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Cyclocondensation of 2-Methylresorcinol with Formaldehyde. A Synthesis of Conformationally Mobile Metacyclophanes

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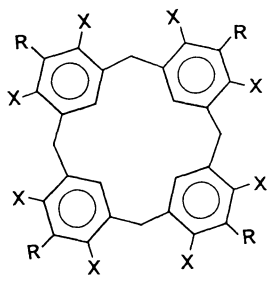
The acid-catalyzed condensation of 2-methylresorcinol with formaldehyde gave a complex mixture, from which a cyclic tetramer(1) was isolated as a hexamethylphosphoric triamide adduct.

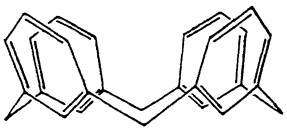
There is much current interest in the synthesis of [1.1.1.1]-metacyclophanes possessing eight peripheral hydroxyl groups.[1-6] The fourfold condensations of various aldehydes with resorcinols give the metacyclophanes, which have four substituents in the bridge methylene positions. The intramolecular hydrogen bonds between the hydroxyl groups of the resorcinol units play an important role in determining the conformation of the macrocyclic ring in the solid state.[6] However, since the substituents on the bridges restrict the conformational mobility of the ring, the effect of the hydrogen bonds on the conformational change in solution is not elucidated.

Here we describe the synthesis of conformationally mobile metacyclophanes with unsubstituted methylene bridges. Although formaldehyde condenses with a variety of aromatic compounds to form macrocyclic compounds, the reaction with resorcinol does not give cyclic oligomers but produces a cross-linked polymer.[7] Therefore, we have chosen 2-methylresorcinol as the aromatic component of the metacyclophane.

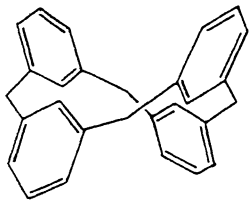
The reaction of 2-methylresorcinol with an equimolar amount of formaldehyde in 10% hydrochloric acid (ethanol-water 1/1) under refluxing for 24 h gave a light tan precipitate, which was shown to be a severely complex mixture by ^{1}H NMR spectroscopy. A cyclic tetramer was eventually isolated by recrystallization of the crude product from hexamethylphosphoric triamide(HMPA)-water as a HMPA adduct.[8] Repeated trituration of the adduct with hot methanol-water gave the metacyclophane (1)[9] as an amorphous powder in 14% yield. Treatment of the the HMPA adduct with acetic anhydride in the presence of pyridine gave the octaacetate (2) in 73% yield.[10] The ^{1}H and ^{13}C NMR spectra of the products revealed the highly symmetrical structure. The tetrameric structure of 1 was confirmed by fast atom bombardment mass spectrometry.[11]



(1) R=Me, X=OH
(2) R=Me, X=OAc



Cone Conformation



1,3-Alternate Conformation

In the 270 MHz ^{1}H NMR spectra, in the presence of 4 molar equivalents of NaOD, 1 in D_2O at 5 °C showed an AB quartet (δ 3.237 and 3.957, J=13.1 Hz), and the signals coalesced into one broad peak at 38 °C(Tc). These spectral features are explained, as reported for calix[4]arene,[12,13] by the interconversion between two equivalent cone conformations with C_{4V} symmmetry. On the NMR time scale, the interconversion is frozen at low temperature. The free energy of activation for the conformational inversion at Tc is calculated to be 14.5 kcal mol^{-1}. The value of the free energy of activation depended upon the amount of added NaOD. In the alkaline solution, 1 exists as tetraphenoxides.[14] In this case, the intramolecular hydrogen bonds effectively maintain the metacyclophane in the cone conformation.

On the other hand, in pyridine-d_5, the methylene groups appeared as a singlet over a temperature range from -50 °C to 70 °C. In addition, the chemical shifts of all protons other than the hydroxyl groups showed very little change. These data strongly indicate that the metacyclophane possesses a 1,3-alternate conformation with effective D_{2d} symmetry. Since pyridine is a basic, hydrogen-bonding solvent, it is concluded that the conformational preference is a consequence of the disruption of the intramolecular hydrogen bonding.[12]

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8) Analytical sample was obtained by recrystallization from acetone, and dried in vacuo at 80 °C for 8 h. Anal. Found: C, 58.78; H, 7.94; N, 8.55%. Calcd for $(C_{32}H_{32}O_8)(C_6H_{18}N_3OP)_2(C_3H_6O)$: C, 58.73; H, 7.76, N, 8.75%.
9) ^{1}H NMR(DMSO-d_6) δ 1.986(s, 12H, CH_3), 3.582(s, 8H, CH_2), 6.768(s, 4H, aromatic), 8.597(s, 8H, OH). ^{13}C NMR(DMSO-d_6) δ 9.9(q, CH_3), 30.0(t, CH_2), 112.2(s), 120.7(s), 127.7(d), 150.0(s).
10) mp>320 °C(acetonitrile). Anal. Found: C, 65.51; H, 5.48%. Calcd for $C_{48}H_{48}O_{16}$: C, 65.44; H, 5.49%. ^{1}H NMR (DMSO-d_6, 80 °C) δ 1.879 (s, 12H, CH_3), 2.254(s, 24H, CH_3), 3.512(s, 8H, CH_2), 6.493(s, 4H, aromatic).
11) FAB-MS were recorded by using xenon ionization techniques with diethanolamine as matrix on a JEOL JMS-DX 303 spectrometer.
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