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Hydrogen Bonding in Calix[n]arenes. A Preliminary ^{17}O NMR Study

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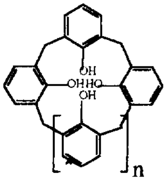
Abstract: ^{17}O NMR spectra at natural isotopic abundance of two calix[n]arenes, (n = 4, 6) and model phenols have been obtained in three different solvents. The difference in the hydrogen bond strength between calix[4]arene and calix[6]arene is manifested in the ^{17}O NMR spectra.

Calixarenes are macrocyclic organic derivatives composed of a cyclic arrangement of phenol and methylene units,[1] which occupy a privileged position in the family of synthetic organic host molecules.[2] One important structural feature of this class of molecules is the presence of an array of strong intramolecular circular hydrogen bonds involving the OH group. The cone conformation is, in the case of calix[4]arenes, stabilized by these hydrogen bonds as shown by the conformational behavior of the dehydroxylated analogs which may prefer other conformations.[3] As shown by IR studies, the hydrogen bonds are stronger for *p-tert*-butylcalix[4]arene than for the larger calix[n]arenes (n > 4).[4]

^{17}O NMR spectroscopy is a very valuable tool for studying hydrogen bonding.[5] However, most efforts have been devoted to the effect of the hydrogen bonding on the chemical shift of the carbonyl oxygen.[6] A shielding effect, which is, *inter alia*, a function of the acidity[7] of the hydrogen bond donor and of the basicity of the carbonyl group,[8] has been observed in such a case.[6]

One might hypothesize that the OH group will be deshielded when acting as a donor and shielded when acting as an acceptor of hydrogen bonds, as compared to a non-associated OH group. There are, however, conflicting observations on this point. Gerothanassis et al.[9] observed that the ^{17}O NMR shift of *p*-cresol is very similar in acetone and CCl_4. Boykin et al.[6] observed a constant shielding for the OH group when acting as a donor, in agreement with the results of Orendt et al.[10] Frey et al.,[11] very recently, observed for several enols and phenol itself, a clear deshielding on going from chloroform to DMSO solutions, in agreement with the results obtained by numerous groups.[12] An interesting case is that of 2-hydroxyphenol, where, when associated, one OH group serves as an hydrogen bond donor while the other serves simultaneously as an hydrogen bond acceptor; a situation which in this respect resembles that encountered in calix[n]arenes. No apparent deviation has been observed[6] from the results shown by other phenols lacking this particularity. Such being the *state of the art*, we have chosen to compare calix[n]arenes with model systems using identical experimental conditions. The *p-tert*-butylcalix[n]arenes have poor solubility in most solvents but the de-tert-butylated analogs[13] have sufficient solubility to allow determination of their ^{17}O NMR spectrum at natural isotopic abundance. The results are collected in Table 1.



1, n = 1
2, n = 3

Table 1. ^{17}O NMR Data for Calix[n]arenes and Reference Phenols.[a]

N°	Compounds	$\delta(^{17}O)$	$\nu_{1/2}$, Hz	$\delta(^{17}O)$	$\nu_{1/2}$, Hz	$\delta(^{17}O)$	$\nu_{1/2}$, Hz
		C_6H_6,[b] ppm		$CHCl_3$,[c] ppm		C_5H_5N,[b] ppm	
1	Calix[4]arene	77.5	550	75	650	78	600
2	Calix[6]arene	68	1000	68	2500	80	1000
3	Phenol	75	165	73.0	200	83.5	300
4	2,6-dimethylphenol	67.7[d]	195	65.4	220	74	380

a) Spectra (Varian VXR-300, 40.662 MHz) of **1** and **2** were obtained from their saturated solutions while data for **3** and **4** are mean values of three different sets of measuraments at three different concentrations (1.2, 0.6 and 0.3 M) in each solvent. The observed shifts were constant within the experimental error (± 1 ppm for half-height line-widths < 1000 Hz and ± 2 ppm in the other cases). b) Spectra obtained at 65 °C. c) Spectra obtained at 50 °C. d) A $^1J(OH)$ of 91.2 Hz has been measured.

Notably, the chemical shifts of phenols **3** and **4** are constant in the 0.3-1.2 M concentration range. It therefore seems likely that even at the lowest concentration studied the phenol molecules are intermolecularly hydrogen bonded.[14]

In order to better understand the influence of the hydrogen bonding on the ^{17}O NMR shift in our systems, we tried to separate this effect from other possible effects, such as electronic effects and steric hindrance due to 2,6-disubstitution. In the related ether anisole, 2,6-dimethyl substitution causes a substantial upfield shift of *ca.* 30 ppm.[15] Due to the reduced steric requirement of an OH compared with a methoxy group, the upfield shift of **4** compared with **3** is only *ca.* 7.5 ppm, in both benzene and chloroform solutions. Calix[6]arene **2** has an ^{17}O NMR shift very close to that of **4** in these solvents. In the case of calix[4]arene **1**, the hydrogen bonding effects counterbalance those of di-*ortho* substitution.[1] The larger chemical shift observed for calix[4]arene in $CHCl_3$ or benzene (75-77.5 ppm), as compared with calix[6]arene (68 ppm) can be rationalized, since as shown by independent spectroscopic data, the intramolecular hydrogen bonds are stronger in the former.[4a]

We found both for the calix[n]arenes as well as for the two phenols a deshielding effect on changing the solvent from chloroform to pyridine. This effect is, roughly, 10 ppm for **2-4**, but for calix[4]arene **1** it is reduced to only 3 ppm. In chloroform and benzene solutions phenols **3** and **4** do not form strong hydrogen bond with the solvent and the main hydrogen bond interactions involve OH containing solute molecules, which act as donors as well as acceptors. In pyridine, **3** and **4** act only as hydrogen bond donors since the OH ··· OH hydrogen bond is disrupted and replaced by the stronger OH ··· N bond and the net result is the observed deshielding.

Notably, the $\Delta\delta$ value [$\Delta\delta = \delta$(pyridine) - δ($CHCl_3$)] is larger for calix[6]arene than for calix[4]arene,[4] as expected since, as shown by dynamic NMR data,[4b] the somewhat weaker H-bonds in calix[6]arene should be more disrupted by the presence of the hydrogen bond accepting solvent.

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