Shaping Calix[8]arene Framework by Intramolecular Bridging. Synthesis of Conformationally Blocked Calix[8]arene Derivatives

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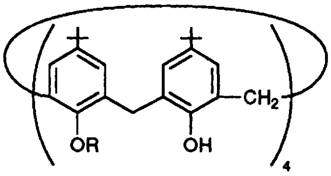
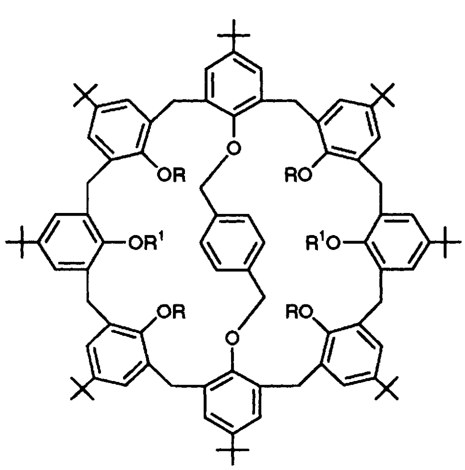
The first examples of 1,5-intrabridged calix[8]arene derivatives are described, which are conformationally frozen in a double-conical shape suitable for ditopical recognition.

The term calixarene was coined by Gutsche to describe cyclic oligomers of phenols (above all *p-tert*-butylphenol) and formaldehyde, with reference to the hollow structure of the smaller members of the family.[1] These, calix[4]arenes, are apt to include small molecules into their cavities and therefore are particularly attractive in supramolecular chemistry as building blocks for the assembly of receptor molecules.[1] Calix[8]arenes, however, are relatively flat molecules that in the solid state,[2a] and possibly also in solution, adopt a conformation named 'pleated loop'.[2b] In order to enhance their host properties it is desirable to hinder the conformational mobility giving a preorganized shape suitable for molecular recognition. The observation that, due to the large dimensions of the annulus, this cannot be effectively achieved by simple derivatization of the phenolic hydroxy with common bulky groups[3,4] prompted us to explore the alternative strategy consisting in the introduction of appropriate scaffolding elements at the lower rim.[5] This communication deals with the results obtained following these lines and leading to the synthesis of the first examples of intramolecularly bridged, conformationally blocked calix[8]arenes.

Initial attempts at the preparation of intrabridged compounds by reacting the parent *p-tert*-butylcalix[8]arene **1** with various bis-bromomethylated reagents were unsuccessful since, even under high-dilution conditions, only polymeric materials were formed. Hence, we turned our attention to the 1,3,5,7-derivatives of **1** as starting materials.[4] The use of these compounds, readily accessible in fair yields (40–50%) by a recently published procedure,[4] restricts the possible products to the 1,3- and 1,5-intrabridged calixarenes, and to polybridged double calixarenes. When tetraester **2**[4b] in dry THF was refluxed for 24 h with 2.2 equiv. of 1,4-bis(bromomethyl)benzene and Cs_2CO_3 as the base, the 1,5-intrabridged derivate **4** was isolated in 35% yield after chromatography of the crude reaction mixture.† With the same conditions the 1,3,5,7-tetrabenzyl compound **3**[4] gave the corresponding intrabridged calix[8]arene **5** in 30% yield. In the intrabridging of **2**, replacement of caesium carbonate with caesium fluoride and concomitant reduction of the molar amount of alkylating agent (1.2 mol per mol of **2**) resulted in the formation of the 1,5-intrabridged derivative **6** having two free hydroxy groups.



1 R = H
2 R = $CH_2CO_2Bu^t$
3 R = p-$CH_2C_6H_4Bu^t$



	R	R¹
4	$CH_2CO_2Bu^t$	p-$CH_2C_6H_4CH_2Br$
5	p-$CH_2C_6H_4Bu^t$	p-$CH_2C_6H_4CH_2Br$
6	$CH_2CO_2Bu^t$	H

Molecular mass determination (FAB MS) showed that the isolated compound was a singly bridged calixarene. In the ^1H NMR spectrum (assignments of the resonances were aided by 2D COSY and HETCOR techniques) four *tert*-butyl signals were observed at δ 1.35, 1.33, 1.09 and 0.64, in a 1:2:1:2 ratio, indicative of a structure possessing two orthogonal two-fold elements of symmetry. This inference was substantiated by the presence in the methylene region of a pair of AB systems (δ 4.85 and 3.41, J = 14.5 Hz; δ 4.41 and 3.72, J = 16.9 Hz) assignable to the methylenes of two $ArCH_2Ar$ groups in the calixarene ring, and three singlets of the same intensity attributable to the oxymethylenes of bridging (δ 3.42) and pendant (δ 4.73) groups, and to the bromomethylenes of the pendant groups (δ 4.53). The oxymethylene groups of the ester moieties give rise to an additional AB system (δ 4.44 and 4.33, J = 15.4 Hz). The aromatic protons of the phenylene bridge resonate as a singlet at high field (δ 5.83) due to the shielding by the aromatic rings of the annulus. Two aromatic singlets at δ 7.22 and 6.75, and a typical *meta*-coupled AB system (δ 7.12 and 6.82, J = 1.9 Hz) were associated with the aromatic protons of the calixarene ring, and an *ortho*-coupled AB system (δ 7.55 and 7.41, J = 8.0 Hz) to the aromatic protons of the pendant groups. The ^{13}C NMR spectrum was consistent with structure **4** showing *inter alia* two methylene signals for $ArCH_2Ar$ groups at δ 29.6 and 30.5, three OCH_2 resonances at δ 70.7, 75.5, and 74.4 relative to the ester, bridge, and pendant groups, respectively. The bromomethyl carbon of the pendant group resonates at a typical value (δ 33.6).[6] Compounds **5** and **6** also showed highly symmetrical

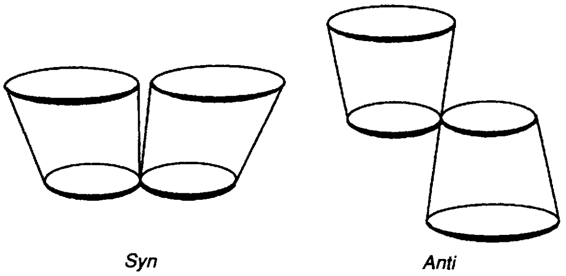


Fig. 1 Schematic representation of the *syn* and *anti* conformations for compounds **4–6**

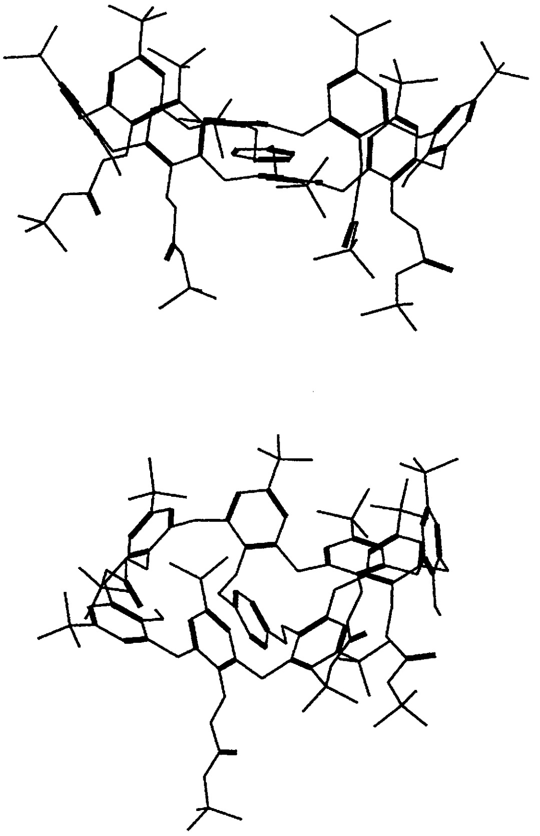


Fig. 2 Computer-plot of idealized (top) and MM2-minimized (bottom) structure of the *syn* conformer of **6**

^{1}H- and ^{13}C-NMR spectra, fully compatible with the given structures.

The presence of two AB systems for the bridging methylenes of the macrocycle in the ^{1}H NMR spectrum of **4** (the same holds true for **5** and **6**) was the first evidence for a drastically reduced conformational mobility upon bridging. Dynamic NMR studies on **4** in Me_2SO showed no hint of coalescence for these signals raising the temperature up to 390 K, indicating absence of conformational interconversion. Instead, an apparent coalescence in the vicinity of 340 K was observed for the AB system of OCH_2CO protons due to temperature-dependent decreasing of their chemical shift separation. Cooling a sample of **4** in $CDCl_3$ resulted in a broadening of all the signals as the temperature was lowered but no signal separation was observed down to 220 K. These results can be interpreted assuming that a symmetrical averaged conformation, present above 250 K, upon cooling is frozen in an asymmetrical structure.

Bridging originates two identical subunits, each defined by three aromatic nuclei and a common portion, the bridge and the bridgehead rings. Each of these subunits can be viewed as a calix[4]arene in which an aryl has been replaced by a bridge-bridgeheads moiety. The calix[4]arene portions have a pronounced 'cone' character, as judged from the large separation of the doublets of the pertinent $ArCH_2Ar$ protons ($\Delta\delta = 1.44$ ppm), whereas the bridghead aryls adopt an 'out' orientation ($\Delta\delta = 0.69$ ppm).[7] The equivalence of the two subunits observed in the ^{1}H NMR spectrum imposes that they are *syn* or *anti* to each other (Fig. 1).

MM2 molecular mechanics calculations[8] performed on **4** and **6** confirmed the above conclusion since, starting for each compounds from idealized conformations either *syn* or *anti*, unsymmetrical geometries were obtained upon fully minimization (Fig. 2). Deviations from idealized cones are due to the self-filling of the cavities and to the geometry adopted by the moiety comprising the bridge and the bridgehead aryls. In fact, this portion of the molecule can be either linearly extended or folded in an U- or Z-shape (similarly to the self-anchored rotaxanes described by Gutsche[5a]). Therefore, *syn* and *anti* conformations have to be considered as conformational ensembles. Evaluation of their relative enthalpy by Molecular Dynamics simulations, using a $CHCl_3$ continuum model solvent and MM2 force-field, indicate that the *syn* conformation is more stable than the *anti* by *ca.* 2–3 kcal mol^{-1} (1 cal = 4.184 J). On this basis intrabridged compounds **4** and **6** (and **5**, by analogy) should adopt the *syn*-cones conformation (Fig. 2).

Owing to the presence of ester moieties, compounds **4** and **6** act as neutral ligands for alkali metal cations as suggested by the presence of an intense $[M + Na]^+$ ion peak in their FABMS spectra. In addition, each subunit in these derivatives can be considered as an independent coordination site, therefore, compounds **4** and **6** should possibly act as ditopic receptors. This consideration parallels the observed proclivity of unbridged calix[8]arene to form 1:2 complexes.[9]

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Footnote

† Satisfactory microanalytical and spectral data were obtained for all new compounds.

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