Pergamon

Tetrahedron Letters, Vol. 37, No. 33, pp. 5959-5962, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01287-7

Syntheses of *p-tert*-Butyloxocalix[4]-, [5]-, and [6]arenes and Their Behavior in Solution

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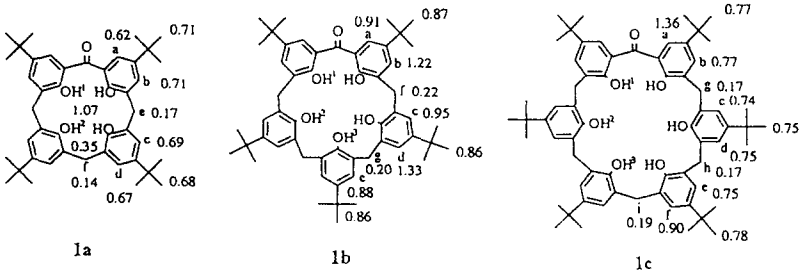
Abstract : *p-tert*-Butyloxocalix[4]-, [5]-, and [6]arenes were synthesized by a stepwise procedure. NMR studies demonstrated that strong intramolecular hydrogen bonding between the bridging CO and neighboring phenolic OH groups in the oxocalixarenes weakened the circular hydrogen bonding of the parent calixarenes, resulting in greater conformational flexibility of the oxocalixarenes. Copyright © 1996 Elsevier Science Ltd

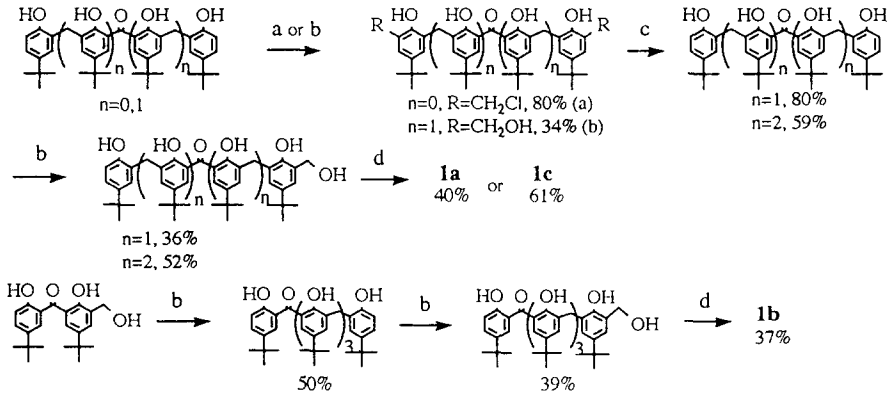
Numerous works have been done on the modification of the so-called "lower rim" and the "upper rim" of calixarenes to develop their potential as versatile synthetic hosts.[1] The methylene bridge(s) is of choice as the sites to be modified, but only a few approaches to the subject have been made. Thus, quite recently, calix[4]arenes bearing alkyl or aryl groups at the methylene bridge were synthesized.[2,3] Besides, Moshfegh *et al.*[4] have described CrO_3 oxidation of the methylene bridges of *p*-chlorocalix[4]arene acetate. Hydrolysis of the product reportedly yielded the tetraoxocalixarene, but no spectral data were given for the characterization. Independently, Ninagawa *et al.*[5] have reported the synthesis of *p-tert*-butyloxocalix[4]- (**1a**) and [6]arenes (**1c**) from the parent calixarenes (**2**) in the similar manner. Görmar *et al.*,[6] however, failed to reproduce the method, the fully CO-bridged calixarene being formed in the attempted preparation of **1a**.

We synthesized *p-tert*-butyloxocalix[n]arenes **1** (**a**: n=4; **b**: n=5; **c**: n=6) unambiguously by a stepwise procedure *via* the corresponding CO-bridged acyclic analogs;[7] hydroxymethylation of the carbonyl compounds, followed by acid-catalyzed cyclization under high dilution conditions



1a 1b 1c

Fig. 1. T_1 values [s] of **1**



Scheme 1. a) (HCHO)n, HCl, H_3PO_4, AcOH, 100°C. b) 35%HCHOaq, 20%NaOHaq, dioxane or methanol, 60°C. c) *p-tert*-butylphenol (or *p-tert*-butylphenol-formaldehyde trimer), *p*-TsOH, benzene, reflux. d) HCl, AcOH, high dilution conditions ($0.5\sim1.2\times10^{-3}$ M), reflux.

(Scheme 1). The yields in the cyclization are in the range of 37-61%.

The oxocalixarene **1a** forms crystalline inclusion complexes with some organic solvents; 2:1 (host:guest) complexes with benzene, toluene, dioxane, and 1,2-dichloro- and 1,2-dibromoethanes, while no complexes with acetone, methanol, and dichloromethane. The behavior is in sharp contrast with that of the parent calixarene **2a** which forms 1:1 complexes with benzene, toluene, dioxane, dichloromethane, and the dihaloethanes, and 1:2 complexes with acetone and methanol.

Inspection of the IR and ^{1}H NMR spectral data[8] shows that the circular hydrogen bonding characteristic of calixarenes is appreciably weakened by strong intramolecular hydrogen bonding between the phenolic OH and bridging CO groups in the oxocalixarene molecules. For example, the IR spectra of **1** in $CHCl_3$ display OH stretching bands at 3290-3307cm^{-1} (**1c<1a<1b**); the parent calixarenes **2** show the bands in the 3150-3280cm^{-1} region.[9] Variable temperature ^{1}H NMR study as described below suggests that **1** are conformationally much more mobile than **2**, being reflected the weakening the circular hydrogen bonding.

The oxocalixarene **1a** exhibits two CH_2 carbon signals at δ 30.4 and 32.1 in the ^{13}C NMR spectrum indicative of *syn*-oriented adjacent phenol rings in calix[4]arenes,[10] while two singlets for the CH_2 protons (δ 3.94 and 4.00 in a 1:2 ratio) and two OH signals (δ 8.57 and 11.44; 1:1) in the ^{1}H NMR spectrum (270 MHz; $CDCl_3$). The first (OH^1) and the second OH (OH^2) groups from the CO bridge form hydrogen bonds with the CO, or with the neighboring OH, and exchange the OH protons rapidly (Fig. 2). In addition, these facts suggest that, in $CDCl_3$ solution at room temperature, **1a** preferentially exists in a cone conformation and that the two mirror-image cone conformations interconvert rapidly. By lowering the temperature of the sample solution, the CH_2 protons merge into a broad singlet at around -40°C, followed by splitting again into three broad lines. The spectrum is not completely resolved even at -90°C. On the other hand, the two OH signals finally split into four peaks with an equal intensity at -60°C (Fig. 3). The behavior means that the conformational equilibrium is frozen and a single species, A or B, exists, in which all the four OH groups are in the different environments (Fig. 2). The coalescence temperatures (T_c) are -35°C (ν = 349Hz; $\Delta G^{\ddagger}$=10.7 kcal mol^{-1}) for the OH^1 protons and -48°C (ν=132Hz; $\Delta G^{\ddagger}$

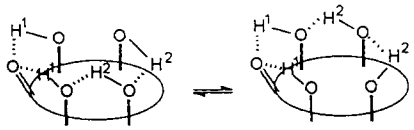


Fig. 2.

=10.5 kcal mol^{-1}) for the OH^2, respectively, from which a free energy barrier (Δ G‡) for the conformational change is estimated to be 10.6 kcal mol^{-1}. The Δ G‡ value is almost the same as those of *p-tert*-butyldihomooxacalix[4]arene (10.3 kcal mol^{-1})[9] and 6,13,22,29-tetra-*tert*-butyl-9,16,25,32-tetrahydroxy[3.1.3.1]metacyclophane (10.5 kcal mol^{-1})[11] which are obtained on the basis of the OH resonances in the same solvent.

The larger oxocalixarenes, **1b** and **1c**, exhibit singlets for both the CH_2 (two for **1b** and three for **1c**) and OH protons (three for each) down to −50°C, while the T_c for the CH_2 resonance are −2 °C for **2b** and 11°C for **2c**, respectively.[12] This indicates that **1b** and **1c** are also much more flexible than **2b** and **2c**. The rule[10] based on the CH_2 carbon chemical shifts to determine the conformation of the calix[4]arenes was recently extended to the higher homologs.[13] Thus, the observed carbon resonances (31.4, 31.5 for **1b** and 31.6, 31.8, 32.1 for **1c**) suggest that the cone conformations are preferred for both compounds.

Dynamic properties of **1** were studied *via* ^{1}H relaxation time (T_1) measurements,[14] which had been successfully utilized for elucidating complexation of some calixarene derivatives.[15] The oxocalixarenes **1** are characterized by high T_1 values for the *tert*-butyl groups and low for the CH_2 groups (Fig. 1). Regardless of the position, the butyl groups in each oxocalixarene have practically the same values, and the values depend on the size of the oxocalixarene bearing the butyl groups (**1b**>**1c**>**1a**). The results are consistent with the above inference drawn from the NMR spectroscopic behavior of the CH_2 groups on the rapid inversion of *p-tert*-butylphenol units through the annulus of the macrocyclic ring; the motion is most pronounced in **1b** (**1b**>**1c**>**1a**). Further, the differences in the T_1 values of two *meta* protons on the same aromatic rings suggest another type of movement, *e.g.* twisting, of the phenol rings coupled with the ring inversion. As for OH groups,[14] two sets of none quivalent OH in **1a** are different from each other in T_1 value, that is, in mobility; the OH^1 groups are significantly more mobile than the OH^2 groups. The phenomenon can be attributed to the favorable hydrogen bond formation of the CO oxygen with the neighboring OH^1 protons, which results in the rapid seesaw motion of the OH^1 groups around the axis between the CO and CH_2 bridges.

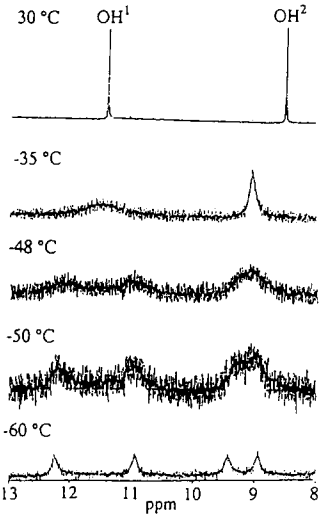


Fig.3. Variable temperature ^{1}H NMR spectra of **1a** (270 MHz; $CDCl_3$)

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8. The ^{1}H NMR assignments were confirmed by NOE and COSY experiments.
   1a: mp 220-222°C(dec.).MS(70eV) m/z 662(M^+,18%). IR($CHCl_3$) 3304,1618cm^{-1}. ^{1}H NMR($CDCl_3$) δ 1.22(s,18H, *t*-Bu^1),1.24(s,18H,*t*-Bu^2),3.94(s,2H,H_a),4.00(s,4H,H_f),7.04(d,J=2.3Hz,2H,H_c), 7.15 ((d,J=2.3Hz, 2H, H_d), 7.45 (d, J=2.3Hz,2H,H_e),7.50(d,J=2.3Hz,2H,H_b),8.57(s,2H,OH^2),11.44(s,2H,OH^1). ^{13}C NMR($CDCl_3$) δ 30.4, 31.3, 31.5, 32.1,33.9,34.2,119.7,125.4,125.8,126.2,127.4,127.6,129.2,134.1,141.3,143.2,148.7,155.8,203.1. Calcd for $C_{44}H_{64}O_5$: C,79.72;H, 8.21. Found:C,79.74;H,8.35.
   1b: mp 255°C(dec.).MS(70eV) m/z 828(M^+,88%). IR($CHCl_3$) 3307,1628cm^{-1}.^{1}H NMR($CDCl_3$) δ 0.92(s,18H,*t*-Bu^1) 1.26(s,9H,*t*-Bu^2),1.30(s,18H,*t*-Bu^3),3.76(s,4H,H_g,3.93(s,4H,H_f),6.90(s,2H,OH^2),7.11(d,J= 2.3 Hz,2H,H_d),7.12(d,J= 2.3H,2H,H_b),7.16(s,2H,H_a),7.19(d,J=2.3Hz,2H,H_c),7.26(d,J=2.3Hz,2H,H_e),7.27(s,1H,OH^3),9.31(s,2H, OH^1). ^{13}C NMR($CDCl_3$) δ 30.9,31.4,31.5,33.7,33.9,34.0,123.9,125.3,125.5,125.9,126.1,126.3,126.5,126.7, 126.9,131.3, 142.4,144.0,144.1,147.5,147.9,152.4,202.3. Calcd for $C_{55}H_{68}O_6$: C,80.06;H,8.31. Found: C, 80.10; H,8.40.
   1c: mp 240°C(dec.).MS(70eV) m/z 986(M^+,12%). IR($CHCl_3$) 3290,1620cm^{-1}. ^{1}H NMR($CDCl_3$) δ 1.20(s,18H,*t*-Bu^1), 1.26(s,18H,*t*-Bu^2),1.28(s,18H,*t*-Bu^3),3.76(s,4H,H_g),3.86(s,4H,H_h),3.94(s,4H,H_i), 6.79(d,J=2.3Hz,2H,H_f), 7.17(d, J=2.3Hz,2H,H_c),7.19(d,J=2.3Hz,2H,H_d),7.20(d,J=2.3Hz,2H,H_e),7.39(d,J=2.3Hz,2H,H_a),7.51(d,J=2.3Hz,2H,H_b), 7.76(s,2H,OH^3),8.86(s,2H,OH^2),11.34(s,2H,OH^1). ^{13}C NMR($CDCl_3$) δ 31.3,31.4,31.5, 31.6, 31.8, 32.1, 33.9,34.0, 34.1, 122.4,124.5,125.1, 125.6,125.8,126.3,126.5,126.7,127.5,127.7, 128.0,132.9, 142.7,143.3, 144.2, 147.1, 148.9, 152.6,203.2. Calcd for $C_{66}H_{82}O_7$: C,80.28;H,8.37. Found: C,79.98;H,8.24.
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(*Received in Japan* 25 *May* 1996; *revised* 27 *June* 1996; *accepted* 28 *June* 1996)