Conformational Properties of Octahydroxy[1.4]metacyclophanes with Unsubstituted Methylene Bridges

Hisatoshi Konishi* and Osamu Morikawa

Department of Materials Science, Faculty of Engineering, Tottori University, Koyama-minami, Tottori 680, Japan

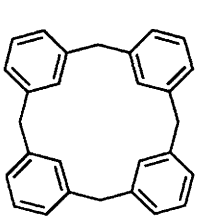
Octahydroxy[1.4]metacyclophanes with long alkyl substituents on the aromatic rings have been prepared; the preferred conformation of the tetrahexyl derivative **8** in $CDCl_3$ is a cone and its free energy of activation, $\Delta G^{\ddagger}_{298}$, for the ring inversion has been determined to be 12.0 kcal mol^{-1} (1 cal = 4.184 J) using dynamic ^1H NMR spectroscopy and complete line shape analysis.

[1.4]Metacyclophane **1** is a flexible molecule.[1,2] Its conformational characteristics are greatly affected by substituents on the aromatic rings and the bridge positions. The calix[4]arene **2** preferably exists in the cone conformation, in which the four phenolic OH groups at the inner positions of the macrocycle decrease the conformational mobility of the system due to the cyclic hydrogen bond.[3]

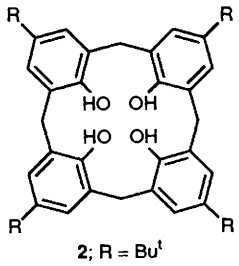
The octahydroxy[1.4]metacyclophanes **3** and **4** which possess eight phenolic OH groups at the outer positions of the macrocycles also favour the cone conformation in the solid state[4] and in solution.[5] The alkyl substituents at the bridge positions suppress the conformational freedom and inhibit ring inversion. To investigate the effect of hydrogen bonding by the eight OH groups on the conformational characteristics, we synthesized the metacyclophanes with unsubstituted methylene bridges.[6] However, the tetramethyl derivative **5** is insoluble in common nonpolar solvents and not suited for temperature-dependent NMR spectroscopy. We envisaged that higher alkyl groups at the 2-position of the resorcinol nucleus might improve the solubility of the macrocycles. Here, we report the synthesis of the metacyclophanes with long alkyl substituents on the aromatic rings and their conformational properties.

A solution of 2-hexylresorcinol with paraformaldehyde (1 equiv.) in ethanol–conc. HCl (4:1 v/v) was heated under reflux for 6 h. The reaction mixture was diluted with water and extracted with diethyl ether. After removal of the solvent, the residue was recrystallized from chloroform to afford the cyclic tetramer **8** in 55% yield; m.p. 213 °C (decomp.). Compounds **6** and **7** were analogously synthesized in 66 and 45% yields, respectively. The products were characterized by microanalyses, FAB mass, IR, ^1H and ^{13}C NMR spectroscopy.

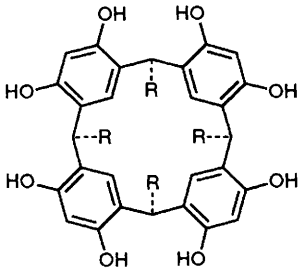
The 270 MHz ^1H NMR spectra of the metacyclophanes in [$^2H_6$]DMSO (dimethyl sulfoxide) show a singlet for the bridge



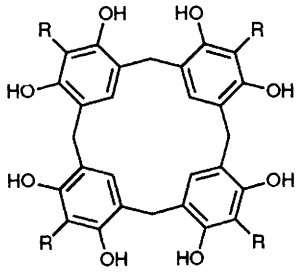
1



2; R = Bu^t



3; R = Bu^n
4; R = n-$C_{11}H_{23}$



5; R = Me
6; R = Et
7; R = Bu^n
8; R = n-C_6H_{13}

methylene protons at room temperature. This indicates that the metacyclophanes exist in a 1,3-alternate conformation or fast equilibrium among the conformational flexible species. The solubility of **8** in $CDCl_3$ is adequate for temperature-dependent ^1H NMR spectroscopy. At −60 °C in $CDCl_3$, the aromatic protons appear as a singlet (δ 7.19) and the methylene protons appear as an AB quartet (δ 3.51 and 4.08, J 13.9 Hz). The chemical shifts and the coupling constant of the methylene protons are similar to those of **2** in cone conformation[7] and strongly suggest that **8** exists in a cone conformation with effective C_{4V} symmetry on the NMR time scale. At −22 °C, the methylene signal coalesces to a broad singlet at the centre of the AB quartet pattern. It is inferred from the temperature-dependent ^1H NMR spectra and complete line shape analysis that **8** prefers the cone conformation and that the spectral change is related mainly to the cone $\rightleftarrows$ cone ring inversion. The following activation parameters were determined: $\Delta G^{\ddagger}_{298}$ = 12.0, $\Delta H^{\ddagger}$ = 9.8 kcal mol^{-1} and $\Delta S^{\ddagger}$ = −7.5 cal mol^{-1} (1 cal = 4.184 J). No activation parameters for **6** and **7** are available owing to their poor solubility. The free energy of activation, $\Delta G^{\ddagger}$, for **8** is 4.4 kcal mol^{-1} lower than the value for calix[4]arene, **2**, in $CDCl_3$ at 298 K.[7]

In the ^1H NMR spectrum of **8** in $CDCl_3$, the hydroxy protons resonate at δ 6.30. This small downfield shift (*ca.* 1.6 ppm) for the hydroxy protons as compared with those for 2-hexylresorcinol can be taken as evidence for weak hydrogen bonding. The weakness of the intramolecular hydrogen bonding relative to that in **2** is reflected in their OH stretching frequencies. In $CHCl_3$, **8** shows hydrogen bonding OH stretching at 3420 cm^{-1}, which is much higher than that found for **2** in CCl_4 (3138 cm^{-1}).[8]

Although we could not perform a complete molecular mechanics search for the most stable conformer in that too many possible conformations would have to be analysed, the cone arrangement still seems to be the preferred conformer amongst the 'reasonable' structures we have calculated.

In summary, the most stable conformation of **8** is a cone in $CDCl_3$. The intramolecular hydrogen bonding of the hydroxy groups on the outer positions of the metacyclophanes is responsible for the stability of the conformation. However, the strength of the hydrogen bonding is much weaker than that of the hydroxy groups on the inner positions of the macrocycles.

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