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Are 1,3-Di-*O*-benzoylcalix[4]arenes an Exception to the ^{13}C-NMR Rule for Conformational Determination?

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Introduction

Calix[4]arenes are not planar and can adopt four different stable conformations [cone, partial cone (paco), 1,2-alternate (1,2-alt), and 1,3-alternate (1,3-alt)] when the phenolic hydroxyls ("lower rim") are replaced by bulky groups, preventing free rotation of the aromatic rings.[1] These conformationally frozen compounds are increasingly used as building blocks or molecular platforms in supramolecular chemistry.[1,2] In most cases, complexation or molecular recognition has been shown to be dependent on the conformational isomer employed.[3]

Among the different techniques used to elucidate calixarene conformations in solution, we suggested a simple rule based on the ^{13}C-NMR chemical shifts of bridged methylene carbons.[4,5] According to our rule, signals appear at *ca.* 30−31 ppm when neighboring aromatic rings are oriented to the same side and at *ca.* 37−40 ppm when they point to the opposite side (Figure 1). However, Shu *et al.*[6] pointed out recently that the rule was not applicable to partially substituted calix[4]arenes. Indeed, *syn-* and *anti*-1,3-dibenzoylcalix[4]arenes **1** and **2** showed methylene ^{13}C-NMR signals at 33 and 34 ppm, respectively. Although the relative orientation of the opposite substituted rings was assessed by chemical methods, the relative conformation of unsubstituted phenols remained uncertain. We report herein a full conformational characterization of both isomers in $CDCl_3$ by variable-temperature ^{1}H-NMR and 2D-NMR experiments and comment on its implications on the applicability of the ^{13}C-NMR rule for calixarene conformations.

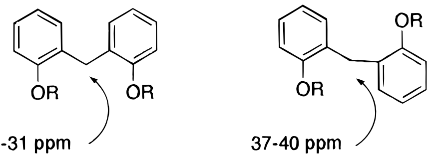
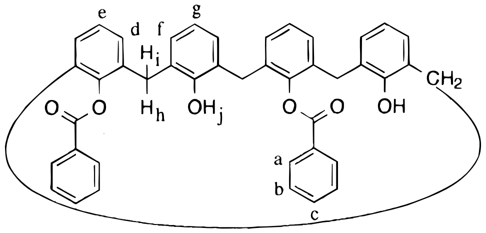


Figure 1. ^{13}C-NMR rule for the assignment of the orientation of neighboring aromatic rings in calixarenes.

Results and Discussion

***syn*-1,3-Di-*O*-benzoylcalix[4]arene (1).** All ^{1}H-NMR signals of **1** were unambiguously assigned by COSY-45, HMQC, and HMBC experiments, the latter being necessary to assign calixarene aromatic signals through long-distance correlation between the hydroxylic proton and the aromatic signals of the unsubstituted rings. A ROESY (500 MHz, 298 K) experiment showed NOEs between *endo* H_h and H_j protons, as well as between *exo* H_i and aromatic H_d and H_f protons.[7] This pattern is only compatible with an *all-syn* (cone) conformation. Chemical shifts of nonexchangeable protons remained constant in the temperature range from 215 to 325 K, suggesting that a single conformation is appreciably populated in solution. The observation of long-distance couplings between methylene and calixarene aromatic protons, easily detected in the COSY-45 spectra (Figure 2) gives additional insight into the conformation of **1**. Protons H_f show a long-range coupling exclusively to the *endo* H_h methylene proton, while protons H_d show the coupling only to the *exo* H_i.



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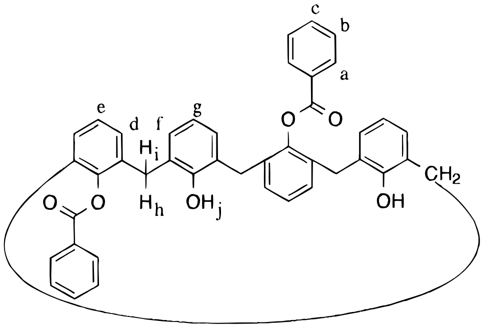

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Benzylic coupling is expected to be sensitive to the dihedral angle between the methylene CH bond and the

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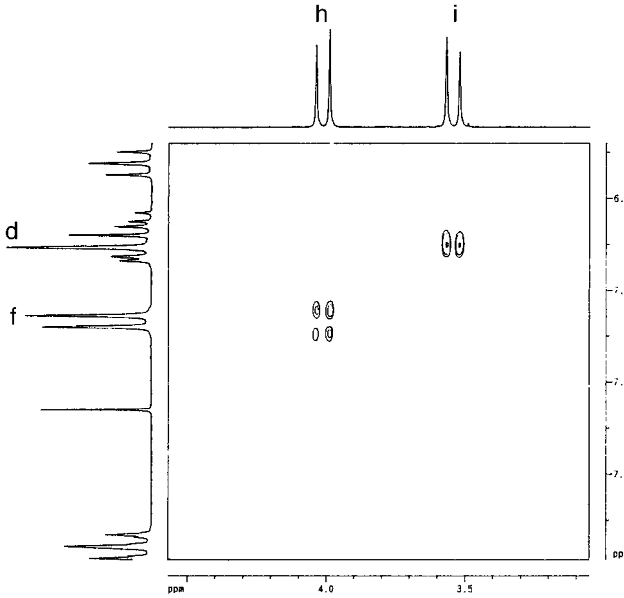

Figure 2. Long-distance coupling between H_h and H_f and between H_d and H_i in **1** (COSY-45, 3.0−4.5 ppm × 6.7−7.5 ppm).

plane of the aromatic ring. The largest coupling constant should be found when this angle is 90°. Under this situation, overlap between the CH bond and the π system is optimal. The complementary couplings in **1** are not compatible with a perfect symmetrical cone (C_{4v}) and can only be explained, considering the symmetry of the spectra, by a flattened cone of C_{2v} symmetry where the free phenols are flattened, pointing inside the cavity and hydrogen bonded. The flattened cone conformation has been predicted for some distal disubstituted calix[4]arenes from computational studies[8] and has also been observed for some derivatives in the solid state.[9] It has been established recently that tetra-*O*-alkyl-*p*-*tert*-butylcalix[4]arenes display a degenerated equilibrium between flattened cones in solution, the perfect cone being just the transition state.[10] The different substitution of adjacent rings breaks the degeneracy, and apparently only one of the C_{2v} conformations is appreciably populated in solution. This can be rationalized on the basis of steric hindrance of the substituted phenols and extensive intramolecular hydrogen bonding of the free phenols. The experimental value of 32.5 ppm for the bridge methylene carbons is a consequence of the flattened conformation that relieves the steric congestion found in the pure cone conformation and that is absent in a typical *anti* arrangements.

A very similar value (32.6 ppm) was found in an ionophoric calix[4]arene tetraester reported to undergo a C_{2v}−C_{2v} equilibrium. This value shifted to 30.7 ppm upon Na^+ complexation involving a C_{4v} conformation.[11]

***anti*-1,3-Di-*O*-benzoylcalix[4]arene (2).** As for compound **1**, all of the ^{1}H- and ^{13}C-NMR signals of **2** could be assigned using COSY-45 and HMQC experiments. NOEs between H_h and H_j or H_f protons were observed both at 298 and 183 K in ROESY experiments at 500 MHz. These two mutually exclusive NOEs indicate a rapid equilibrium involving rotation of the nonsubstituted aromatic rings. This rotation can lead to an equilibrium between two types of conformations for the calixarene: 1,2-alt and paco (Figure 3). Each of these conformations could show two different AB systems, but rapid equilibration between them can explain the observation of a single averaged AB system between 183 and 298 K. It is interesting to note that in spite of the rapid equilibrium between these conformations the absence of a symmetry axis relating protons in the same methylene group in any of the conformations explains the lack of coalescence of the AB system at room temperature.

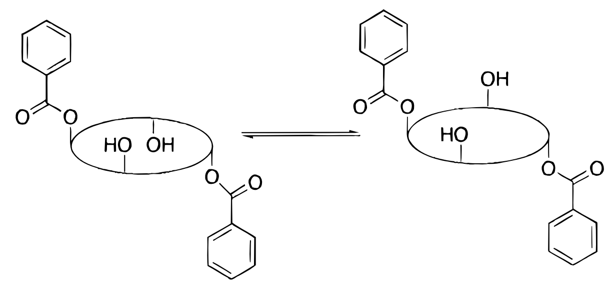

Figure 3. Equilibrium between paco and 1,2-alt conformations in **2**.

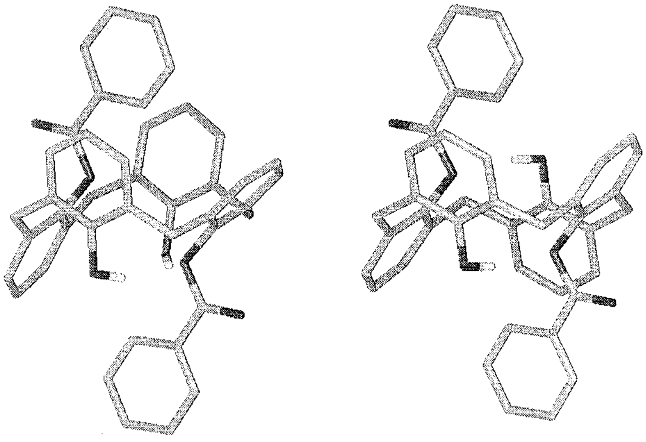

Figure 4. Optimized structures for paco and 1,2-alt conformations in **2**.

Temperature strongly affects the H_h chemical shift, which changes from 3.87 ppm at 298 K to 3.79 at 183 K. This suggests a small energy difference between conformations involved in a fast exchange so that a small variation in kT causes an appreciable shift in the population at equilibrium. The fact that only one of the methylene protons shows strongly temperature dependent shifts is consistent with the observation that, at 183 K, only this proton comes close and, therefore, shows NOE contacts with aromatic and phenolic protons.

The observation of a single averaged set of signals even at 183 K is indicative of a low barrier for the rotation of the phenolic ring ($\Delta G^\ddagger$ < 38 kJ/mol). The barrier is much lower than the 66 kJ/mol cone-cone interconversion barrier reported for *p*-*tert*-butylcalix[4]arene.[7b] Rotation of the phenol rings in **2** require disruption of much weaker hydrogen bonds than in unsubstituted *p*-*tert*-butylcalix[4]arene, where a strong circular array of hydrogen bonds is present.[12]

In contrast to the sharp signals arising from the calixarene ring, benzoyl signals are considerably broad-

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ened at the lowest temperature studied, indicating that they are involved in a conformational exchange process at an intermediate rate at these temperatures. Molecular modeling suggests that one of the phenyl rings could be included in the cavity of the calixarene. The chemical shifts of H_a and H_b (6.99 and 7.05 ppm) are upfield shifted by 0.7 and 0.5 ppm with respect to the same protons in **1**, in agreement with this hypothesis. Inclusion of the benzoyl ring is probably stabilized by both π-staking with the walls of the calixarene cavity and by face to edge CH$-\pi$ interactions[13] with the ring located in front of it. Structures for the two conformations in equilibrium were deduced from molecular mechanics and molecular dynamics simulations (Figure 4).[14]

The rapid equilibration between *syn* and *anti* arrangements provides an explanation for the observed carbon chemical shift of 34 ppm for methylenes in **2**.

Conclusions

We have demonstrated that calix[4]arene **1** has a flattened cone conformation in $CDCl_3$, whereas **2** is in equilibrium between paco and 1,2 alt conformations. The ^{13}C-NMR shifts for the methylene carbons, midway between the standard 31 and 37 ppm values for “pure” *syn* or *anti* arrangements, may be interpreted by either a distorted fixed conformation in compound **1** or a fast equilibrium between *syn* and *anti* arrangements in compound **2**.

Experimental Section

Product Preparation and NMR Procedures. Compounds **1** and **2** were prepared according to published procedures.[6] A Bruker AMX 300 instrument (Universidad Autónoma de Madrid) was employed for ^{1}H-NMR, ^{13}C-NMR, COSY-45, and HMQC experiments, whereas ROESY, HMBC, and variable-temperature ^{1}H-NMR experiments were performed with a Varian-VXR-500 instrument (Universitat de Barcelona). Mixing time for ROESY experiments at −90 °C was 150 ms.

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Supporting Information Available: Copies of 1D and 2D NMR spectra of **1** and **2** (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[13] Nishio, M.; Umezawa, Y.; Hirota, M.; Takeuchi, Y. *Tetrahedron* **1995**, *51*, 8665.

[14] INSIGHT-II 2.3.0/Discover packages (Biosym Technologies, 9685 Scranton Road, San Diego, CA 92121-2777), implemented on a Silicon Graphics INDIGO XS24 workstation, were employed. Standard potentials and atomic charges, as provided by the AMBER forcefield, were employed without modifications. For each paco and 1,2-alt structure, three initial conformations were considered, depending of the relative orientations of the benzoyl groups (*in-in*, *in-out*, *out-out*). Calculations were performed in vacuo, with a dielectric constant $\epsilon = 4r_{ij}$, and the initial structures of **2** were slowly relaxed by 300 steepest descent iterations, followed by full optimization with enough conjugate gradients iterations to reach an energy rms gradient of less than 0.001 kcal mol^{-1} Å^{-1}. Minimized structures were subjected to a molecular dynamic protocol through 500 ps (50 ps heating to equilibration at 300 K). Coordinates were saved each 500 fs. Average coordinates taken for each 50 ps were minimized again, obtaining in all cases superimposible structures that therefore may be considered as a global minimum under the simulation conditions.