On the Utility of ^{13}C (CPMAS) NMR in Conformational Studies of Simple Hydroxy-, Alkoxy- and Acetoxycalixarenes in the Solid State

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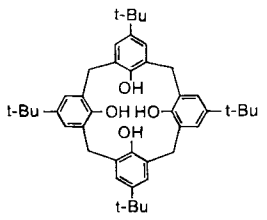
The potentiality of ^{13}C (CPMAS) NMR as a conformational probe for the oligomeric macrocycles *p*-(*tert*-butyl)calix[*n*]arenes (n = 4, 6, 8) and their alkoxy/acetoxy derivatives in the solid state is explored.

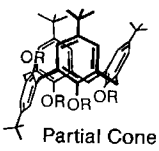
Syntheses, conformational studies and guest-host chemistry of calix[*n*]arenes (Scheme 1) have become dynamic areas in inclusion research and molecular recognition[2-5]. Understanding the host structure and the conformational changes that occur upon guest-host cluster formation[6-11] are important steps toward designing selective receptors, capable of controlling the reactivity/selectivity of electrophiles by encapsulation.

Scheme 1. Parent calix[*n*]arenes (n = 4, 6, 8) and conformations of calix[4]arenes.

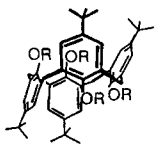


p-tert-Butylcalix[4]arene
1

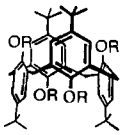
Cone



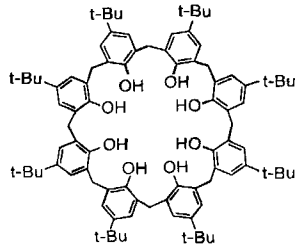
Partial Cone



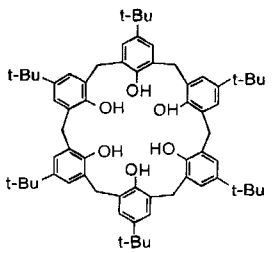
1,2-Alternate



1,3-Alternate

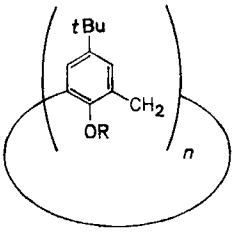


p-tert-Butylcalix[8]arene 2



p-tert-Butylcalix[6]arene 3

For calix[4]arenes, four conformations are possible, viz. cone, partial cone, 1,2-alternate and 1,3-alternate (Scheme 1). In hydroxy-calixarenes, the cone conformation is the most stable due to hydrogen bonding at the lower rim[2,11]. Cone stability increases in polar aprotic solvents[7,10], in the presence of a cationic template[7,8,12], and by increasing steric bulk at the upper rim[7-10]. On the other hand, removal of a bulky substituent (e.g. tBu) from the upper rim stabilizes the 1,3-alternate[13], whereas OH depletion stabilizes the partial cone conformation[14]. The predominant conformation for the OMe, OEt and OCOMe derivatives of *p*-tBu-calix[4]arenes **1** is the partial cone[11]; but simultaneous presence of other conformations, including the less frequently noted 1,2-alternate, has been shown[15].



	n
1	4
2	8
3	6

1–3	R
a	H
b	CH_3
c	C_2H_5
1d	C_4H_9
2d	$[CH_2]_2C(CH_3)_2$
3d	–
e	$CO-CH_3$

Parent *p*-tBu-calix[8]arene **2a** is flat and shows identical conformational behavior to that of **1a**, whereas *p*-tBu-calix[6]arene **3a** has a very different conformational behavior, to which a "winged" or a "hinged" structure is assigned[2,16]. Conformational rigidity of **2a**, despite its much larger global flexibility, is due to intramolecular H-bonding[11]. The esters and ethers of type **2**–**3** have also been studied by dynamic ^1H NMR "DNMR"[17].

In the calixarene series, the number and multiplicity of the axial/equatorial methylene bridge protons provide a diagnostic conformational tool. Thus, ^1H-NMR studies (also including NOE and 2DNMR) have been quite extensive[2,11,18,19]. In most cases, good agreement is found with X-ray analyses. It was shown very recently that the much less studied ^{13}C NMR can be used as an effective conformational probe in solution, since a bridging CH_2 connecting two *syn* (or two *anti*) phenol rings has a different chemical shift than a CH_2 joining two phenols with *syn/anti* relationship. Hence two CH_2's are observed for the 1,2-alternate and partial cone conformations, whereas only one signal is seen for the cone or the 1,3-alternate conformations, with the former usually more upfield[24].

The reported solution ^{13}C data for simple hydroxy-, alkoxy-, and acetoxy-*p*-tBu-calixarenes are rather scarce[11,12,25], and chemical

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shifts reported by various groups in a given solvent are not near identical. The $ArCH_2Ar$ resonance can occur in between, upfield or downfield from the tBu signals, and is in most cases within 1–2 ppm of the tBu resonances. Thus, conformational utility of ^{13}C NMR for *p*-tBu-calixarenes hinges on resolution of CH_2 absorption(s) from the tBu signals.

In relation to our previous and ongoing studies on encapsulated onium ions[26], ion-molecule reactions within clusters[27] and in cyclophane chemistry[28,29] we wondered about the extent of utility of ^{13}C (CPMAS) NMR spectroscopy for calixarene hosts (Scheme 1), and whether it can provide the same kind of information as solution NMR and be useful as a complementary method to X-ray analyses, which are still rather limited[2].

Inclusion of trimethylphenylammonium cation inside *p*-sulfonatocalix[4]arene has been probed by solid state NMR, but only the guest shifts were given[30]. To our knowledge, the only reported CPMAS carbon NMR spectrum of a calixarene is that of **1a**/toluene clathrate[31], in which the bridging CH_2's give rise to a tiny peak, ca. 1.5 ppm upfield from the tBu(Me) resonance.

Results and Discussion

The NMR spectrum of **1a** purified by crystallization from toluene according to the literature[32], shows four peaks in the diagnostic alkyl region (Figure 1a); two large equally intense signals at δ = 31 and 34.5 assigned to tBu(Me), a medium size signal at δ = 33 assigned to tBu(C) and a smaller peak at δ = 31, which in analogy with the reported solid-state spectrum of **1**/toluene clathrate[31] is assigned to the bridging CH_2's. The presence of two kinds of tBu(Me) is attributed to incomplete removal of toluene from the *endo*-calix complex formed during crystallization. Since the absorption at δ = 33 is very close to the reported value for the **1a**/toluene clathrate (32.12), the more downfield tBu(Me) must be attributed to the uncomplexed calixarene. Shielding of the tBu(Me) in the solid state ^{13}C NMR of the guest-host cluster is in accord with solution ^1H-NMR titration (solvent-induced shifts)[5b], showing an upfield shift for tBu(Me) in **1a**/toluene complex; a guest-host model in which the nearby tBu groups are transannularly shielded by the phenyl ring of the guest in a tight insertion complex.

The X-ray structure of **1a**/toluene showed that tBu groups are disordered in two orientations by 29°[22], however, solid state NMR spectrum of the **1a**/toluene clathrate shows only one tBu(Me) signal[31]. Thus, disordered methyl groups are chemical shift equivalent, and it is unlikely that the disorder is responsible for the presence of two different methyl absorptions for **1a** in the solid state. In agreement with this, acetoxycalix[8]arene **2e**, which was also shown by X-ray analysis[23] to have disordered tBu groups in at least two orientations by 60° rotation, shows only one tBu(Me) resonance in its ^{13}C (CPMAS) NMR spectrum (see later).

The presence of just one CH_2 resonance supports the *cone* conformation for **1a**, as established by both X-ray analysis[21] and solution NMR[2,11].

Methoxycalix[4]arene **1b** has a partial cone conformation in solution (^1H NMR)[11]. The ^{13}C (CPMAS) NMR spectrum of **1b** shows a tBu(Me) at δ = 32 and a tBu(C) resonance at δ = 34. The CH_2 signal appears as a small peak at $\delta \approx 30.5$; almost overlapping with the tBu(Me) and not sufficiently resolved to afford conformational information.

Ethoxycalix[4]arene **1c** has a partial cone conformation based on solution ^1H NMR[11]. Such a conformation would require two bridging CH_2 carbon resonances[24]. However, only one absorption (δ = 38.8) was reported in its solution ^{13}C-NMR spectrum[11]. The solid-state NMR spectrum of **1c** shows the tBu(Me) at δ = 33 and tBu(C) at δ = 34 (almost overlapping), two bridging CH_2 signals at δ = 30 and 32 (not well resolved) and two OEt(Me) signals at δ = 17 and 19, in agreement with the *partial cone* conformation.

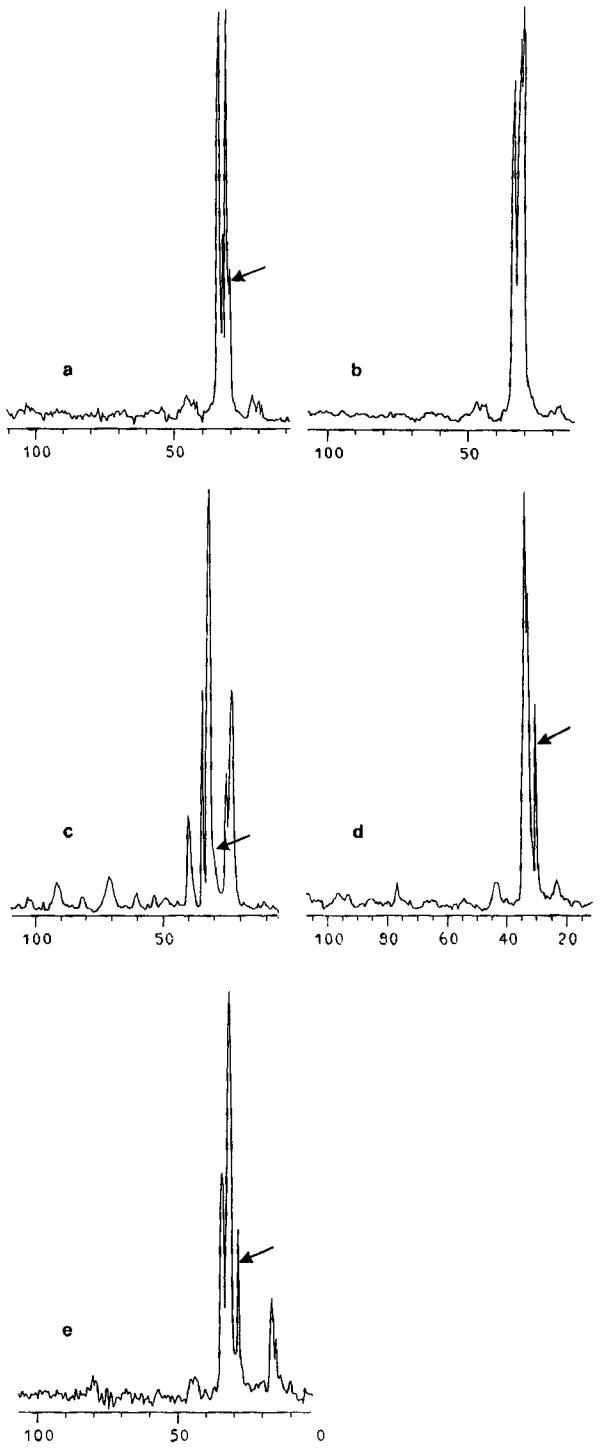

Figure 1. Partial (alkyl region) ^{13}C (CPMAS) spectra of selected calix[n]arenes (δ values). a: **1a**; b: **2a**; c: **2d**; d: **3a**; e: **3c**

The CH_2 resonance lines in the solid state NMR spectra of *n*-butylcalix[4]arene **1d** (previously shown to exist as a mixture of cone and partial cone in solution)[9] and tetraacetoxycalix[4]arene **1e** (shown to exist as a partial cone in solution)[11] are not resolved and are presumably buried under the tBu resonances at δ = 32 and 33, hence conformational information cannot be deduced.

The much larger calix[8]arene **2a** shows three sharp peaks in the alkyl region, the most upfield of which at $\delta = 30.5$ is the most intense, assigned to tBu(Me). The second most intense signal at 31.5 is attributed to tBu(C), and the most downfield signal at $\delta = 33.7$ is for the bridging CH_2's (Figure 1b). Thus all phenol rings within the macrocycle have the same relative orientation, in the solid state, in agreement with X-ray analysis of **2a**[23], and in line with ^1H DNMR studies pointing to a flat "pleated loop" structure[17].

The alkyl region of the solid state spectrum of methoxycalix[8]arene **2b** is identical with that of **1b**, indicative of similar conformational behavior, as was observed in solution[11]. Similarly, **2b** shows an identical spectrum with that of **1c**, viz. two types of bridging CH_2 absorptions, again indicative of conformational similarity.

The isopentyloxycalix[8]arene **2d** (Figure 1c) exhibits six absorptions in the alkyl region of the solid-state NMR spectrum. The two most upfield signals at $\delta = 23$ and 26 are for the iPr group. The tBu resonance lines are at $\delta = 33$ and 35, the bridging CH_2's appear as a small, rather broad peak, barely resolved from the tBu(Me) resonance at $\delta \approx 31$. A resonance at $\delta = 40$ is observed for the CH_2 attached to the iPr side chain (β position to oxygen).

The acetoxycalix[8]arene **2e** shows four absorptions in the alkyl region. The tBu(Me) at $\delta = 31$, the tBu(C) at $\delta = 35$, a singlet for the bridging CH_2's at $\delta = 33$ and one resonance for the acetyl(Me) at $\delta = 20$; in agreement with the reported solution ^{13}C spectrum of **2e**[25a], which showed single lines for the CH_2 and COMe at $\delta =$ 31.85 and 20.23, respectively.

The solid-state NMR spectrum of the intermediate-size macrocycle **3a** (Figure 1d) exhibits three resolved absorptions in the alkyl region with tBu(Me) at $\delta = 34$, the tBu(C) at $\delta = 33$ and a single resonance for the bridging CH_2's at $\delta = 30$. The origin of the change in the relative positions of tBu absorptions may be complexation to acetone (crystallization solvent). In the solution ^{13}C spectrum of **3a**, the tBu(Me) is most upfield, and a single CH_2 signal was observed at $\delta = 34$, slightly more downfield of the tBu absorptions[25b].

A distinct CH_2 signal could not be detected in the spectrum of **3b**, but the tBu(Me) line was seen upfield from the tBu(C) absorption ($\delta = 31$ and 34, respectively). Similar observations were made with **3a**, viz. a resonance for the bridging CH_2 was not observed, but the tBu ($\delta = 31$ and 35) and COMe ($\delta = 20$) signals were resolved. With **3c**, on the other hand, a single, well-resolved, resonance line is observed for the bridging CH_2's at $\delta = 28.5$ (Figure 1e); with tBu absorptions at $\delta = 31.7$ and 34.2. In addition, two OEt(Me) absorptions are seen at $\delta = 16.6$ (major) and 16 (minor).

In summary we find that ^{13}C (CPMAS) NMR provides corroboratory conformational information on calixarenes, which can be very useful in cases where X-ray structure is not available.

For *p*-(*tert*-butyl)-substituted calixarenes reported herein, the small $\Delta\delta$'s between the tBu signals and the bridging methylenes, coupled to inherently broader line widths in the solid-state NMR, makes the technique somewhat limiting. Consequently, calixarenes with sulfonato, nitro, acyl and halo substituents should be more readily amenable to solid-state NMR studies.

Finally, we note that the difference in chemical shifts between *syn*/*anti* methylenes in the partial cone conformation is three times smaller in the solid state as compared to solution (ca. 2 ppm versus 7 ppm), indicative of a conformation with reduced steric compression (in the crystal), if, as suggested[24], the origin of $\Delta\delta$ is steric.

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Experimental

The calixarenes were synthesized according to published procedures[32,33,25b,13,11]. Crystallization of **1** from toluene leads to an *endo*-calix complex[32]. In our hands, complete removal of toluene guest could not be achieved by heating in vacuo.

The identity of the compounds was confirmed by their melting points, IR and by ^1H NMR prior to recording solid-state spectra.

The NMR spectra were recorded with a GN-300 wide-bore instrument at 75.5 MHz at ambient temperature. The crystalline powder samples were loaded in Kel-F rotors and spun at ca. 2 kHz at the magic angle. A plot of tBu(Me) signal intensity versus contact time for **1** indicated 3 ms to give a maximum signal; contact time was set to this value for all measurements. A pulse delay time of 3 s and a 90° pulse of 5 μs were used. Under the above conditions and with the maximum attainable spinning of ca. 2 kHz, the aromatic and alkoxy carbons were broad and contained numerous side bands, whereas the alkyl signals were sharp and had no side bands. As only the latter region was of interest with regard to number of CH_2's, side-band suppression, which would have increased the data acquisition time, was not performed. The spectra were externally referenced relative to a standard hexamethylbenzene sample.

CAS Registry Numbers

1a: 60705-62-6 / **1b**: 105880-81-7 / **1c**: 132697-23-5 / **1d**: 133908-47-1 / **2a**: 68971-82-4 / **2b**: 82452-95-7 / **2c**: 136237-07-5 / **2d**: 136202-83-0 / **3a**: 78092-53-2 / **3b**: 98127-73-2 / **3c**: 136202-82-9 / **3e**: 78077-35-7

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