Unusual thermodynamic stabilities of the four conformers of tetraacetoxy-*p*-*tert*-butylcalix[4]arene

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The relative stability of four conformers of tetraacetoxy-*p*-*tert*-butylcalix[4]arene 2 is determined by ^{1}H NMR spectroscopy; the four conformers are not flexible in Me_2SO at room temperature, but equilibrate at a higher temperature into a mixture with relative stability in the order 1,3-alternate (most stable) > 1,2-alternate > partial cone > cone (most unstable).

Conformational investigations of calix[4]arene **1a** and its derivatives have been carried out because of the importance of these compounds either as host molecules or as building blocks for the construction of more sophisticated host molecules.[1] In the case of *p*-*tert*-butylcalix[4]arene **1b**, typically only the cone conformation is found in solution at room temperature since the stability of this conformation is greatly enhanced by hydrogen bonding.[1] In contrast, for the tetramethyl ethers of **1b** and **1a**, this is no longer a factor and consequently, all four conformers are found in solution.[2–7] Basically, tetra-*o*-substituted calix[4]arenes can exist as one of four conformers: the cone, the partial cone, the 1,2- and the 1,3-alternates. For example, Shinkai *et al.*[6] and Groenen *et al.*[7] reported the relative stabilities of the four conformers and thermodynamic parameters for their interconversion of the tetramethyl ethers of **1b** and **1a** based on ^{1}H NMR spectroscopy and molecular mechanical studies. The relative stabilities among the four conformers of the tetramethyl ethers of **1a** and **1b** are in the order of the partial cone (most stable) > cone > 1,2-alternate > 1,3-alternate (least stable). The introduction of more bulky groups onto the hydroxy groups, however, suppresses the oxygen-through-the-annulus rotation and results in a larger energy gap between the conformational isomers.[3,5,7] The tetraethyl ether of **1b** is not flexible at room temperature, but it also equilibrates in solution above 100 °C to a mixture of all the four possible conformers.[7] Furthermore, it was found that (i) the conformational inversion can be inhibited by alkyl groups bigger than ethyl,[3,5,7] and (ii) thermodynamically, the partial cone conformation[8–12] is the most stable of the tetramethyl[6,7] and tetraethyl ethers of **1b**.[7] As already described, there are many reports concerning the effect of *o*-substituents on the conformational stabilities of the calix[4]arene derivatives. However, no relative stabilities among the four conformers of tetraacetoxy-*p*-*tert*-butylcalix[4]arene **2** and its homologues have been reported. Here we report the relative stabilities of the four conformers of **2**.

The four conformers, the cone, the partial cone, 1,2- and 1,3-alternates, of **2** have been previously prepared by several research groups by the reaction of **1b** with various acetylation reagents. In order to obtain the four conformers of **2**, the following reactions were carried out according to the method and/or modified method reported in the literature. Treatment of **1b** with acetic anhydride in the presence of a small amount of conc. sulfuric acid gave **2** [1,2-alternate (6%), 1,3-alternate (19%) and partial cone (46%)].† The cone conformer of **2** was also obtained in 35% yield together with the triacetyl ester of **1b** (partial cone, 13% yield) and monoacetyl ester of **1b** (cone, 4% yield) by the treatment of **1b** with acetyl chloride in the presence of sodium hydride in dry THF.‡ The four conformers do not undergo any conformational change in solution at room temperature. Therefore, we first heated the cone in $[^2H_6]Me_2SO$ at 150 °C and analysed the mixture after several intervals of time using ^{1}H NMR spectroscopy. The results are summarized in Fig. 1. After 30 min, an equilibrium between the cone and partial cone was reached. During that period, the amounts of cone and partial cone were 0 and 100%, respectively, and the 1,2- and 1,3-alternates could not detected in any amounts. Upon continued heating, the amount of the partial cone gradually decreased and the amounts of the 1,2- and 1,3-alternates increased.

In the equilibrium mixture after 384 h the amounts of the partial cone, 1,2- and 1,3-alternates reached 18.0, 42.6 and 33.3%, respectively. The probability for the inversion of the partial cone to the 1,2-alternate and the partial cone to the 1,3-alternate is 2 : 1, because the former could have occurred due to inversion of the two phenyl groups (Ph2 and Ph4) on the left and right sides from Ph1. The inversion of partial cone to 1,3-alternate however needed only one phenyl group (Ph3) interconversion. Therefore, the results suggest that the relative thermal stability of the four conformers of **2** is in the order 1,3-alternate (most stable) > 1,2-alternate > partial cone > cone (most unstable). Clearly, the order of the relative stability of the conformers of **2** is very different from those of the tetramethyl ethers of **1a** and **1b** (for **1a**: partial cone > cone > 1,2-alternate > 1,3-alternate, for **1b**; partial cone > cone > 1,2-alternate = 1,3-alternate)[6,7] and tetraethyl ethers of **1a** and **1b** (partial cone > 1,2-alternate > cone > 1,3-alternate).[7] The high instability of the cone conformation of **2** is attributed to the steric repulsion between the four acetyl groups because the acetyl group is sterically much bigger than the methyl and ethyl groups of **1a** and **1b** due to chain branching. In order to obtain more insight on the conformational change, we heated the

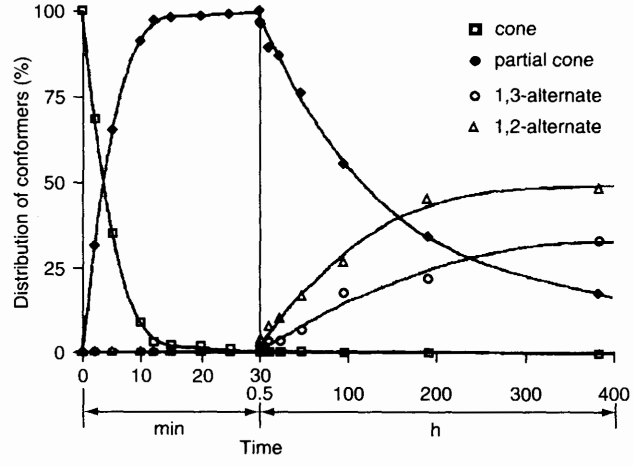

Fig. 1 Dependence on heating times of the distribution of conformers in $[^2H_6]Me_2SO$ at 150 °C

partial cone, 1,2- and 1,3-alternates at 150 °C for 384 h.§ The results appear to represent incomplete equilibration of the conformational isomers which, controlled by the kinetics of competing processes, the role of the partial cone as an intermediate is evident from the consideration of the conformations and possible processes for interconversion. The apparent first order rate constants (*k*) for inversion from the cone to the partial cone, and the partial cone to the 1,2- and 1,3-alternates isomerization were determined from the decreased amounts of cone and partial cone at different temperatures.¶ The rate constant (3.076×10^{-3} s^{-1}) for inversion of the cone to the partial cone at 150 °C was very fast (1600 times) compared with that (1.923×10^{-6} s^{-1}) for the inversion of the partial cone to the 1,2- and 1,3-alternates.

Footnotes

† C. D. Gutsche *et al.* reported that the reaction of **1** with acetic anhydride in the presence of conc. H_2SO_4 gave only partial cone in 42% yield. C. D. Gutsche, B. Dhawan, K. H. No and R. Muthukrishnan, *J. Am. Chem. Soc.*, 1981, **103**, 3782.

‡ K. H. No *et al.* reported that the reaction of **1b** with acetyl chloride in the presence of sodium hydride in dry THF gave only the cone conformer of **2** in 89% yield. K. H. No and H. J. Koo, *Bull. Korea Chem. Soc.*, 1994, **15**, 483. C. Jaime *et al.* also reported that the reaction of **1** with acetyl chloride using toluene-*p*-sulfonic acid as catalyst gave the 1,3-alternate (36%) together with the partial cone (3%) and 1,2-alternate (15%). C. Jaime, J. Mendoza, P. Prados, P. M. Nieto and C. Sanchez, *J. Org. Chem.*, 1991, **56**, 3372.

§ The 1,3-alternate was isomerized to the partial cone and the 1,2-alternates in 3 and 2% yield together with unisomerized starting material in 94% yield, whereas the 1,2-alternate give the partial cone and the 1,3-alternate in 12 and 13% yields together with starting material (81%). The partial cone was also isomerized to the 1,2- and 1,3-alternates in 41 and 20% yields, respectively.

¶ The apparent first order rate constants for the isomerization of the cone to the partial cone at 80, 100, 120, 140 and 150 °C were 0.0105×10^{-3}, 0.106×10^{-3}, 0.234×10^{-3}, 1.96×10^{-3} and 3.076×10^{-3} s^{-1}, respectively. The apparent first order rate constants for isomerization of the partial cone to the 1,2- and 1,3-alternates at 130, 140, 150, 160 and 170 °C were 0.225×10^{-6}, 1.34×10^{-6}, 1.92×10^{-6}, 2.11×10^{-6} and 4.88×10^{-6} s^{-1}, respectively.

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