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Paula M. Marcos[a]; José R. Ascenso[b]; Roger Lamartine[c]; J. L. C. Pereira[d]
[a] Departamento de Química, Faculdade de Ciĕncias de Lisboa, Fac. Farmácia Univ. Lisboa, Lisboa, Portugal [b] Departamento de Química, Faculdade de Ciĕncias de Lisboa, Inst. Superior Técnico, Lisboa, Lisboa, Portugal [c] Departamento de Química, Faculdade de Ciĕncias de Lisboa, Univ. Claude Bernard, Lyon, France, Lisboa, Portugal [d] Departamento de Química, Faculdade de Ciĕncias de Lisboa, Fac. Ciĕncias Univ. Lisboa., Lisboa, Portugal

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# Synthesis and NMR conformational studies of *p-tert*-butyldihomooxacalix[4]-arene derivatives

PAULA M. MARCOS*[1], JOSÉ R. ASCENSO[2], ROGER LAMARTINE[3] and J. L. C. PEREIRA[4]

[1]*Fac. Farmácia Univ. Lisboa and Departamento de Química, Faculdade de Ciências de Lisboa, R: Escola Politécnica, 58, 1200 Lisboa, Portugal,* [2]*Inst. Superior Técnico, Lisboa,* [3]*Univ. Claude Bernard, Lyon, France and* [4]*Fac. Ciências Univ. Lisboa.*

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**The tetramethyl (2) and tetraethyl (3) ethers, and the tetraacetate (4) derivatives of the *p-tert*-butyldihomooxacalix[4]arene were prepared. The mobility of these compounds studied by temperature-dependent $^1$H NMR spectroscopy. For the tetraacetate derivative, at room temperature, 1,2- or 1,3-alternate conformations are suggested. Those conformations were confirmed by NOE difference and COSY spectra for the tetraethyl ether derivative in $CDCl_3$ at -20°C.**



## INTRODUCTION

Calixarenes are macrocycles prepared by base-induced condensation of *p*-alkylphenols, mainly the *p-tert*-butylphenol, and formaldehyde. They can be obtained in ring sizes ranging from 4 to 10 aromatic units.[1]

The most common compounds, calix[4]arenes and calix[6]arenes, have cavities that are either small or too large for certain applications. The calix[5]arene is difficult to obtain, but in the condensation reaction of *p-tert*-butylphenol and formaldehyde a cyclic tetramer was also isolated where a methylene bridge ($-CH_2-$) is replaced by a dimethyleneoxa bridge($-CH_2OCH_2$). The resulting compound, designated as *p-tert*-butyldihomooxacalix[4]arene (**1**), was first synthesized by Gutsche,[2,3] and its synthesis recently optimized.[4]

This compound has a bigger cavity, and consequently shows an increased conformational mobility.[5] This fact suggests an improvement over the calix[4]arenes, as an includer or carrier of ions.

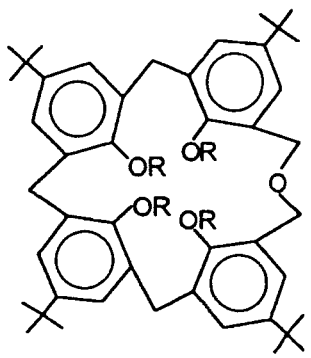
Three derivatives of the *p-tert*-butyldihomooxacalix[4]arene were synthesized: the tetramethyl (**2**) and tetraethyl (**3**) ethers, and the tetraacetate (**4**). A temperature-dependent $^1$H NMR spectroscopic study was carried out with the ethyl ether derivative.

## RESULTS AND DISCUSSION

The tetramethyl ether derivative (**2**) shows, in chloroform solution at room temperature, free rotation through the ring; that is, the rate of conformational interconversion is faster than the $^1$H NMR time scale at that temperature. Three sharp singlet methylene resonances (δ 4.30, 3.84 and 3.80 ppm) were obtained, as shown in Fig. 1.

The tetraethyl ether derivative (**3**), also in chloroform, shows at 50°C and room temperature, a slow conformational interconversion rate, as demonstrated by the set of broad singlets assignable to the $CH_2$ resonances (Figs. 2a and b). The mixture of conformations collapses at -20°C to a fixed conformation.

The $^{13}$C NMR at -20°C indicates the complete symmetry of the molecule, and the $^1$H spectrum shows two ethyl groups strongly shielded: $CH_3$ (triplet) at 0.17 ppm. This suggests either two 1,2- or one 1,3-alternate




**1** R = H

**2** R = $CH_3$

**3** R = $CH_2CH_3$

**4** R = $COCH_3$

*To whom correspondence should be addressed.

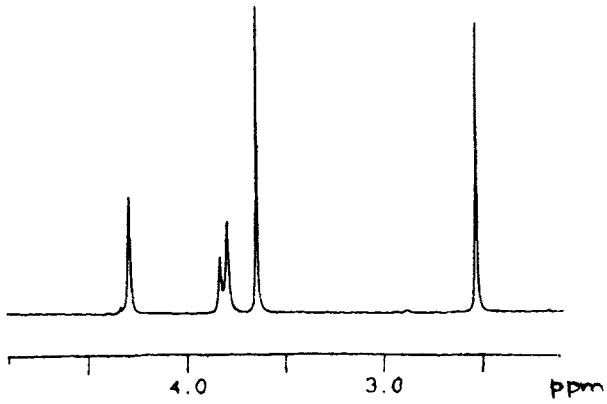



**Figure 1** Partial 300 MHz $^1$H NMR spectrum of the tetramethyl ether derivative (**2**) in $CDCl_3$ solution at 24°C.

conformation (**A**, **B** and **C**, respectively, Figure 3) are possible, with two of the ethyl groups lying in the shielding zone of the benzenic rings. 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. The latter singlet indicates that both methylene hydrogens are equivalent and this is only compatible with the alternate conformations **B** and **C** of Figure 3, having a $C_2$ symmetry axis going through the oxygen bridge and the opposite methylene group.

NMR further demonstrates that rotation around the O-$CH_2$ bond in the ethyl groups is hindered. This is indicated by the non-equivalence of the methylene hydrogens at δ 3.88 and 3.60, and at δ 2.73 ppm.

Proton-proton correlations observed in the COSY spectrum of Fig. 4 have confirmed the previous assignements.

Further evidence for those alternate conformations was derived from a series of 1D NOE difference experiments at -20°C, where the relevant proton resonances in the spectrum were saturated. The relevant NOE enhancements used to probe the alternate conformation **C** in Figure 5 are also compatible with the alternate conformation **B**.

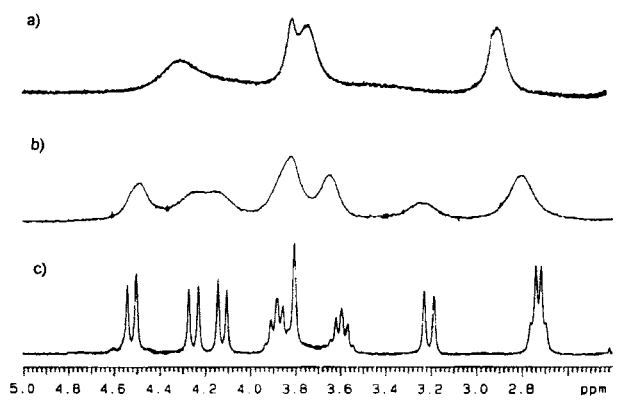



**Figure 2** Partial 300 MHz $^1$H NMR spectra of the tetraethyl ether derivative (**3**) in $CDCl_3$ solution. a) 50°C b) 24°C c) -20°C.

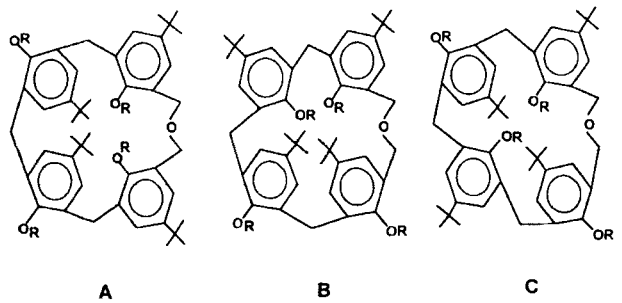



**Figure 3** 1,2- and 1,3-alternate conformations.

A fixed conformation was obtained, at room temperature in chloroform solution, for the tetraacetate derivative (**4**), demonstrating that the acetate group is large enough to stop the conformational interconversion at room temperature.

This derivative shows also two AB quartets and one singlet (doublets at δ 4.46, 4.14 with $J$ = 12.0 Hz and δ 3.63, 3.33 with $J$ = 13.8 Hz, and the singlet at 3.77 ppm) for $CH_2$ protons resonances. There is also a strongly shielded singlet (0.92 ppm) corresponding to two methyl from the acetate groups (Fig. 6). This pattern also supports the two previous alternate conformations.

## CONCLUSIONS

The tetramethyl (**2**) and the tetraethyl (**3**) ethers of the *p-tert*-butyldihomooxacalix[4]arene have NMR properties displaying greater mobilities than the equivalent derivatives of the *p-tert*-butylcalix[4]arene.[6-8]

For the tetraethyl derivative of the *p-tert*-butylcalix[4] arene a fixed partial cone conformation exists[6] at room temperature. With the homologous homooxa derivative (**3**), only at -20°C is a fixed conformation obtained.

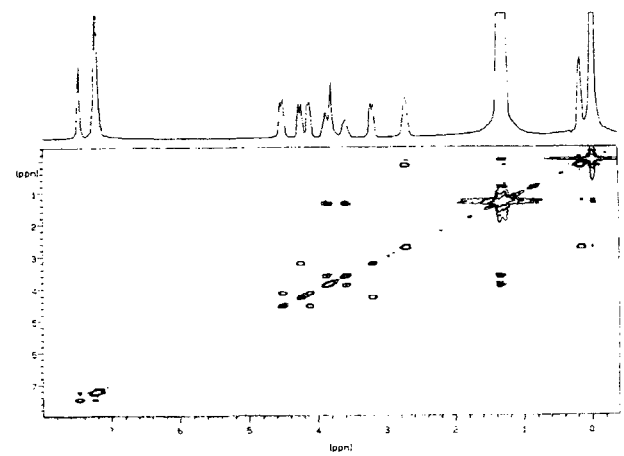


**Figure 4** $^1$H NMR and COSY spectra of the tetraethyl ether derivative (**3**). 300 MHz, $CDCl_3$, -20°C.

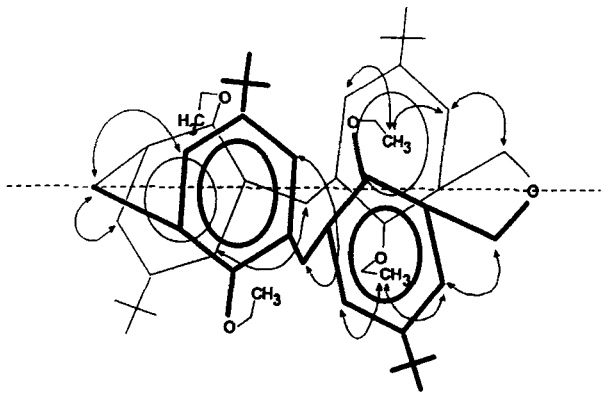


Figure 5 Relevant NOE enhancements for the ethyl derivative (3).

1D NOE difference experiments support the attribution of two alternate conformations (**B** and **C**) for this derivative.

The homooxa tetraacetate (**4**) has a NMR that also agrees with the same alternate conformations.

In both ethyl and acetate homooxa derivatives, two of the four methyl groups are strongly shielded, showing their inclusion inside the cavity, probably due to solvent effects.

## EXPERIMENTAL

Melting points were measured on a Electrothermal 9200 apparatus. Infrared spectra were obtained as KBr pellets on a Perkin Elmer 1760 FTIR spectrometer. $^1H$ and $^{13}C$ NMR spectra were recorded on a Varian Unity 300 spectrometer with TMS as internal reference and $CDCl_3$ as solvent. In the NOE difference experiments proton resonances were presaturated with low power for 2 s. COSY −45 spectrum was collected as a 256 × 2K complex points. Mass spectra were obtained on a MS 9 updated with V.G. console.

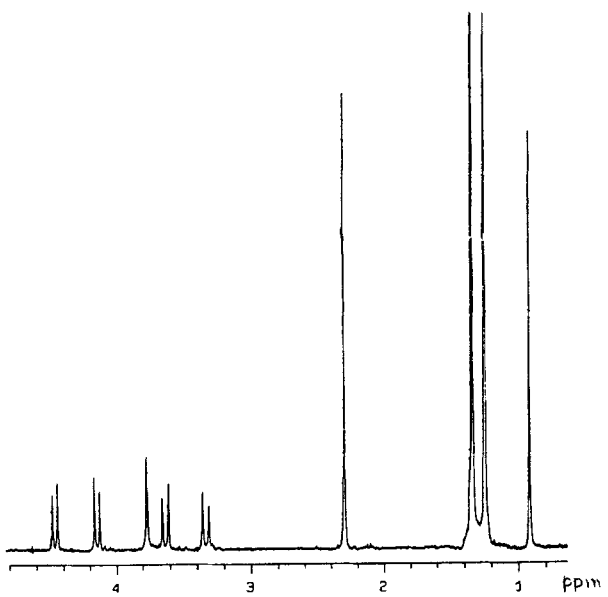



Figure 6 Partial 300 MHz $^1H$ NMR spectrum of the tetraacetate derivative (4) in $CDCl_3$ solution at 24°C.

### 7,13,19,25-tetra-*tert*-butyl-27,28,29,30-tetramethoxy-2,3-dihomo-3-oxacalix[4]arene (2)

1 g of dihomooxacalix[4]arene **1** in THF (50 ml) - DMF (5 mL) solution was treated with 1 g of NaH (60% in oil) and 10 mL of $CH_3I$. The mixture was refluxed for 2 h, then cooled and the THF evaporated. The residue was treated with 200 mL of water and then extracted with $CHCl_3$. The organic extract was washed with water, dried and concentrated to a solid residue. Recrystallization of the product from DMF furnished crystals of **2** (78% yield). m.p. 160-161.5°C; IR (KBr) 1200, 1107, 1077 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.29-6.94 (m, 8H, ArH), 4.30 (s, 4H, $CH_2OCH_2$), 3.84 (s, 2H, Ar $CH_2Ar$), 3.80 (s, 4H, Ar $CH_2Ar$), 3.65 (s, 6H, $OCH_3$), 2.54 (s, 6H, $OCH_3$), 1.31-1.21 (2 s, 36H, $C(CH_3)_3$); $^{13}C$ NMR ($CDCl_3$) δ 155.5, 154.3, 145.4, 145.0, 134.9, 133.2, 133.0, 130.3, 128.1, 126.6, 126.0, 125.6 (Ar), 65.6 ($CH_2OCH_2$), 60.7, 60.4 ($OCH_3$) 34.1, 34.0 ($C(CH_3)_3$), 31.7 ($ArCH_2Ar$), 31.6, 31.5 ($C(CH_3)_3$); 29.7 ($ArCH_2Ar$); mass spectrum (FAB, nitrobenzyl alcohol), m/e 734.

### 7,13,19,25-tetra-*tert*-butyl-27,28,29,30-tetraethoxy-2,3-dihomo-3-oxacalix[4]arene (3)

This compound was prepared as described for the previous. It was obtained as crystals in 88% yield. m. p. 166-167°C; IR (KBr) 1200, 1106, 1076; $^1H$ NMR ($CDCl_3$, -20°C) δ 7.48 (d, 2H, ArH), 7.24 (d, 4H, ArH), 7.20 (d, 2H, ArH), 4.55, 4.51 (d, 2H, $CH_2OCH_2$), 4.28, 4.24 (d, 2H, $ArCH_2Ar$), 4.15, 4.11, (d, 2H, $CH_2OCH_2$), 3.90-3.86 (quint., d 2H, $OCH_2CH_3$), 3.81 (s, 2H, $ArCH_2$ Ar), 3.63-3.56, (quint., 2H, $OCH_2CH_3$), 3.24, 3.19 (d, 2H, $ArCH_2Ar$), 2.75-2.68 (m., 4H, $OCH_2CH_3$), 1.35, 1.29 (2s, 36H, $C(CH_3)_3$), ≈ 1.30 (t, 6H, $OCH_2CH_3$) 0.19-0.15 (t, 6H, $OCH_2CH_3$); $^{13}C$ NMR ($CDCl_3$, -20°C) δ 153.6, 153.0, 145.5, 144.0, 135.4, 133.2, 133.2, 129.8, 127.9, 127.1, 125.5, 125.0 (Ar), 69.1, 68.9 ($OCH_2CH_3$), 64.7 ($CH_2OCH_2$), 38.4 ($ArCH_2Ar$), 34.2, 34.0 ($C(CH_3)_3$), 31.5, 31.5 ($C(CH_3)_3$), 27.7 ($ArCH_2Ar$), 16.1, 15.3 ($OCH_2CH_3$); mass spectrum (FAB, nitrobenzyl alcohol), m/e 790.

### 7,13,19,25-tetra-*tert*-butyl-27,28,29,30-tetraacetate-2,3-dihomo-3-oxacalix[4]arene (4)

In a three-necked round bottomed flask under a nitrogen atmosphere, 0.5 g of the calixarene **1** was dissolved in 20 mL of pyridine and 0.6 mL of acetyl chloride was slowly added. The solution was stirred for 1 h at room temperature and then refluxed for 3 h. After cooling, the pyridine was evaporated, the residue taken up in $CH_2Cl_2$ and the organic phase successively washed with $NaHCO_3$ satu-

rated solution (25 mL), $H_2O$ (25 mL), HCl 1N (2 × 25 mL) and several times with water until pH 6-7. The $CH_2Cl_2$ solution was then dried and evaporated to give a solid product, that was three times recrystallized from ethanol 96%. m.p. 306-307°C; IR. (KBr) 1759, 1090; $^1$H NMR ($CDCl_3$) δ 7.37-7.04 (m, 8H, ArH), 4.49, 4.45 (d, 2H, $CH_2OCH_2$), 4.17, 4.13 (d, 2H, $CH_2OCH_2$), 3.77 (s, 2H, $ArCH_2Ar$), 3.66, 3.61 (d, 2H, $ArCH_2Ar$), 3.36, 3.31 (d, 2H, $ArCH_2Ar$), 2.30 (s, 6H, $COCH_3$) 1.34-1.24 (2s, 36H, $C(CH_3)_3$), 0.92 (s, 6H, $COCH_3$); $^{13}$C NMR ($CDCl_3$) δ 169.7, 169.1 (CO), 148.5, 147.7, 145.6, 145.3, 133.4, 132.0, 131.9, 128.8, 127.5, 126.5, 126.4, 124.7 (Ar), 70.7 ($CH_2OCH_2$), 38.2 ($ArCH_2Ar$), 34.4, 34.3 ($\mathbf{\mathit{C}}(CH_3)_3$), 31.5, 31.4 ($C(\mathbf{\mathit{C}}H_3)_3$), 31.3 ($ArCH_2Ar$), 21.1, 19.9 ($COCH_3$); mass spectrum (FAB, nitrobenzyl alcohol), m/e 846.

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