetry in which four aromatic and two cyclohexenone rings are present. The molecule crystallizes from MeCN but the crystal readily turns opaque upon filtering from the solvent, probably owing to the release of the solvent molecules. A single crystal was grown from MeCN, and X-ray diffraction data were collected using a sealed capillary tube containing a crystal and the solvent.‡ Compound **4** has two β-bromoannulated spirodienone rings and has crystallographic C_i symmetry.§

The numbering scheme and a stereoscopic view of the molecule are displayed in Figs. 1 and 2. The formation of **4** probably involves, at the first stage, the oxidation of **1b** into a system containing two spirodienone moieties at non-vicinal positions, which under the reaction conditions undergoes addition of bromine and β-annulation. According to the crystal structure, one C–O bond is located β and one α to a given carbonyl group while the bromine atoms are α and *exo*. The C–O ether bonds are both attached to the same face of a given cyclohexenone ring. The **1b** → **2** and **1b** → **4** reactions result in the transformation of the six phenol groups of the calix[6]arene into rather complex architectures consisting of three stereocentres, three carbonyls and three ether groups (in the case of **2a** and **2b**) or six stereocentres, two carbonyl and four ether groups (in the case of **4**).

The reagent used for the preparation of the spirodienones is an ammonium tribromide, where the Br_3^- acts both as an oxidizing agent and as a source of bromine. Once a monospirodienone group is formed, the bromoannulation reaction may compete with the further oxidation of the macrocycle, resulting in lower yields of the tris(spirodienone) derivatives. We therefore examined the oxidation of the calixarenes with $K_3Fe(CN)_6$ in the hope that it might afford higher yields of the tris(spirodienone) systems. This reagent has been reported to oxidize some bisnaphthol systems to their corresponding spirodienones.[11] Oxidation of a toluene solution of **1a** with excess of $K_3Fe(CN)_6$–aq. KOH yielded a mixture of the three isomeric bis(spirodienone) derivatives previously described.[6] Oxidation of **1b** under similar conditions resulted in the formation of **2a** (20%) together with polymeric material. Interestingly, as observed previously for the derivatives of **1a**, the product with a homodirectional arrangement of spirodienone groups (**2a**) is the one formed preferentially.

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Footnotes

† The three isolated bis(spirodienone)derivatives of **1a** slowly mutually interconvert in solution, but their Diels–Alder adducts are configurationally stable (ref. 6).

‡ *Crystal data* for **4**: $C_{66}H_{78}O_6Br_2\cdot5CH_3CN$, space group $P\bar{1}$, a = 13.634(5), b = 14.117(5), c = 11.820(3) Å, α = 109.48(3), β = 114.09(3), γ = 65.02(2)°; V = 1847(2) Å^3, Z = 1, D_c = 1.20 g cm^{-3}, μ(Mo-Kα) = 11.35 cm^{-1}, no. of unique reflections = 6341, no. of reflections with $I \geqslant 3\sigma(I)$ = 3315, R = 0.052, R_w = 0.063. One *tert*-butyl group (the one connected to C-4) is disordered. One pair of the MeCN molecules related by the inversion centre [N(2)C(36)C(37)] is disordered in two orientations with relative occupancies of 0.7 and 0.3. The nitrogen atom of an additional MeCN molecule [N(3)] is located near the inversion centre and is disordered in two orientations. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

§ We have previously observed an α-annulation of the monospirodienone derivative of **1a**.[8b]

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