

## **Pillar[5]arenes: fascinating cyclophanes with a bright future**

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## Computer verification of DMpillar[5]arene and pillar[5]arene conformational preferences

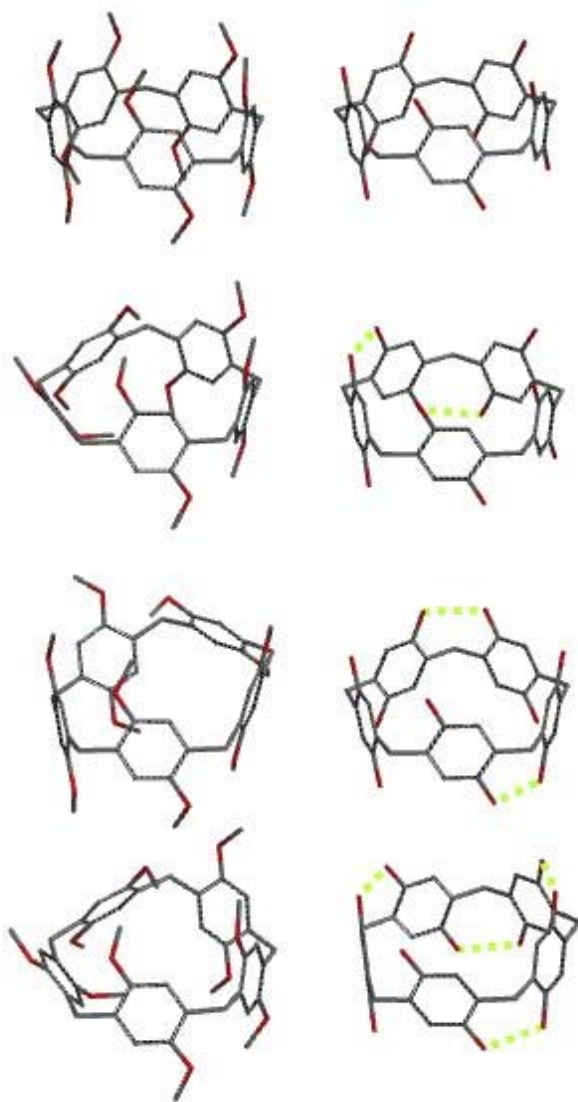
The published data on 1,4-dimethoxypillar[5]arene (DMpillar[5]arene) and pillar[5]arene, including crystal structures<sup>1,2</sup>, give a very convincing, and intuitive, argument for the roles of steric hindrance and hydrogen bonding in the conformers adopted by these two macrocycles. To verify that the optimum conformers were indeed those determined crystallographically, the structures were subjected to a simple molecular mechanics protocol and the resulting energies compared.

### Molecular mechanics protocol

Atomic coordinates taken from the X-ray crystal structures of DMpillar[5]arene and pillar[5]arene were subjected to molecular mechanics geometry optimisation (MMFF94 force field in SPARTAN '10<sup>3</sup>). Aromatic moieties in the resulting structures were then systematically rotated by 180° to generate all four conformers for each macrocycle. These were subjected to molecular mechanics geometry optimisation and the steric energies determined. Table 1 gives the relative energies for the two macrocycles together with the number of hydrogen bonds present in the resulting conformer. Only the *Rp* enantiomer was analysed as the equivalent conformers for the *Sp* enantiomer will have identical energies. The method used can be reproduced with any molecular mechanics software packages to give the same rank order although the magnitudes of the relative energies may vary depending upon the force field and geometry optimisation algorithm employed.

	Relative steric energies (kJmol <sup>-1</sup> )			
	<i>cone</i>	<i>partial cone</i>	<i>1,2-alternate</i>	<i>1,3-alternate</i>
DMpillar[5]arene	0.0	17.3	19.9	36.6
H-bonds formed	0	0	0	0
Pillar[5]arene	45.6	28.2	34.3	0.0
H-bonds formed	0	2	2	4

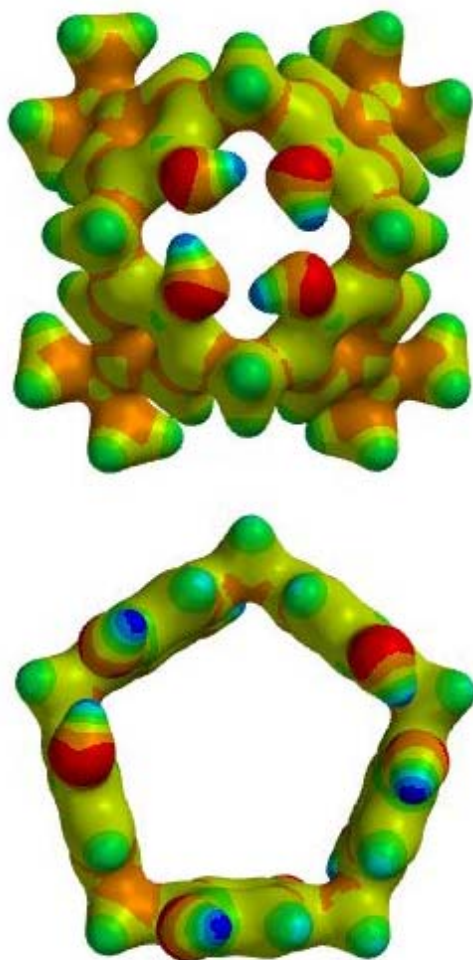
**Table S1.** Relative steric energies for conformers of DMpillar[5]arene and pillar[5]arene



**Figure S1.** Conformers of DMpillar[5]arene, left, and pillar[5]arene, right with hydrogen bonds indicated: (from top) *cone*, *partial cone*, *1,2-alternate*, *1,3-alternate*

### Hydrogen bonding in pillar[5]arene

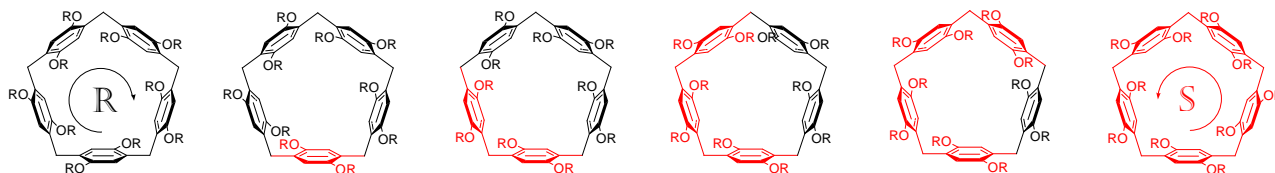
While the strength and extent of the hydrogen bonding network for pillar[5]arene in the *1,3-alternate* conformer is also evident from the crystal structure, it can also be illustrated with an electron density map. This was calculated from a MMFF94 geometry optimised structure followed by a semiempirical (PM6) single point energy calculation in SPARTAN '10. The same protocol was adopted to refine the structure of 4-*t*-butylcalix[4]arene<sup>4</sup> to give a comparison with a macrocycle which is well known to form strong hydrogen bonds.



**Figure S2.** Hydrogen bonding in 4-t-butylcalix[4]arene (top) and pillar[5]arene (bottom)

### Through-the-annulus rotation

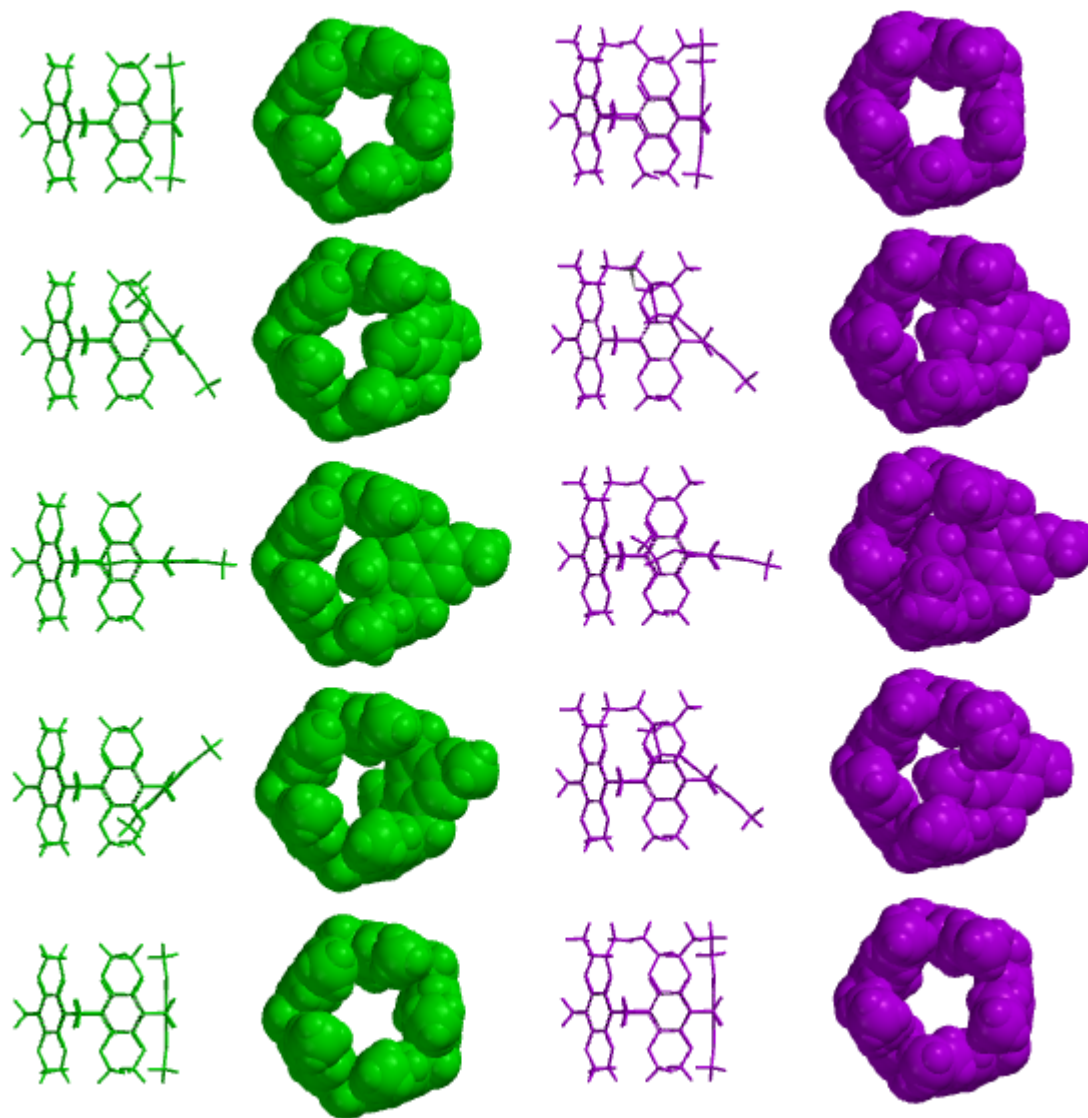
Although the exact sequence of events necessary to interconvert between the *Rp* and *Sp* enantiomers is unknown, a concerted stepwise route may be envisaged as below.



**Figure S3.** Stepwise *Rp* → *Sp* interconversion

<sup>1</sup>H NMR evidence indicates that only pillar[5]arene and DMpillar[5]arene are able to achieve through-the-annulus rotation. The introduction of one more carbon into the asymmetric 1-ethoxy-4-methoxypillar[5]arene (EMpillar[5]arene) results in splitting of the methylene signals as the macrocycle is frozen into one conformer because the ethyl group cannot fit through the central

cavity. This can be visualised as a sequence of snapshots and space filling models which indicate that only the former can rotate fully. As a consequence the aromatic rings in EMpillar[5]arene swing back and forth without passing through the annulus.



**Figure S4.** Rotation of DMPillar[5]arene (green) and EMPillar[5]arene (purple)

#### **A note on Cannizzaro's possible synthesis of $[1_n]$ paracyclophanes**

Gribble and Nutaitis commented that “it is possible that Cannizzaro prepared  $[1_n]$ PCPs as early as 1854 during his studies on the acid-promoted polymerization of benzyl alcohol and derivatives.”<sup>5</sup> In Cannizzaro's paper of 1854 he states:

“Boron trifluoride acts on the benzoic acid-alcohol exothermically, forming boric acid and a resin-like substance. The latter is washed with alkaline water, then with pure water, with alcohol and with ether and dried at 170°. It is dissolved in carbon disulfide or chloroform and, following re-

evaporation of the solvent, gives an amorphous, translucent, amber-yellow substance which is insoluble in water and alcohol, sparingly soluble in ether and turpentine, and soluble in chloroform and carbon disulfide. It melts with gentle heating and decomposes at even higher temperatures to give a volatile product and a coal-like residue. Analysis gave 92.860% carbon and 6.817% hydrogen.”<sup>6</sup>

Apart from general similarities to pillar[5]arenes (employing boron trifluoride as a Lewis acid during synthesis and the product’s poor solubility properties) the key data are the elemental analysis results. The theoretical values for [1<sub>n</sub>]paracyclophanes (C<sub>7</sub>H<sub>6</sub>)<sub>n</sub> are 93.29% C and 6.71% H, close to Cannizzaro’s experimental results of 92.86% and 6.82%, respectively, and well within the margin of error for the mid-nineteenth century. If these results do indeed reflect the synthesis of a [1<sub>n</sub>]paracyclophane it would represent the earliest example of a macrocycle incorporating aromatic repeat units.

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