

## New Parent Homooxacalixarenes through Thermal Dehydration of a Bishydroxymethylated Triphenol

Bernardo Masci\*

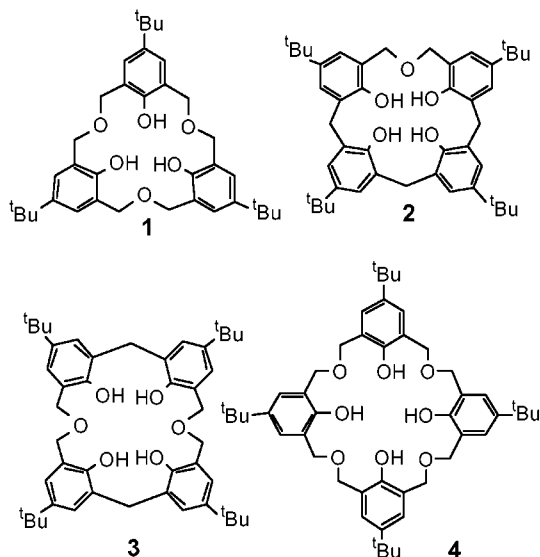
Dipartimento di Chimica and Centro CNR di Studio sui Meccanismi di Reazione, Università La Sapienza, p.le Aldo Moro 5, I-00185 Rome, Italy

bernardo.masci@uniroma1.it

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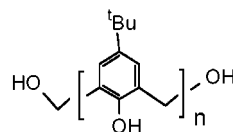
### Introduction

Homooxacalixarenes are calixarene<sup>1,2</sup> analogues in which CH<sub>2</sub>OCH<sub>2</sub> bridges partly or completely replace CH<sub>2</sub> bridges between the aromatic units. Special attention has been given to hexahomotrioxacalix[3]arenes as hosts,<sup>3</sup> but we have shown that several homooxacalix[4]arenes strongly bind organic cations.<sup>4–6</sup> We think that other possible ring systems deserve to be searched for. The difficulty to obtain parent compounds strongly handicaps the chemistry of homooxacalixarenes. At first we prepared simple or bridged ether derivatives of homooxacalix[4]arenes bypassing the parent macrocycle,<sup>5–7</sup> while now we report on the preparation of new parent compounds. Known ring systems of parent homooxacalixarenes are those of compounds **1–4**. Only in the case of compound



**2** a one-step synthesis analogous to those used for typical calixarenes is available,<sup>8</sup> thermal dehydration of bishydroxymethylated phenols as reported by Dhawan and

Gutsche<sup>9</sup> being an apparently more general and directed method. Namely, compounds **1** (and also a small amount of **4**),<sup>10</sup> **2**, and **3** could be obtained from **5**, **8**, and **6**, respectively, in refluxing xylene.<sup>9</sup> The reproducibility of



**5:** n = 1

**6:** n = 2

**7:** n = 3

**8:** n = 4

the reaction has been questioned in some instances,<sup>11</sup> and alternative acid catalyzed, high dilution procedures have been developed to obtain **1** and analogues,<sup>11,12</sup> while reports on **3** are scanty and thermal dehydration in general is not employed confidently.<sup>13</sup> On the other hand, we repeatedly checked that it works quite well in the preparation of **1** and **3** and we became interested in what actually happens in the dehydration of **7** which did not give any useful product according to the original report of Dhawan and Gutsche.<sup>9</sup>

### Results and Discussion

No experimental information is given in ref 9 on the dehydration of **7**; it is only indicated that no characterization was possible for the highly refractory material obtained. Since the reaction was apparently a very delicate one, we accurately purified the starting material, operated under milder conditions with respect to refluxing xylene, and monitored through <sup>1</sup>H NMR the mixture composition during the dehydration.

On heating at 120 °C a 0.4 mol L<sup>-1</sup> stirred solution of **7** in xylene, the reactant dissolved in a few minutes, but soon afterward an abundant precipitate formed. Small aliquots of the stirred mixture were taken at varying times and analyzed by <sup>1</sup>H NMR in CDCl<sub>3</sub> solution. The observed signal patterns and sequence for the phenol protons in the region 8–11 ppm were consistent with consumption of the reagent and formation of an intermediate open-chain dimer gradually giving the cyclodimer. The low solubility of the main product was exploited for its purification, compound **9** being actually obtained in 63% yield by simply filtrating the cooled reaction mixture. The compound is a tetrahomodioxacalix-

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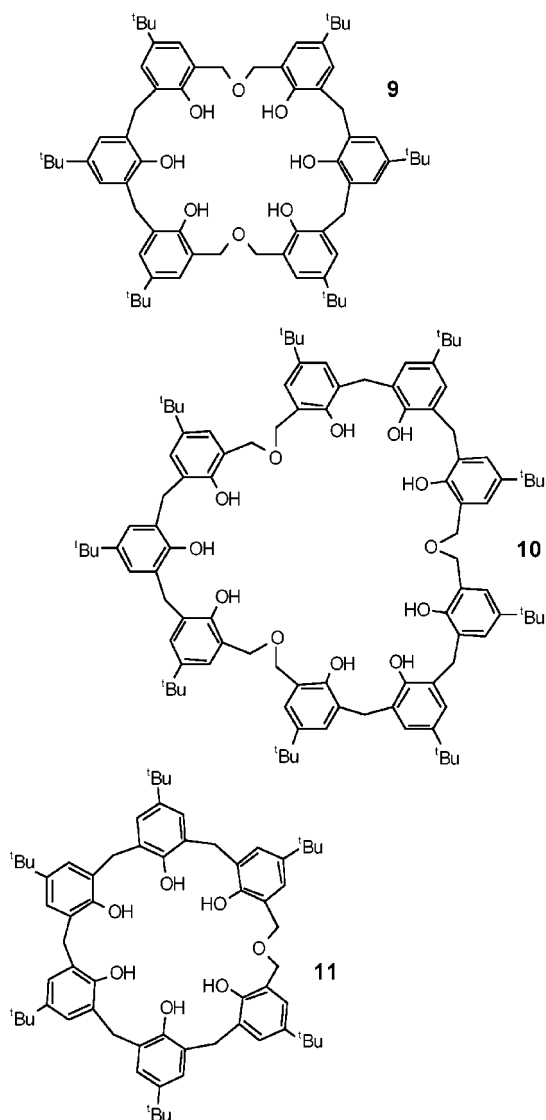
(13) Nevertheless the reaction appears to be currently used by some authors to obtain hexahomotrioxacalix[3]arenes, see ref 3a–c. It has also been recently employed to prepare *p*-phenyl analogues of **2** and **3**; see: No, K. *Bull. Korean Chem. Soc.* **1999**, *20*, 33.

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[6]arene according to current abridged names, while the relative position of the ether oxygen atoms can be precisely given indicating it as a [3.1.1.3.1.1]metacyclophane.<sup>6</sup>

From the mother liquors small samples were isolated of two new macrocycles, namely the hexahomotrioxacalix[9]arene **10**, which is a [3.1.1.3.1.1.3.1.1]metacyclophane, and the dihomooxacalix[6]arene **11**, which is a [3.1.1.1.1.1]-metacyclophane. A small amount of the well-known **2** was also formed.



In principle, the formation of cyclooligomers **9** and **10** is expected, and an extensive polymerization should actually occur at the used high concentration of **7** in the absence of special factors promoting cyclization. On the other hand, the presence of **11** indicates that formaldehyde can be somehow lost<sup>14</sup> and parallels the reported

formation of a small amount of **2** in the dehydration of **6**.<sup>9</sup> The occurrence of some more complex transformation is suggested by the presence of compound **2** also in the present case.

The intramolecular hydrogen bondings apparently act as a template in promoting the formation of the macrocycle **9** despite the high concentration of open-chain compounds.<sup>15</sup> In principle, a dihomooxacalix[3]arene could also be formed from **7** by an intramolecular reaction, since the ring of the [3.1.1]metacyclophane does not appear to be exceedingly strained and a related compound has been actually reported in the series of homocalixarenes.<sup>16</sup> To favor the formation of the cyclomonomer the dehydration reaction was carried out at a much lower concentration of **7**, namely 4 mmol L<sup>-1</sup>, but no apparent change was observed in the <sup>1</sup>H NMR spectrum of the crude reaction product. Both residual strains hampering ring formation and possible product decomposition can account for the absence of the smaller ring product. Strains can be not only those classically relevant in medium ring formation, but also those due to distortion of intramolecular hydrogen bondings.

Since the main course of the reaction was firmly established we could check that the formation of compound **9** easily takes place in different reaction conditions, namely in even more concentrated solution (almost 1 mol L<sup>-1</sup>) or in refluxing xylene, with no major change in the yields. We also carried out experiments using less pure samples of **7**, namely material not subjected to a final recrystallization from benzene-petrol ether and even using the overall crude reaction product of the bishydroxy methylation reaction. The idea was that the scarcely soluble **9** could be isolated through washings with xylene or chloroform. <sup>1</sup>H NMR analysis confirmed that 95–97% pure **9** could be quickly obtained.

The solubility of **9** in commonly tested solvents is low, namely lower than that of typical parent calixarenes. It could be nevertheless extracted by hot chloroform, recrystallized, and then easily characterized through <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra in CDCl<sub>3</sub>, mass spectra, and elemental analysis, at variance with the material obtained in early attempts.<sup>9</sup>

By comparison of the obtained yield of **9** with those previously reported for other homooxacalixarenes,<sup>9</sup> it is found that the ease of formation of **1**, **3**, **9**, and **2** increases regularly on increasing the number of phenol units in the series **5**–**8**. This can be due to different effectiveness of intramolecular hydrogen bondings which promote cyclization in concentrated solution; nevertheless, it should be noted that cyclization is preceded by two intermolecular steps in the formation of **1** from **5** (30% yield), by one intermolecular step in the formation of **3** from **6** (45% yield) and **9** from **7** (63% yield), and by none in the formation of **2** from **8** (96% yield). Interestingly a higher yield is obtained in the cyclodimerization of the triphenol **7** than in the cyclodimerization of the diphenol **6**.

When the reliable preparation of the precursor **7**, the good yield in concentrated solution, and the fast purifica-

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(15) For the physical basis of template effects in ring closure reactions, see: (a) Illuminati, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1983**, *105*, 555. (b) Ercolani, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1983**, *105*, 6146. (c) Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1984**, *106*, 168.

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tion are taken into account, **9** should be regarded as one of the most readily available parent homooxocalixarenes, namely samples in the order of 20 g can be easily prepared. It can also be regarded as a new platform in the general calixarene family, namely its low solubility does not hamper lower rim functionalization to be carried out.<sup>17</sup>

On the other hand, thermal dehydration of bis-hydroxymethylated phenols appears to be a really general method to obtain parent homooxocalixarenes, and the results can be quite good.

At variance with **9**, the homooxocalixarenes **10** and **11** were formed in small quantities and could be isolated through column chromatography thanks to the almost complete removal of **9** through filtration. Work is in progress to obtain the interesting compound **11** through a directed synthesis.

### Experimental Section

NMR spectra were recorded, at 298 K if not otherwise indicated, on a Bruker AC 300 spectrometer, using CDCl<sub>3</sub> (Merck) stored on activated 4 Å molecular sieves with TMS as an internal standard. Mass spectra were obtained with a Fisons Instruments VG-Platform Benchtop LC-MS (negative ion electrospray mass spectra, ES(-) MS; flow injection analysis in MeOH of samples in MeOH/MeONa or MeOH/MeOBu<sub>4</sub>N). Melting points (uncorrected) were obtained in sealed evacuated capillaries. Column chromatography was carried out on 230–400 mesh silica gel (Merck).

Compound **7** was prepared as reported,<sup>9</sup> but the whole material was recrystallized from benzene–petroleum ether (bp 40–70 °C), mp 143–145 °C (lit.<sup>9</sup> 143–145 dec). A mixture of **7** (12.2 g, 22.8 mmol) and xylene (48 mL) was heated at 120 °C and magnetically stirred under a nitrogen atmosphere in a two-necked 100 mL flask fitted with a condenser and with a septum. Small samples (about 10 μL) of the heterogeneous mixture were taken at varying times through a syringe, solvent was removed quickly through nitrogen flushing, and CDCl<sub>3</sub> was added for the <sup>1</sup>H NMR analysis. The relative intensity of the signals of the starting material at 8.94 and 9.06 ppm (area ratio 2:1) continuously decreased, three peaks in the area ratio 1:1:1 appeared at 8.84, 9.10, and 9.16 ppm and after a maximum intensity decreased and disappeared, while two more peaks appeared at 9.03 and 9.56 ppm (area ratio 2:1) and eventually reached a plateau intensity value. After 8 h heating the cooled reaction mixture was filtered and the solid washed twice with xylene (10 mL) and then twice with petroleum ether (bp 40–70 °C) and dried under vacuum to give **9**, 7.4 g 63% yield. The filtrate was evaporated under vacuum and the residue subjected to column chromatography (eluent toluene). Compounds **11**, **2**, **9**, and **10** were eluted in the order. The analysis of the eluted fractions largely relied on the <sup>1</sup>H NMR signals of the phenolic protons.

Removal of the contaminant **2** through recrystallization from chloroform–methanol gave pure **11** (50 mg, 0.4% yield). Compound **10** was, on the other hand, purified from unidentified byproducts through a second chromatography (eluent hexane/ethyl acetate 10:1) and a final recrystallization from acetone–methanol (60 mg, 0.5%, apparently less than half the formed product).

In the dehydration of a more concentrated solution of **7**, namely 8.0 g (15 mmol) in xylene (9 mL), **9** was obtained in 61% yield after 6 h heating at 120 °C. At this same concentration of **7**, in refluxing xylene, reaction time 5 h, the yield was 60%.

A 0.5 g sample of product was obtained after four extractions of a 2.0 g sample of compound **9** with 500 mL of hot chloroform. On the other hand, continuous extraction could be carried out through a Soxhlet apparatus.

The recrystallized **9** thus obtained did not significantly differ in the analytical tests from the material subjected to extraction.

**7,13,19,27,33,39-Hexa-tert-butyl-41,42,43,44,45,46-hexahydroxy-2,3,22,23-tetrahydro-3,23-dioxocalix[6]arene (9)**: mp dec above 330 °C; MS (ES)<sup>-</sup> *m/z* 515 [M - 2H]<sup>2-</sup>, 1032 [M - H]<sup>-</sup>, 1054 [M - 2H + Na]<sup>-</sup>; <sup>1</sup>H NMR 1.23 (s, 18H), 1.25 (s, 36H), 4.0 (br s, 8H), 4.64 (s, 8H), 6.98, (d, *J* = 2.4 Hz, 4H), 7.14 (s, 4H), 7.29 (d, *J* = 2.4 Hz, 4H), 9.03 (s, 4H), 9.56 (s, 2H); <sup>13</sup>C NMR at 303 K 31.4, 31.5, 32.1, 33.9, 34.0, 71.6, 123.2, 124.8, 125.6, 127.7, 128.2, 128.5, 143.2, 146.8, 150.4. Anal. Calcd for C<sub>68</sub>H<sub>88</sub>O<sub>8</sub>: C, 79.03; H, 8.58. Found: C, 79.05; H, 8.87.

**7,13,19,27,33,39,47,53-Nona-tert-butyl-61,62,63,64,65,66,67,68,69-nonahydroxy-2,3,22,23,42,43-hexahydro-3,23,43-trioxocalix[9]arene (10)**: mp 167–169 °C; MS (ES)<sup>-</sup> *m/z* 773 [M - 2H]<sup>2-</sup>, 895 [M - 3H + Bu<sub>4</sub>N]<sup>2-</sup>, 1015 [M - 4H + 2Bu<sub>4</sub>N]<sup>2-</sup>; <sup>1</sup>H NMR: 1.23 (s, 81H), 3.94 (s, 12H), 4.58 (s, 12H), 6.92, (d, *J* = 2.4 Hz, 6H), 7.11 (s, 6H), 7.23 (d, *J* = 2.4 Hz, 6H), 8.69 (s, 6H), 9.01 (s, 3H); <sup>13</sup>C NMR 31.5, 31.5, 31.7, 33.9, 33.9, 71.0, 122.6, 124.7, 125.6, 127.5, 127.6, 127.6, 142.9, 143.8, 147.6, 150.4. Anal. Calcd for C<sub>102</sub>H<sub>132</sub>O<sub>12</sub>: C, 79.03; H, 8.58. Found: C, 78.68; H, 8.86.

**7,13,19,25,31,37-Hexa-tert-butyl-39,40,41,42,43,44-hexahydroxy-2,3-dihydro-3-oxocalix[6]arene (11)**: mp dec above 305 °C; MS (ES)<sup>-</sup> *m/z* 1002 [M - H]<sup>-</sup>; <sup>1</sup>H NMR 1.25 (s, 36H), 1.26 (s, 18H), 3.9 (br s, 10H), 4.6 (br s, 4H), 6.98 (d, *J* = 2.4 Hz, 2H), 7.13 (s, 4H), 7.15 (d, *J* = 2.4 Hz, 2H), 7.19 (d, *J* = 2.4 Hz, 2H), 7.29 (d, *J* = 2.4 Hz, 2H), 9.4 (br s, 2H), 10.3 (br s, 2H), 10.6 (br s, 2H); <sup>13</sup>C NMR 31.5, 32.3, 32.8, 32.9, 33.9, 34.0, 71.3, 122.9, 125.9, 125.9, 126.0, 127.5, 127.5, 127.8, 143.2, 143.3, 143.3, 147.1, 147.2, 150.1; <sup>13</sup>C NMR at 318 K 31.5, 32.4, 33.0, 34.0, 34.0, 71.4, 123.0, 124.8, 125.9, 126.0, 126.1, 127.5, 127.6, 127.7, 127.8, 127.9, 143.3, 144.4, 144.4, 147.1, 147.3, 150.2. Anal. Calcd for C<sub>67</sub>H<sub>86</sub>O<sub>7</sub>: C, 80.20; H, 8.64. Found: C, 79.95; H, 8.96.

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(17) Masci, B. et al. Unpublished results.