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NMR Conformational Studies of Tetraalkylated Dihomooxacalix[4]arenes

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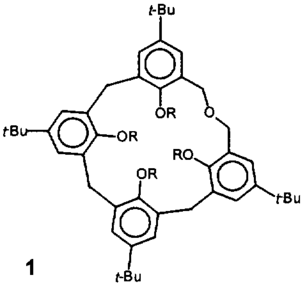
Abstract: Four tetraethers (methyl, ethyl, allyl and benzyl) of *p-tert*-butyldihomooxacalix[4]arene were synthesized and their conformational behaviour studied by means of variable temperature ^{1}H NMR, including the determination of coalescence temperatures and $\Delta G^{\neq}$. It was shown that the methyl ether still has some conformational mobility at -100 °C, the ethyl ether displays a fixed conformation at -20 °C and the other two derivatives are conformationally rigid at room temperature. The conformations obtained are the 1,2-alternate B and cone, depending on the derivative formed.

INTRODUCTION

Calixarenes are cyclic oligomers composed of phenolic units linked via the *ortho* positions by methylene bridges. The increasing interest in this compouds is due to their ability to form complexes with cations and neutral molecules. They can be obtained with different numbers of oligomeric units and, among them, the cyclic tetramer and the cyclic hexamer have been intensively studied.[1-4]

Calix[4]arenes and calix[6]arenes have cavities that are either small or too large for certain applications. The dihomooxacalix[4]arenes, where a -CH_2O- moiety is incorporated into the calix[4]arene macrocycle, and the calix[5]arenes fall between these two compounds. The *p-tert*-butylcalix[5]arene is difficult to obtain, although recently improved synthesis procedures make it available in nearly 15 % yield.[5, 6] However, the yield of *p-tert*-butyldihomooxacalix[4]arene (**1a**), first synthesized by Gutsche,[7, 8] was also enhanced up to 25 %,[9] making it into a potential host molecule after appropriate functionalization.

In this work, compound **1a** has been converted to methyl (**1b**), ethyl (**1c**), allyl (**1d**) and benzyl (**1e**) ethers and their conformational behaviour were studied by dynamic ^{1}H NMR.



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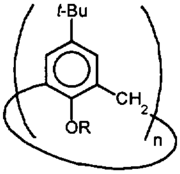


2 n = 4
3 n = 5

1, 2, 3	R
a	H
b	CH_3
c	CH_2CH_3
d	$CH_2CH{=}CH_2$
e	$CH_2C_6H_5$

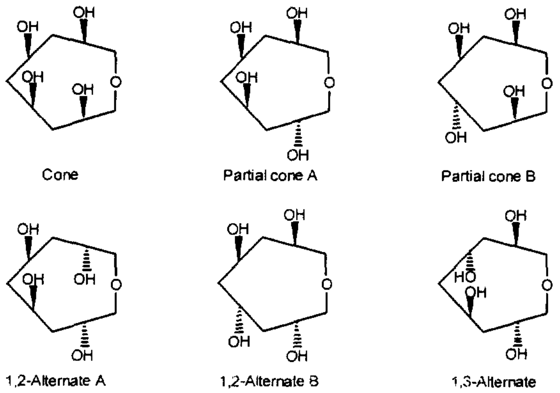
RESULTS AND DISCUSSION

Conformations of *p-tert*-butyldihomooxacalix[4]arene (1a). The parent calix[4]arenes favourably adopt a cone conformation due to strong intramolecular hydrogen bonding among the hydroxyl groups.[10] Similar cone conformation exists in the dihomooxacalix[4]arenes, although in this case the hydrogen bonding is somewhat weaker, as indicated by the OH stretching frequencies in the IR[1] (3300 cm^{-1} for compound **1a** and 3164 cm^{-1} for compound **2a**). The same frequency (3303 cm^{-1}) is observed for *p-tert*-butylcalix[5]arene.

The increased size of the annulus of compound **1a** enhances his conformational mobility. According to Gutsche *et al.*[10] **1a** is more flexible than the *p-tert*-butylcalix[4]arene and comparable to the analogous calix[5]arene, as demonstrated by the free energies of activation in chloroform solution (**2a** 15.7 Kcal mol^{-1}, **3a** 13.2 Kcal mol^{-1} and **1a** 12.9 and 13.0 Kcal mol^{-1}).

Substitution of all four phenolic hydrogen atoms of a calix[4]arene generally suppresses the conformational freedom by inhibiting the oxygen-through-the-annulus rotation and results in conformational isomers.[1] In *p-tert*-butylcalix[4]arene the n-propyl is the smallest group to inhibit this rotation.[11, 12] Calix[4]arenes and calix[5]arenes can exist in four basic conformers (cone, partial cone, 1,2-alternate and 1,3-alternate), but dihomooxacalix[4]arenes can have six different conformers (Figure 1). It is possible to distinguish by ^1H NMR between conformers with a symmetry plane (cone and 1,2-alternate A), a symmetry axis (1,2-alternate B and 1,3-alternate) and no element of symmetry (partial cone). Further conformers differentiation from ^1H NMR spectrum is quite difficult. However, with ^{13}C NMR spectra it may be possible, as one has shown for the calix[4]arenes[13] conformations and latter also observed in calix[5]arenes.[14, 15]

Mendoza *et al.*[13] have found that when adjacent aryl rings are in a syn orientation (both to the same side) the $ArCH_2Ar$ resonance appears around δ 31, and at *ca.* δ 37 when they are anti oriented (one up, one down). Assuming that it occurs in dihomooxacalix[4]arenes as well, it is possible to distinguish between the



Cone Partial cone A Partial cone B

1,2-Alternate A 1,2-Alternate B 1,3-Alternate

Figure 1 Conformations of dihomooxacalix[4]arenes.

conformations cone and 1,2-alternate A, between 1,2-alternate B and 1,3-alternate, and between partial cone A and B (see Table 1).

Table 1 ^{1}H and ^{13}C NMR spectral patterns for the conformers of *p*-*tert*-butyldihomooxacalix[4]arene

		^{1}H NMR			^{13}C NMR				
Symmetry element	Conformation	ArH	CH_2	$C(CH_3)_3$	Ar	CH_2	$\mathit{C}(\mathrm{CH}_3)_3$	$\mathrm{C}(\mathit{C}\mathrm{H}_3)_3$	$\mathrm{Ar}\mathit{C}\mathrm{H}_2\mathrm{Ar}$
Plane	Cone	2 pairs of doublets (1:1)	3 pairs of doublets (2:2:1)	2 singlets (1:1)	12	3	2	2	1 *ca.* δ 31 1 *ca.* δ 31
	1,2-Alternate A								1 *ca.* δ 31 1 *ca.* δ 37
Axis	1,2-Alternate B	2 pairs of doublets (1:1)	2 pairs of doub. and 1 singlet (2:2:1)	2 singlets (1:1)	12	3	2	2	1 *ca.* δ 31 1 *ca.* δ 37
	1,3-Alternate								1 *ca.* δ 37 1 *ca.* δ 37
None	Partial cone A	4 pairs of doublets (1:1:1:1)	5 pairs of doublets (1:1:1:1:1)	4 singlets (1:1:1:1)	24	5	4	4	1 *ca.* δ 31 1 *ca.* δ 31 1 *ca.* δ 37
	Partial cone B								1 *ca.* δ 31 1 *ca.* δ 37 1 *ca.* δ 37

Tetramethyl ether. Derivative **1b** shows, in chloroform solution at room temperature, free rotation through the annulus, that is, the rate of conformational interconversion is faster than the ^{1}H NMR time scale at that temperature.[16] It exists as a mixture of conformations, as indicated by the three sharp singlet methylene resonances (δ 4.30, 3.84 and 3.80 ppm) shown in Figure 2. With decreasing of the temperature these singlets gradually broaden and resolve into five broad peaks at -100 °C (in CD_2Cl_2).

Relatively to the tetramethyl and pentamethyl ethers of *p-tert*-butylcalix[4]arene and *p-tert*-butylcalix[5]arene respectively, the former[17, 18] is fixed at -30 °C, predominantly in a partial cone conformation and the latter[14] exists as a mixture of conformers at temperatures below -70 °C.

In the solid state, the X-ray crystallographic structure of compound **1b**[19] establish that it exists in a distorted 1,2-alternate B conformation, in which two benzene rings are almost perpendicular to the mean plane of the methylene groups, while the others two have larger inclinations.

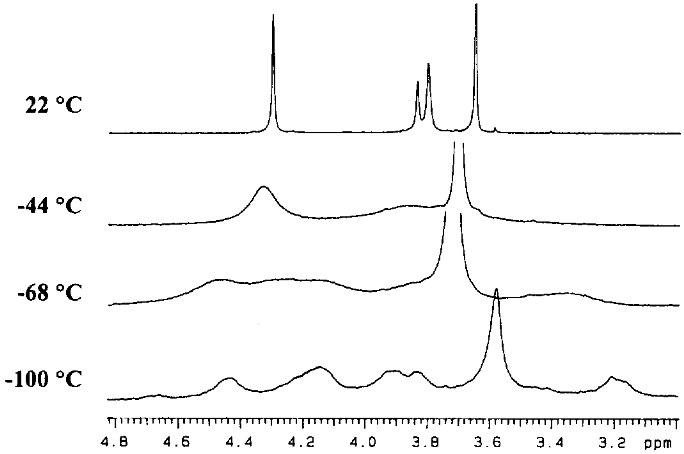


Figure 2 Variable temperature ^{1}H NMR spectrum of tetramethyl ether **1b** in CD_2Cl_2 or $CDCl_3$ at 300 MHz.

Tetraethyl ether. Compound **1c** shows a temperature dependent ^{1}H NMR spectrum. The methylenic proton pattern displayed at -20 °C in chloroform (Figure 3) is compatible with both the 1,2-alternate B and the 1,3-alternate conformations. The resonances from the CH_2 bridge protons appear as a set of two AB quartets (at δ 4.52, 4.13 with $J = 11.7$ Hz arising from CH_2OCH_2, and at δ 4.25, 3.21 with $J = 13.2$ Hz arising from $ArCH_2Ar$) and one singlet at δ 3.81 arising from the CH_2 opposite to the oxygen atom.[16] The latter singlet indicates that both methylene hydrogens are equivalent and this is only possible with the conformations having a C_2 symmetry axis (see Table 1).

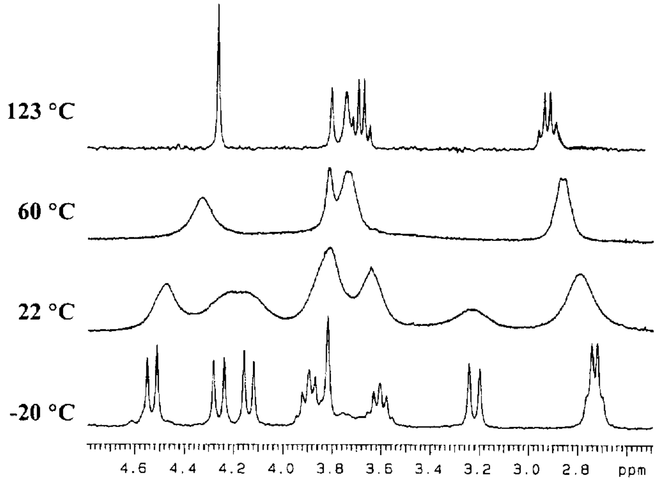


Figure 3 Variable temperature ^1H NMR spectrum of tetraethyl ether **1c** in $CDCl_3$ or DMSO at 300 MHz.

Those alternate conformations were confirmed by NOE 1D difference experiments,[16] but it was not possible to distinguish between them.

According to Mendoza *et al.*[13] the ^{13}C NMR spectrum allows to distinguish between the 1,2-alternate B and the 1,3-alternate conformations. The spectrum shows one ArCH_2Ar resonance at δ 38.4 corresponding only to one carbon atom and another at δ 27.7 corresponding to two carbon atoms. This agrees with the 1,2-alternate B conformation.

In the solid state,[19] this compound adopts the same distorted 1,2-alternate B conformation as found for **1b**. This situation is also observed in solution at -20 °C. In effect, the ^1H NMR spectrum at this temperature shows a high field position (δ 0.17 ppm) for one of the two CH_3 resonances of the ethoxy groups, indicating that two shielded ethoxy groups are pointing inside the cavity.

In other solvents, like acetone, DMSO and pyridine, the proton spectra remain also compatible with the two alternates conformations.

The proton spectra recorded at higher temperatures show increasingly higher conformational interconversion rates, as demonstrated by the broad singlets assignable to the CH_2 resonances (Figure 3). The spectrum becomes sharp at 123 °C in DMSO.

At room temperature the ethyl ether **2c** is fixed in a partial cone conformation,[17] while the ethyl ether **3c** has a coalescence temperature of - 33 °C.[14] Again, the mobility of **1c** lies between that of this two derivatives, with a coalescence temperature (T_C) of 49 °C and a free energy of activation ($\Delta G^{\ddagger}$) for the conformational inversion of 15.0 Kcal mol^{-1} (Table 2).

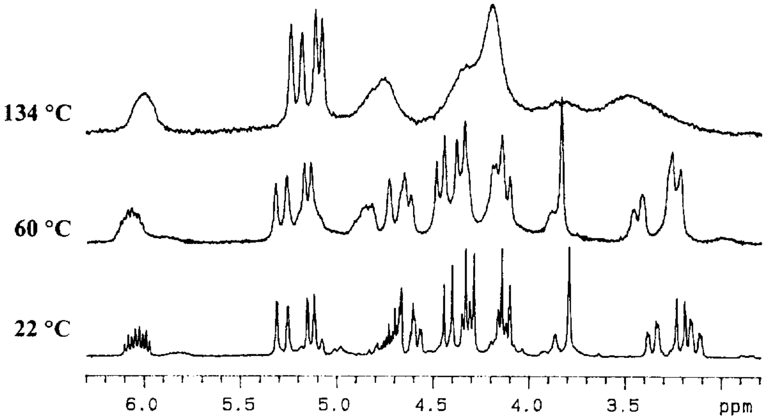


Figure 4 Variable temperature ^{1}H NMR spectrum of tetraallyl ether **1d** in $CDCl_3$ or $CDCl_2CDCl_2$ at 300 MHz.

Tetraallyl ether. The ^{1}H NMR spectrum of **1d** at room temperature in chloroform shows a complex pattern in the δ 3-6 ppm region (Figure 4) due to the overlapping resonances from the methylene groups of the calixarene ring and the allyl groups. However, the CH_2 spectral pattern is compatible with both the 1,2-alternate B and the 1,3-alternate conformations.

The previous ^{1}H NMR spectrum displays two AB quartets (at δ 4.44, 4.13 with J = 12.7 Hz arising from CH_2OCH_2, and at δ 4.32, 3.23 with J = 13.1 Hz arising from $ArCH_2Ar$) and one singlet at δ 3.81 arising from the CH_2 opposite to the oxygen atom. These assignments were confirmed in the COSY spectrum shown in Figure 5.

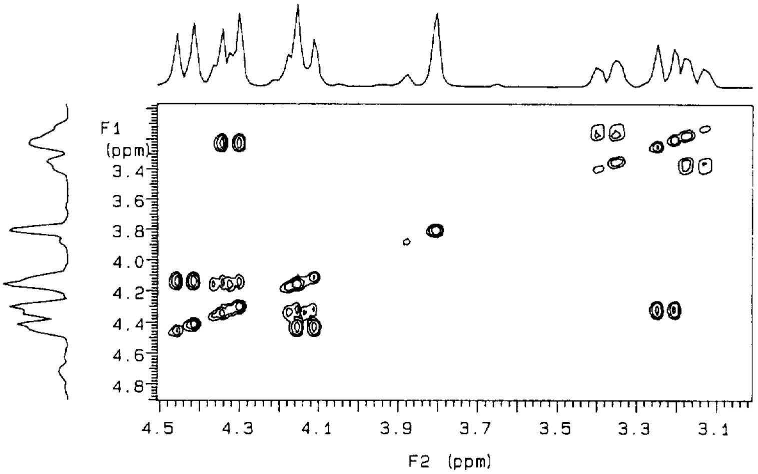


Figure 5 ^{1}H NMR and COSY spectra of compound **1d** in $CDCl_3$ at 22 °C and 300 MHz.

Furthermore, the 1,2-alternate B conformation was confirmed by the ^{13}C NMR spectrum, which bears one ArCH_2Ar resonance at δ 38.5 corresponding to one carbon atom and another at δ 28.5 corresponding to two carbon atoms. In the solid state, this allyl ether adopts a more regular 1,2-alternate B conformation, as shown by its X-ray crystallographic structure.[19]

When the temperature is raised to 60 °C the spectrum becomes less well resolved and at 134 °C (in $CDCl_2CDCl_2$) the peaks collapse into broad signals, passing through a coalescence point at 122 °C corresponding to a $\Delta G^{\ddagger}$ of 18.5 Kcal mol^{-1}. Unlike, tetraether **2d**[17] remains in a fixed cone conformation with the increase of the temperature, while pentaether **3d**[14] is still conformationally mobile at room temperature.

Tetrabenzyl ether. Compound **1e** shows, at room temperature in chloroform, an ^{1}H NMR spectrum that is only compatible with conformations having a symmetry plane. The spectrum displays, besides the two previous AB quartets (at δ 4.70, 4.42 with J = 11.1 Hz arising from CH_2OCH_2, and at δ 4.30, 2.98 with J = 13.6 Hz arising from $ArCH_2Ar$) another AB quartet (at δ 4.18, 3.02 with J = 12.5 Hz) corresponding to only two protons and arising from the CH_2 opposite to the oxygen atom. This third AB quartet indicates the nonequivalence of the methylene hydrogens presents in conformations having a symmetry plane.

The ^{13}C NMR spectrum points out to a cone conformation, showing two ArCH_2Ar resonances at δ 31.1 (one carbon atom) and at δ 29.5 (two carbon atoms).

Further evidence for this conformation was obtained from a series of 1D NOE differences experiments, as shown in Figure 6.

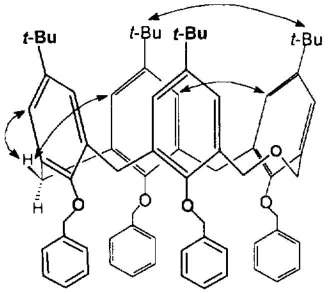


Figure 6 Relevant NOE enhancements for compound **1e**.

In the absence of a suitable crystal for the X-ray crystallographic structure determination, some molecular dynamics and molecular mechanics calculations were performed, using the DISCOVER program.[20] The lowest energy conformer obtained for **1e** is the 1,3-alternate, and the cone conformation shows the biggest energy. These calculations do not reproduce the experimental NMR data. In effect, the electrostatic repulsions between the benzyl groups dominate the energy, making the alternate conformations the most stable, as they are the conformations in which fewer benzyl groups are close to each others.

Furthermore, the calculations shown that the interaction of the benzyl groups would force the preferential adoption of any other conformation except the cone, if the benzyl groups could swing through the annulus. So, the obtained cone conformation in solution for **1e**, can be rationalised by assuming that during the stepwise substitution reaction the free OH groups remain attached by strong intramolecular hydrogen bonding.

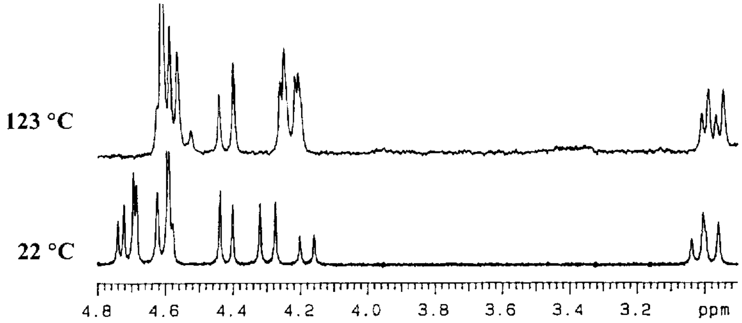


Figure 7 Variable temperature ^{1}H NMR spectrum of tetrabenzyl ether **1e** in $CDCl_3$ or DMSO at 300 MHz.

The cone conformation remains unchanged up to temperatures as high as 123 °C in DMSO (Figure 7). Thus, benzyl group seems to be large enough to prevent the rotation of the aryl units and calixarene **1e** is conformationally rigid. In both calixarenes **2e**[17,21] and **3e**[14] the same cone conformation was found.

In other solvents, like acetone and pyridine, the proton spectra remain compatible with a fixed cone conformation to temperatures as high as 49 °C in acetone and 113 °C in pyridine (Figure 8). This was expected, since the polarity of the solvent has practically no effect on the conformation of this type of derivatives.

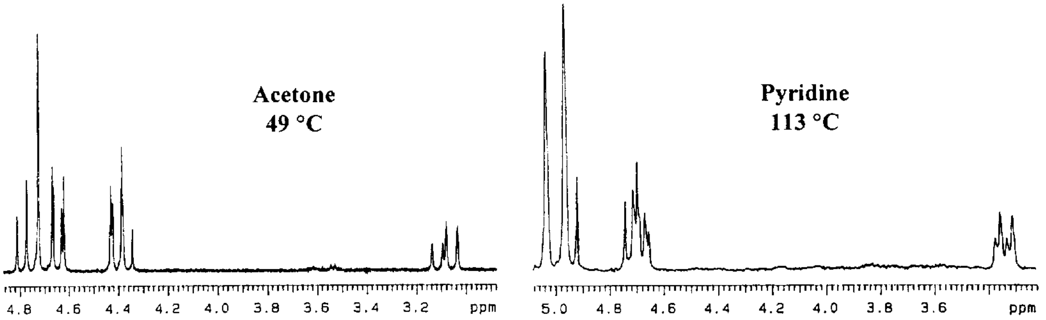


Figure 8 300 MHz ^{1}H NMR spectrum of tetrabenzyl ether **1e** in acetone at 49 °C and pyridine at 113 °C.

CONCLUSIONS

p-tert-Butyldihomooxacalix[4]arene is conformationally mobile at room temperature, but upon conversion to its ether derivatives, the mobility decreases and some of them are rigid at room temperature.

Dihomooxacalix[4]arene tetraethers (**1b** - **1e**) show an intermediate behaviour between the homologous derivatives of calix[4]arenes and calix[5]arenes, for their conformational characteristics. As the size of R group increases from Me to Bz, the barrier to conformational inversion ($\Delta G^{\ddagger}$) increases and, therefore the conformational mobility decreases, being the tetraallyl rigid at room temperature and the tetrabenzyl conformationally fixed.

It is observed that, in contrast to most of the tetrasubstituted calix[4]arenes isolated in the cone or in the partial cone conformation,[22] the dihomooxacalix[4]arene derivatives in which the alkyl group substituent can swing through the annulus, prefer the 1,2-alternate B conformation (see Table 2), as for the calix[5]arene derivatives.[14] However, it was also shown that the three benzyl ethers **1e**, **2e** and **3e** are obtained in the cone conformation.

Table 2 Conformational features of *p-tert*-butyldihomooxacalix[4]arene tetraethers

Compound	Conformation		T_c[23]	$\Delta G^{\ddagger}$[24]	Solvent
	Solution	Solid state[19]	(°C)	(Kcal mol^{-1})	
Methyl (**1b**)	mixture	1,2-alternate B	-56	10.0	$CDCl_3$
Ethyl (**1c**)	1,2-alternate B	1,2-alternate B	49	15.0	$CDCl_3$
Allyl (**1d**)	1,2-alternate B	1,2-alternate B	122	18.5	$CDCl_2CDC_2$
Benzyl (**1e**)	cone	—	»130	»20	$CDCl_2CDCl_2$

EXPERIMENTAL

Melting points were measured on an Electrothermal 9200 apparatus. TLC analyses were carried out on Merck silica gel 60 F_{254} plates (layer thickness 0.2 mm). ^1H and ^{13}C NMR spectra were recorded on a Varian Unity 300 spectrometer with TMS as internal reference. The NOE 1D difference spectra were acquired with a saturation delay of 5 s and 256 transients. COSY 45 spectrum was collected as a 256 x 2K complex points. A relaxation delay of 1.5 s and a sine filter in both dimensions were used. All temperatures were corrected to MeOH or ethylene glycol, and the readouts are considered accurate to ± 1 °C. FAB Mass spectra were obtained on a VG Trio 2000 quadrupole instrument, using *m*-nitrobenzyl alcohol as a matrix.

Compounds **1b** and **1c** were already described in reference 16. However, they were prepared as **1d** using methyl or ethyl iodide respectively, as the alkylating agent.

7,13,19,25-tetra-*tert*-butyl-27,28,29,30-tetraallyloxy-2,3-dihomo-3-oxacalix[4]arene (1d). 1 g (1.48 mmol) of *p-tert*-butyldihomooxacalix[4]arene (**1a**) in 55 mL of THF-DMF (10:1, v/v) solution, was treated with 1.67 g (42 mmol) of NaH (60 % oil dispersion) and 8.65 mL (100 mmol) of allyl bromide. The mixture was refluxed for 2.5 h in an atmosphere of N_2. After cooling, the solvent was evaporated and the residue was poured into 200 mL of water and then extracted with $CHCl_3$. The organic layer was washed with water, dried with anhydrous Na_2SO_4 and concentrated to a crude product. Recrystallization from DMF furnished crystals of **1d** in 62 % yield: mp 128-129 °C; ^1H NMR ($CDCl_3$) δ 7.42 (d, 2H, ArH), 7.24 (2d, 4H, ArH), 7.18 (d, 2H, ArH), 6.04 (m, 2H, HC=), 5.30 (m, 2H, *trans* H_2C=, *J*=17.2 Hz), 5.15 (m, 2H, *cis* H_2C=, *J*=10.5 Hz), 4.80-4.57 (m, 6H, HC= and *trans*, *cis* H_2C=), 4.44 (d, 2H, CH_2OCH_2, *J*=12.7 Hz), 4.34 (m, 2H, CH_2C=), 4.32 (d, 2H, $ArCH_2Ar$, *J*=13.1 Hz), 4.15 (m, 2H, CH_2C=), 4.13 (d, 2H, CH_2OCH_2, *J*=12.7 Hz), 3.81 (s, 2H, $ArCH_2Ar$), 3.37 (m, 2H, CH_2C=), 3.23 (d, 2H, $ArCH_2Ar$, *J*=13.1 Hz), 3.15 (m, 2H, CH_2C=), 1.35, 1.29 (2s, 36H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 153.5, 152.8, 145.9, 144.8, 135.3, 133.5, 133.0, 130.3 (Ar), 135.5, 135.0, 127.7, 127.5, 125.4, 125.1 (ArH and HC=), 116.8, 112.9 (H_2C=), 74.9, 72.9 (*C*H_2C=), 63.9 (CH_2OCH_2), 38.5 ($ArCH_2Ar$), 34.3, 34.2 (*C*$(CH_3)_3$), 31.59, 31.55 (C(*C*$H_3)_3$), 28.5 ($ArCH_2Ar$); MS m/z 838. Anal. Calcd for $C_{57}H_{74}O_5$: C, 81.58; H, 8.89. Found: C, 81.29; H, 8.78.

7,13,19,25-tetra-*tert*-butyl-27,28,29,30-tetrabenzyloxy-2,3-dihomo-3-oxacalix[4]arene (1e). A suspension of 0.48 g (12 mmol) of NaH (60 % oil dispersion) and 1 g (1.48 mmol) of *p-tert*-butyldihomooxacalix[4]arene (**1a**) in 56 mL of THF-DMF (7:1, v/v) was stirred in an atmosphere of N_2. After 15 min. a solution of 1.43 mL (12 mmol) of benzyl bromide in 10 mL THF was added, and the mixture was refluxed and stirred for 2.5 h. Following as previous described, it was obtained 0.98 g (64 %) of **1e** as a white powder after recrystallization from MeOH: mp 167-168 °C; ^1H NMR ($CDCl_3$) δ 7.52 (2d, 4H, OCH_2Ar***H***), 7.31-6.97 (m, 16H, OCH_2Ar***H***), 7.05 (2d, 4H, ArH), 6.99 (d, 2H, ArH), 6.63 (d, 2H, ArH), 4.72 (d, 2H, OC***H***$_2$Ar, *J*=13.7 Hz), 4.70 (d, 2H, CH_2OCH_2, *J*=11.1 Hz), 4.60 (d, 2H, OC***H***$_2$Ar, *J*=13.7 Hz), 4.59 (s, 4H, OC***H***$_2$Ar), 4.42 (d, 2H, CH_2OCH_2, *J*=11.1 Hz), 4.30 (d, 2H, $ArCH_2Ar$, *J*=13.6 Hz), 4.18 (d, 1H, $ArCH_2Ar$, *J*=12.5 Hz), 3.02 (d, 1H, $ArCH_2Ar$, *J*=12.5 Hz), 2.98 (d, 2H, $ArCH_2Ar$, *J*=13.6 Hz), 1.23, 0.91 (2s, 36H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 151.6, 151.4, 145.3, 145.1, 138.6, 137.4, 134.6, 133.7, 133.5, 131.6 (Ar), 129.6, 128.8, 128.2, 127.9, 127.6, 127.5, 126.3, 125.73, 125.67, 124.1 (ArH), 76.6, 75.4 (O*C*H_2Ar), 69.7 (CH_2OCH_2), 34.09, 34.03 (*C*$(CH_3)_3$), 31.5 (C(*C*$H_3)_3$), 31.1, 29.5 ($ArCH_2Ar$); MS m/z 1038. Anal. Calcd for $C_{73}H_{82}O_5$: C, 84.35; H, 7.95. Found: C, 84.45; H, 7.98.

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23 Due to overlapping of the resonances from the two kinds of methylene groups (CH_2OCH_2 and $ArCH_2Ar$) and from the alkyl group substituent, it was difficult to distinguish between the two coalescence temperatures. Consequently, the T_C measured (accuracy of ± 4 °C) is an average temperature between the two coalescence points of the two methylene groups.

24 The rate of inversion (K_C) at the coalescence temperature was estimated from the equation $K_C = 2.22\ (\Delta\nu^2 + 6\ J_{AB}^2)^{1/2}$. Two K_C were obtained from the two kinds of methylenic protons. An average of this values was used in the determination of $\Delta G^{\ddagger}$. The J_{AB} values observed for compound **1c**, 11.7 and 13.2 Hz, were used in compound **1b**.

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