Novel Conformational Isomerism of Water-Soluble Calix[4]arenes

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Abstract: The conformer distribution of 5,11,17,23-tetrasulfonato-25,26,27,28tetramethoxycalix[4]arene (1) and 5,11,17,23tetrakis(trimethylammoniomethyl)-25,26,27,28tetramethoxycalix[4]arene (2) was estimated in an aqueous system. Surprisingly, these calix[4]arenes adopt a <u>1,3-alternate conformation</u> which has never been found as a major species in organic solvents but has been predicted to be most stable on the basis of computational studies.

Introduction

It is known that in tetra-O-alkylcalix[4] arenes the methyl group is too small to suppress the oxygen-through-the-annulus rotation.¹⁻³ In fact, there exist four different conformers under an equilibrium.^{4.5} We found on the basis of the ¹H NMR (400 MHz) measurements that at -25 °C in CDCl₃ 5,11,17,23-tetra-tbuty1-25,26,27,28-tetramethoxycalix[4]arene consists of 2% cone, 92% partial cone, 5% 1,2-alternate, and 1% 1,3-alternate. Τn most organic solvents, cone and partial cone appear as major conformers whereas 1,3-alternate is not detected or appears (if any) as an incomparably minor conformer.³⁻⁵ The findings may allow to consider that cone and partial cone are much more stable than 1,3-alternate. Computational studies predict, however, that 1,3-alternate is the most stable conformer among four possible conformers.^{a,e} The discrepancy is probably rationalized in terms of so-called "solvent effects" but the reason is not understood well. We were interested in the conformer distribution in water because water molecules scarcely "solvate" calixarenes and computational studies were frequent persuaded in an aqueous system. We thus synthesized anionic and cationic water-soluble calix[4]arenes (1 and 2, respectively). Surprisingly, the main species in water was 1,3-alternate and the conformer distribution was sensitively affected by the solvent composition.





5,11,17,23,29,35-Hexakis(chloromethyl)-37,38,39,40,41,42hexamethoxycalix[6]arene and 5,11,17,23,29,35,41,47octakis(chloromethyl)-49,50,51,52,53,54,55,56octamethoxycalix[8]arene can be synthesized by direct chloromethylation of the corresponding calix[n]arenes in the presence of Lewis acids $(ZnCl_2 \text{ or } SnCl_4)$.^{7,8} On the other hand, chloromethylation of 25,26,27,28-tetramethoxycalix[4]arene (3) in the presence of Lewis acids resulted in the brown and gummy This is due to the interaction of the acidic metal product. cations with the ionophoric four methyl ethers,^a which eventually causes the demethylation reaction.[®] We thus challenged direct chloromethylation of 3 in the absence of Lewis acids and finally developed a new method in which proton acids are used instead of Lewis acids (see Experimental): 5,11,17,23tetrakis(chloromethyl)-25,26,27,28-tetramethoxycalix[4]arene (4) mp (decomp) 204-206 °C, yield 41%. Treatment of 4 with trimethylamine in DMF gave 2 in 84% yield. Compound 2 (mp (decomp) > 270 °C) was identified by IR and ¹H NMR spectral evidence and elemental analysis.





cone partial cone 1,2-alternate 1,3-alternate

Four conformers of 2 can be distinguished by the characteristic ¹H NMR patterns arising from the ArCH₂Ar methylene protons: judging from their symmetry, cone, partial cone, 1,2alternate, and 1,3-alternate will appear as a pair of doublets, two pairs of doublets, one singlet and a pair of doublets, and one singlet, respectively. It is also expected from their symmetry that aromatic protons should appear, neglecting the metacoupling, as one peak for cone and 1,3-alternate, four peaks for partial cone, and two peaks for 1,2-alternate. The ¹H NMR spectrum of 2 (5.0 x 10⁻³ mol dm⁻³; 400 MHz, 5 °C) in CD₃OD afforded a singlet (3.76 ppm) and two pairs of doublets (3.39 and 4.12 ppm for one pair (J_{HH} = 13 cps) and 3.87 and 3.93 ppm for another pair (J_{HH} = 14 cps)) (Figure 1). The splitting pattern indicates that 2 exists in water as a mixture of 1,3-alternate



Figure 1. Partial ¹H NMR spectrum of 2 in CD₃OD at 5 °C: ○ 1,3-alternate, ● partial cone

and partial cone, the ratio determined from the integral intensities being 49:51. Similarly, the aromatic protons consisted of five peaks. A strong peak at 7.34 ppm is assigned to 1,3alternate and residual four peaks are assigned to partial cone: the ratio was again 49:51. This is the first example for the system where the 1,3-alternate conformer, which has been predicted to be most stable among four conformers on the basis of computational studies,^{3,6} exists as a major species.

We determined the ratio of 1,3-alternate-2 vs. partialcone-2 in D_2O-CD_3OD (or THF-d₈) and $CD_3OD-CDCl_3$ systems by ¹H NMR (Figure 2). It is seen from Figure 2 that 1,3-alternate% increases with decreasing CD_3OD concentration in D_2O and reaches 83% in pure D_2O . The similar trend was observed for a D_2O -THFd_s system. On the other hand, 1,3-alternate% is almost constant (49 ± 4%) in a CD₂OD-CDCl₃ system. The results indicate that 1,3-alternate-2 is specifically stabilized in D_2O and its relative stability is less affected by the solvent polarity (e.g., by the change from CD₃OD to CDCl₃).



Figure 2. Solvent effect on 1,3-alternate% of 2.

The ¹H NMR spectrum of 1 was not so clear as those for 2 because of significant line broadening. In $D_2O(60 \text{ vol}\%)$ - $CD_3OD(40 \text{ vol}\%)$ at 5 °C we observed a singlet at 3.91 ppm which could be assigned to 1,3-alternate. The aromatic region consisted of five peaks, one of which (at 7.59 ppm) was assigned to 1,3-alternate on the basis of its integral intensity. The residual four peaks (at 7.29, 7.51, 7.59, and 7.85 ppm) were reasonably assignable to partial cone. Thus, the ratio of 1,3alternate/partial cone is 24/74 (other isomers also exist in ca. 2%). The increase in the D_2O concentration leads to the increase in 1,3-alternate% and 1,3-alternate/partial cone = 55/45 (no other isomers exist) was attained in pure $D_{x}0$.

Why are 1.3-alternate conformers specifically stabilized in water ? In organic solvents, we previously found for 5,11,17,23-tetra-t-buty1-25,26,27,28-tetramethoxycalix[4]arene that the fraction of cone increases with increasing solvent polarity. $^{3-5}$ This solvent effect reflects the fact that a cone conformer, having four dipoles arranged in the same direction and therefore being more "polar" than other three conformers with one or two reversed dipoles, is more stabilized in "polar" If one could extend this concept to the present syssolvents. tem, the fractions of polar conformers such as cone and partial cone (the order of the dipole monent is cone > partial cone > 1,2-alternate > 1,3-alternate)^a should increase in water. Τn fact, however, the least polar 1,3-alternate conformer increases. Undoubtedly, the conformer distribution in water is governed by somewhat different factors other than the solvent polarity.

The basic skeleton of calix[4]arenes is very hydrophobic. It is expected, therefore, that they change the conformation so that the skeleton may "get wet" in solvent water to the minimal extent. The examination with CPK molecular models suggests that the hydrophobic calix[4]arene core in 1,3-alternate conformers is favorably covered by four sulfonate or ammonium ions, like a unimolecular micelle. In contrast, it seems unavoidable for the core in other three conformers to get wet in solvent water to some extent. That is, a 1,3-alternate conformer can minimize the hydrophobic surface which contacts water molecules. If this supposition is accepted, it follows that the increase in the fraction of partial cone in organic solvents is ascribed to the stabilization by solvation of the hydrophobic surface of a partial cone conformer by organic solvent molecules.

Recently, the X-ray crystallographic structure of 1 was reported by Atwood and Bott.¹⁰ Very surprisingly, <u>1 adopts a</u> <u>1,3-alternate conformation in the solid state</u>. We thus believe that the present NMR study in solution is exactly complementary to their X-ray crystallographic study.

In conclusion, the present paper demonstrated that a 1,3-

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alternate conformer, which has been predicted to be most stable on the basis of computational studies but has never been found as a major species, does exist in an aqueous system. The finding would provide an important crosslink between theoretical chemistry and experimental chemistry on calixarene conformations.

Experimental

Materials

The preparation of 1 was described previously.¹¹

5,11,17,23-Tetramethoxy-25,26,27,28tetrakis(chloromethyl)calix[4]arene (4). To 100 ml of dioxane containing 3 (1.36 g, 2.83 mmol) and paraformaldehyde (1.70 g, 56.6 mmol) were added 9 ml of acetic acid, 18.5 ml of conc. HCl, and 17 ml of 85% phosphoric acid. The mixture was heated at 100 °C for 8 h and then poured into ice-water. The white precipitate was recovered by filtration. The product was dissolved in chloroform and the solution was washed with water until the aqueous layer showed neutral pH. The chloroform solution was separated and dried over MgSO₄. The solution was concentrated in vacuo and the residue was subjected to the purification by column chromatography (silica gel, ethyl acetate:n-hexane = 1:7): mp 204-206 °C, yield 41%; IR (nujol) ν g_{-g_1} 720 cm⁻¹; ¹H NMR (CDCl₃, internal standard TMS, 25 °C) δ (for cone-4) 3.19 and 4.32 (ArCH₂Ar, d each (J=13 Hz), 1H each), 3.81 (OCH₃, s, 3H), 4.32 (CH₂Cl, s, 2H), 6.72 (ArH, s, 2H); δ (for partial-cone-4) 3.02, 3.65, and 3.68 (OCH_a, s each, 3H, 3H, 6H), 3.11 and 4.02 (syn-ArCH₂Ar, d each (J=12 Hz), 2H each), 3.60 (anti-ArCH₂Ar, broad s, 4H), 4.25, 4.30, and 4.60 (ArCH₂Cl, s each, 2H, 2H, 4H), 6.37, 6.95, 7.11, and 7.28 (ArH, s each, 2H Anal. Calcd for (C₉H₉OCl)₄: C, 64.11; H, 5.38%. each). Found: The ratio of cone vs. partial cone was es-64.46: H. 5.48%. timated to be 22:78 from the integral intensities.

5,11,17,23 - Tetramethoxy-25,26,27,28tetrakis(trimethylammoniomethyl)calix[4]arene tetrachloride (2). To 50 ml of DMF containing 4 (1.00 g, 1.48 mmol) was introduced trimethylamine (gas) for 40 min at room temperature. The precipitate was collected by filtration, washed with chloroform, and dried in vacuo: mp (decomp) > 270 °C, yield 69%; ¹H NMR (D₂O, internal standard DSS, 80 °C) δ 3.02 (N⁺CH₂, s, 9H), 3.62 (OCH₃, s, 3H), 3.83 (N⁺CH₂, s, 2H), 4.37 (ArCH₂Ar, s, 2H), 7.31 (ArH, s, 2H). Anal. Calcd for (C₁₂H₁₈NOCl)₄: C, 63.29; H, 7.97; N, 6.15%. Found: C, 62.54; H, 7.65; N, 5.99%.

Spectroscopic Measurements. The ¹H NMR spectra were measured with a 400 MHz NMR apparatus (JEOL GX-400).

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