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Preparation and Conformation of Dioxocalix[4]arene Derivatives

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CrO_3 oxidation experiments conducted on atropisomeric forms of **2** (**2**^{paco}, **2**$^{1,3-alt}$, and **2**$^{1,2-alt}$) indicate that under the reaction conditions only methylene groups located between pairs of geminal rings oriented in an anti disposition are oxidized to carbonyls. NMR data suggest that the tetrahydroxydioxocalix[4]arenes **7** and **9** adopt the partial cone and 1,2-alternate conformations, respectively. In the crystal structure of **7**·2EtOAc the dioxocalixarene adopts a partial cone conformation, whereas **9** adopts in the crystal a 1,2-alternate conformation. In both conformations, pairs of geminal rings connected to a carbonyl are oriented in an anti fashion. The relative stability of the partial cone and 1,2-alternate conformations of **7** and **9** is underestimated by MM3 calculations. The topomerization barriers of **7** and **9** are 12.8 and 13.6 kcal mol^{-1}, respectively.

Introduction

Calixarenes are macrocyclic compounds consisting of a cyclic array of phenols interconnected by methylene groups.[1] The parent compound *p-tert*-butylcalix[4]arene (**1**) is synthetically available in relatively large amounts by base-catalyzed condensation of phenol and formaldehyde. Four basic conformational types are possible for the parent compound arising from the possible "up" or "down" arrangements of the rings. These forms are usually designated as cone, partial cone ("paco"), 1,2-alternate ("1,2-alt"), and 1,3-alternate ("1,3-alt"), (Figure 1). The parent **1** adopts a cone conformation that is stabilized by a circular array of hydrogen bonds both in solution and in the solid state.[1] Tetrahydroxycalix[4]arene **1** is conformationally flexible and undergoes a cone-to-cone inversion (a process involving rotation through the annulus of the aryl rings) with a barrier of 15.7 kcal mol^{-1} in $CDCl_3$.[2]

The replacement of the methylene groups of **1** by carbonyl groups may affect the preferred conformation and the rigidity of the macrocycle. A carbonyl group may disrupt the circular array of hydrogen bonds by serving as an acceptor of hydrogen bonds with the neighboring OH groups. In addition, the electron-withdrawing properties of the carbonyl group may influence the acidity of the phenolic OH groups, therefore affecting their properties as donors or acceptors of hydrogen bonds. In contrast to the methylene bridges in **1**, the carbonyl groups can be conjugated to the aryl rings, and these conjugation effects may influence the conformational preferences of the macrocycle. Finally, if several carbonyls are present,

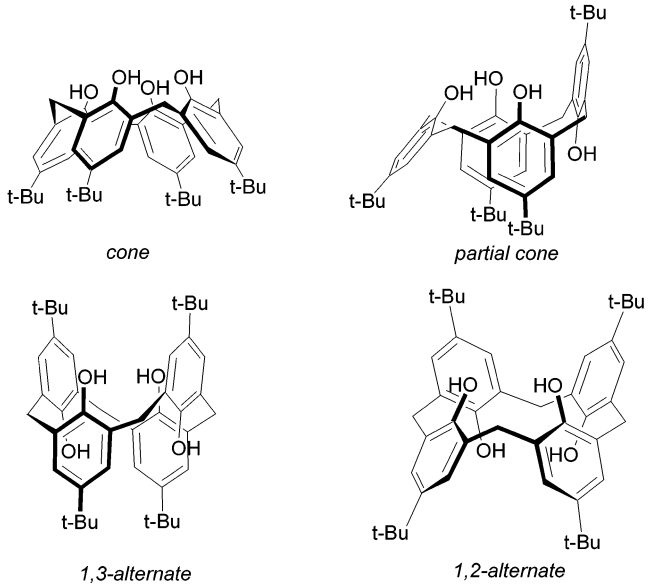

FIGURE 1. Four basic conformational types of the parent *p-tert*-butylcalix[4]arene **1**.

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(1) For reviews on calixarenes see: (a) *Calixarenes, a Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer: Dordrecht, 1991. (b) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713. (c) Gutsche, C. D. *Aldrichimica Acta* **1995**, *28*, 1. (d) Pochini, A.; Ungaro, R. In *Comprehensive Supramolecular Chemistry*; Vögtle, F., Vol. Ed.; Pergamon Press: Oxford, UK, 1996; Vol. 2, p 103. (e) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998. (f) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, 2001. (g) Böhmer, V. In *The Chemistry of Phenols*; Rappoport, Z., Ed., Wiley: Chichester, 2003; Chapter 19.

(2) Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 6052.

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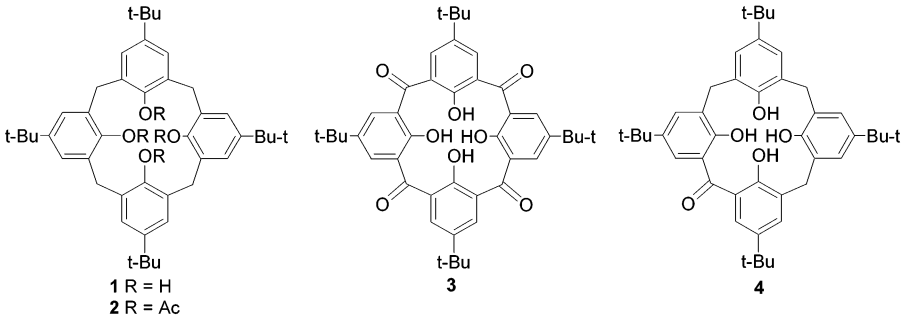
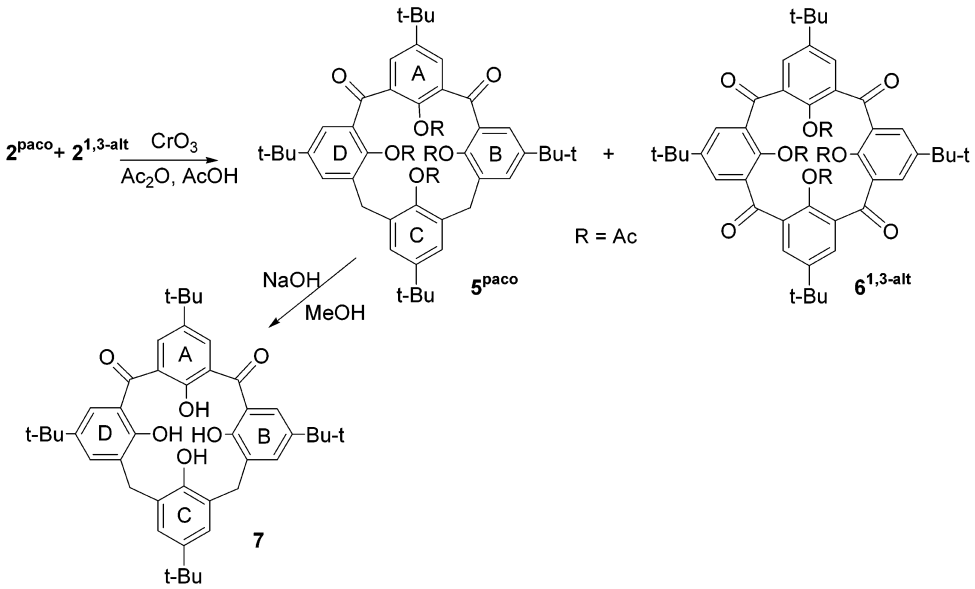


SCHEME 1



dipole-dipole interaction may play a role in determining the preferred conformation.

Ketocalixarene **3**, prepared by Görmar via oxidation of **2**,[3] adopts in the crystal and in solution a 1,3-alternate conformation lacking a circular array of hydrogen bonds.[4] On the other hand, the monooxocalix[4]arene **4** prepared by Sone and co-workers via cyclization of a suitable open-chain oligomer adopts in solution a cone conformation and undergoes a cone-to-cone inversion with a barrier of 10.6 kcal mol^{-1} (in $CDCl_3$).[5,6] The increased flexibility of **4** (as compared to **1**) and the absence of a circular array of hydrogen bonds was interpreted as indicating that a hydrogen bond exists between the carbonyl group and a neighboring phenol ring.[5] In this article we report a reinvestigation of the oxidation reaction of the methylene groups of **2**, and the preparation, solution conformation, rotational barriers, and crystal structures of two dioxocalixarene derivatives.

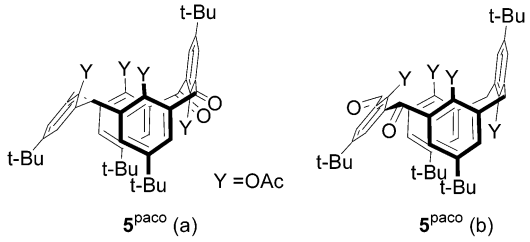
Results and Discussion

Oxidation of Calixarene Tetraacetate 2. The key step in Görmar's procedure for the preparation of ketocalixarene **3** involved the oxidation of the calixarene tetraacetate **2** with excess CrO_3 in boiling Ac_2O/AcOH.[3] In a second step, the acetyl groups of the resulting tetraoxo derivative were hydrolyzed, yielding ketocalixarene **3**.[3] In contrast to **1**, calixarene tetraacetate **2** is conformationally rigid because the rotation of the rings through the annulus is blocked by the bulky *intra*annular ("lower rim") substituents. Thus, the four up−down forms depicted in Figure 1 represent for **2** atropisomers rather than conformational isomers.[7] Different synthetic procedures have been reported for the acetylation of **1**, and under different conditions, different atropisomeric ratios of the forms of **2** have been obtained.[8,9]

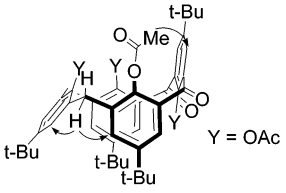
The calix[4]arene tetraacetate **2** was prepared by acetylation of **1** according to the procedure of Gutsche and co-workers.[9] NMR analysis of the product obtained indicated that it consisted of a mixture of forms, with the two major ones (in a nearly 1:1 ratio) being the partial cone and 1,3-alternate forms (i.e., $\mathbf{2}^{paco}$ and $\mathbf{2}^{1,3-alt}$).[10] CrO_3 oxidation of this atropisomeric mixture of **2** in boiling Ac_2O/AcOH for 2 h (these reaction conditions will be

(3) Görmar, G.; Seiffarth, K.; Schultz, M.; Zimmerman, J.; Flämig, G. *Macromol. Chem.* **1990**, *191*, 81.
(4) Seri, N.; Simaan, S.; Botoshansky, M.; Kaftory, M.; Biali, S. E. *J. Org. Chem.* **2003**, *68*, 7140.
(5) Ito, K.; Izawa, S.; Ohba, T.; Ohba, Y.; Sone, T. *Tetrahedron Lett.* **1996**, *37*, 5959.
(6) Compound **4** was first prepared by direct oxidation of **2**. Ninagawa, A.; Cho, K.; Matsuda, H. *Makromol. Chem.* **1985**, *186*, 1379.
(7) The four atropisomeric forms slowly equilibrate in DMSO-d_6 at 150 °C. See: Akabori, S.; Sannohe, H.; Habata, Y.; Mukoyama, Y.; Ishii, T. J. *J. Chem. Soc., Chem. Commun.* **1996**, 1467.
(8) Jaime, C.; de Mendoza, J.; Prados, P.; Nieto, P. M.; Sanchez, C. *J. Org. Chem.* **1991**, *56*, 3372.
(9) Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983**, *39*, 403.
(10) The crystal structure of $\mathbf{2}^{paco}$ has been reported. See: Rizzoli, C.; Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Mol. Struct.* **1982**, *82*, 133.

SCHEME 2



SCHEME 3



referred to as the "standard oxidation conditions") afforded a mixture of two products ($\mathbf{5}^{paco}$ and $\mathbf{6}^{1,3-alt}$) that were separated by fractional crystallization (Scheme 1).[11]

Structural Characterization of Products. Calixarene $\mathbf{5}^{paco}$ displayed in the ^{1}H NMR spectrum two singlets and a pair of doublets in the aromatic region, two doublets integrating for two protons each for the methylene protons (indicating that two methylene groups were oxidized), and three acetate and three *t*-Bu signals, each in a 1:2:1 ratio. This signal pattern is consistent with a structure possessing C_s symmetry with the mirror plane perpendicular to the main macrocyclic plane and bisecting a pair of rings. Necessarily, the two symmetry-related carbonyl groups must be connected to a single aryl ring (for identification purposes this ring will be designated as the ring A, cf. Scheme 1). A cone, 1,3-alternate, or partial cone disposition of the rings is consistent with the signal pattern. However, a single acetate signal (integrating for three protons) resonated in the ^{1}H NMR spectrum at δ −0.37 ppm, indicating that the methyl group of a single acetate unit is located in the shielding region of the neighboring aryl groups. This suggests that the rings exist in the partial cone disposition, since only in such arrangement is a single acetyl group located in the shielding region of three neighboring aryl rings.[12]

Two different partial cone forms are compatible with the ^{1}H NMR spectrum, with either rings C or A pointing in the opposite direction to the rest (forms "$\mathbf{5}^{paco}$ a" and "$\mathbf{5}^{paco}$ b", Scheme 2). The aromatic protons of ring C and one of the aromatic protons of rings B and D displayed in the NOESY spectrum NOE cross peaks with the high field methylene signal (assigned to an equatorial proton), while the aromatic protons of ring A displayed NOE cross peaks with the acetate methyls on rings B and D (Scheme 3). The observed NOE are only consistent with a partial cone conformation in which the A ring is pointing to the opposite direction than the rest of the rings (i.e., form "a" in Scheme 2).[13]

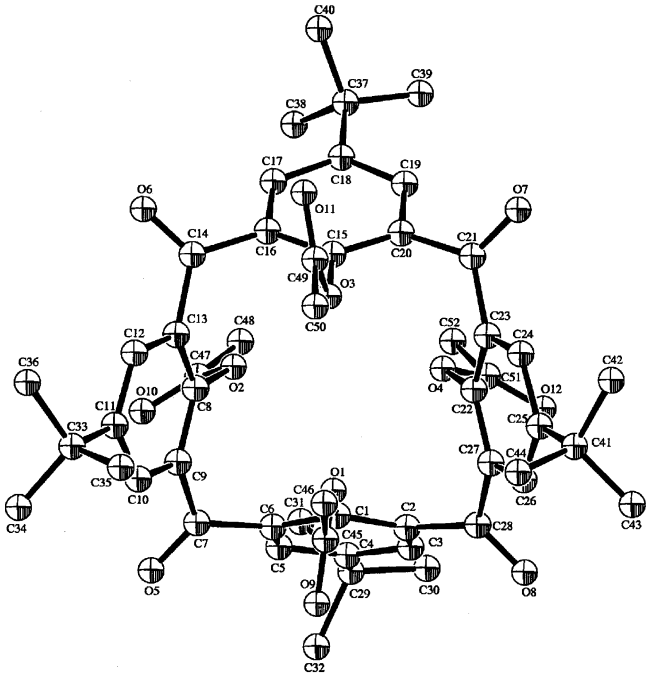


FIGURE 2. X-ray structure of the tetraoxocalix[4]arene tetraacetate $\mathbf{6}^{1,3-alt}$ isolated in the oxidation of a mixture of atropisomers of **2**.

In contrast to $\mathbf{5}^{paco}$, the ^{1}H NMR spectrum of $\mathbf{6}^{1,3-alt}$ displayed single signals for the aromatic, acetyl, and *tert*-butyl groups. Precluding accidental isochrony, the signal pattern suggests that all aromatic rings are symmetry equivalent and therefore that the aromatic rings are arranged in either the cone or 1,3-alternate disposition. X-ray diffraction of a single crystal of $\mathbf{6}^{1,3-alt}$ (grown from chloroform) corroborated the 1,3-alternate disposition of the aryl rings (Figure 2).

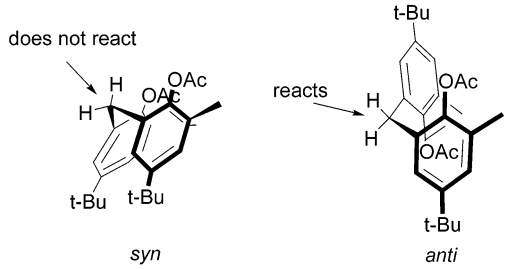
Selectivity of the Oxidation Step. The product ratio between the two major forms isolated in pure form after fractional crystallization ($\mathbf{5}^{paco}$ and $\mathbf{6}^{1,3-alt}$) was similar to the ratio between the $\mathbf{2}^{paco}$ and $\mathbf{2}^{1,3-alt}$ atropisomeric forms in the starting material. Attempted oxidation of $\mathbf{5}^{paco}$ under the standard conditions afforded only unchanged $\mathbf{5}^{paco}$. Notably, oxidation of pure $\mathbf{2}^{paco}$ (isolated from the atropisomeric mixture by recrystallization from AcOH) afforded exclusively $\mathbf{5}^{paco}$. All of these results indicate that under standard oxidation conditions $\mathbf{2}^{paco}$ exclusively generates the dioxo derivative $\mathbf{5}^{paco}$, $\mathbf{2}^{1,3-alt}$ generates $\mathbf{6}^{1,3-alt}$ and $\mathbf{5}^{paco}$ is not intermediate in the formation of $\mathbf{6}^{1,3-alt}$. Clearly, whereas the oxidation of $\mathbf{2}^{1,3-alt}$ proceeds up to its tetraoxo stage, only two methylene groups of $\mathbf{2}^{paco}$ are oxidized. To accommodate these experimental observations and the fact that the dioxo calixarene derivative isolated possessed the carbonyls located at proximal bridges (i.e., both connected to the same ring) rather than at opposite positions, we propose that under the standard oxidation conditions, no rotation through the annulus of the aryl rings occurs and that *only methylene groups connected to rings pointing to opposite*

(11) For a review on the oxidation and reduction of calixarenes, see: Biali, S. E. In *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, 2001; pp 266−279

(12) Although at present the rigidity of the calix[4]arene tetraacetate derivatives **5** and **6** is unknown, we assume, by analogy with **2**, that in these compounds the bulky acetate groups preclude the rotation through the annulus of the rings, allowing the isolation of atropisomers at room temperature in the laboratory.

(13) For simplicity we will refer to the specific atropisomeric forms isolated ($\mathbf{5}^{paco}$(a) and $\mathbf{8}^{1,2-alt}$(a)) as $\mathbf{5}^{paco}$ and $\mathbf{8}^{1,2-alt}$.

SCHEME 4



directions are oxidized (i.e., with an anti disposition of the geminal rings, Scheme 4), whereas methylene groups located between groups oriented syn do not react. This dependence on the orientation of the rings can explain the different reactivity pattern of $\mathbf{2}^{1,3-alt}$ and $\mathbf{2}^{paco}$. In $\mathbf{2}^{1,3-alt}$ the oxidation proceeds up to the tetraoxo stage since all bridging methylene groups are located between pairs of rings oriented anti. On the other hand, in $\mathbf{2}^{paco}$ only a pair of vicinal methylenes is located between rings oriented anti, and only these two methylenes are oxidized. If this hypothesis is correct, then the chemoselectivity of the oxidation reaction under standard conditions can be controlled by the syn or anti disposition of pairs of geminal rings.

Preparation of a Calixarene with a Pair of Opposite Bridges Oxidized. To test the hypothesis described in the previous section, a 9:1 mixture of $\mathbf{2}^{1,2-alt}$ and $\mathbf{2}^{1,3-alt}$ was submitted to oxidation under standard conditions (Scheme 5). On the basis of its ^{1}H and ^{13}C NMR spectra and assuming that there was no rotation through the annulus of the aryl rings during the experimental conditions, the main reaction product was assigned to the 1,2-alternate atropisomer of a calixarene tetraacetate possessing two carbonyl groups at opposite bridges. Two different atropisomeric 1,2-alternate forms are possible for the dioxocalixarene **8** (i.e., $\mathbf{8}^{1,2-alt}$(a) and $\mathbf{8}^{1,2-alt}$(b), Scheme 6). The two protons within a given methylene are diastereotopic in $\mathbf{8}^{1,2-alt}$(a) but homotopic in $\mathbf{8}^{1,2-alt}$(b) since they are related by the C_2 axis collinear with the two methylenes. Because two different signals were observed in the ^{1}H NMR spectrum for the methylene protons, the product isolated must correspond to $\mathbf{8}^{1,2-alt}$(a). This is the product that should be generated from $\mathbf{2}^{1,2-alt}$ if only those methylenes located between pairs of geminal rings oriented anti are oxidized.

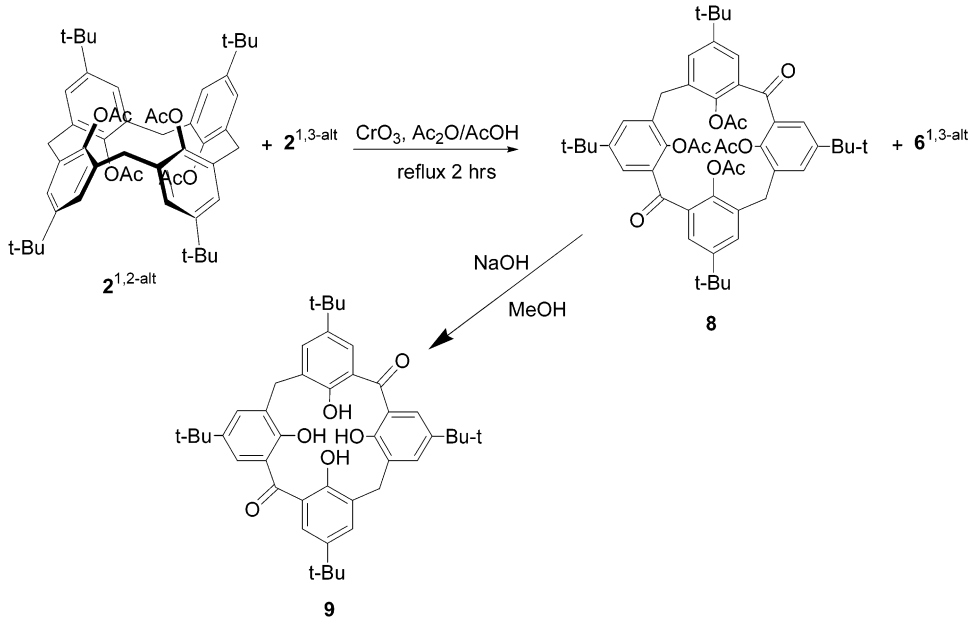
The tetrahydroxydioxocalixarenes **7** and **9** were prepared by basic hydrolysis of $\mathbf{5}^{paco}$ and $\mathbf{8}^{1,2-alt}$, respectively (Schemes 1 and 5).

IR Spectra of 7 and 9. The OH groups of the dioxocalixarene **7** display two stretching frequencies in the IR spectrum (KBr) at 3471 and 3249 (shoulder) cm^{-1}. Dioxocalixarene **9** displays a broad signal for the OH groups (KBr, ν_{OH} = 3500−3200 cm^{-1}). The higher stretching frequencies of ν_{OH} in **7** and **9** as compared to **1** (ν_{OH} = 3177 cm^{-1}) suggests that no circular array of hydrogen bonds involving the four OH groups is present in either **7** or **9**.

Crystal Structure of 7. A single crystal of **7** was grown from chloroform/ethyl acetate and submitted to X-ray crystallography. Calixarene **7** crystallized with two ethyl acetate molecules. Dioxocalixarene **7** adopts in the crystal a partial cone conformation, with ring A pointing to the opposite direction than the rest (Figure 3). The hydroxyl groups on rings B, C, and D are involved in OH···OH intramolecular hydrogen bonds, whereas the OH on ring A does not participate in that array of hydrogen bonds and is hydrogen bonded to one of the ethyl acetate molecules. None of the phenolic OH groups is hydrogen bonded to the carbonyl oxygens.

Crystal Structure of 9. A single-crystal suitable for X-ray crystallography was obtained by slow evaporation of a NMR sample of **9** dissolved in $CDCl_3$. In the crystal a molecule of water (with partial occupancy of 0.68) is hydrogen bonded to one of the phenolic OH groups of the dioxocalixarene. Each of the phenolic OH groups was disordered between two equivalent positions. Notably **9** adopts the 1,2-alternate conformation (Figure 4) with the carbonyls connected to pairs of rings pointing to opposite

SCHEME 5



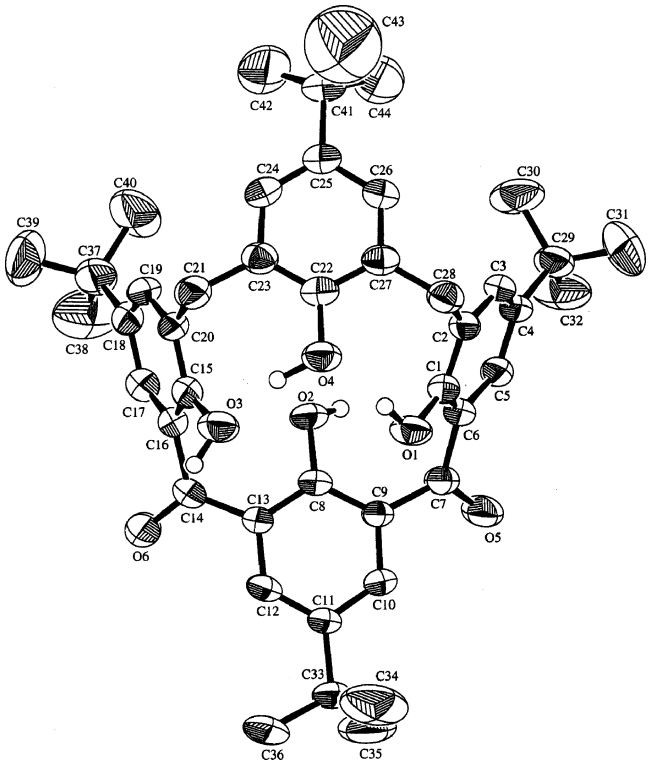
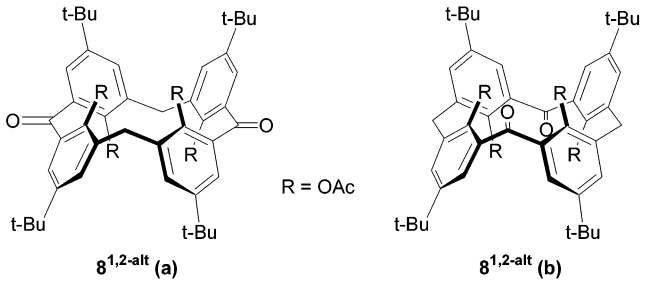


FIGURE 3. Crystal structure of the dioxocalixarene derivative **7**. The macrocycle adopts the partial cone conformation.

SCHEME 6



directions. As observed in the crystal structure of **7**, none of the phenolic OH are hydrogen bonded to the carbonyl groups.

Solution Conformation. Similarly to $\mathbf{5}^{paco}$, dioxocalixarene **7** displayed in the low temperature ^{1}H NMR spectrum (220 K, $CDCl_3$) a pattern of signals (three *t*-Bu signals in a 2:1:1 ratio, a pair of mutually coupled signals for the methylene groups) consistent with a conformation of C_s symmetry. Three signals were observed for the OH groups resonating at δ 8.98 (1H), 8.20 (2H), and 5.76 (1H) ppm. The relatively upfield resonance of the last signal suggests that in this calixarene one of the OH groups does not take part in the array of hydrogen bonds between the phenolic hydroxyls. The symmetry pattern observed in the NMR spectra is consistent with either a cone or partial cone conformation. However, since the cone conformation should display a circular array of hydrogen bonds, we ascribe the solution conformation to a partial cone form in which the A ring is pointing to the opposite direction than the rest (the conformation adopted in the crystal of **7**·2 EtOAc).

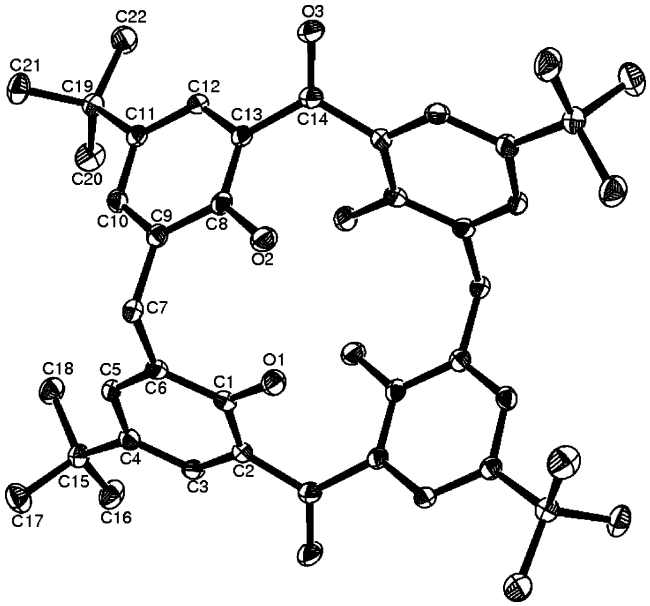
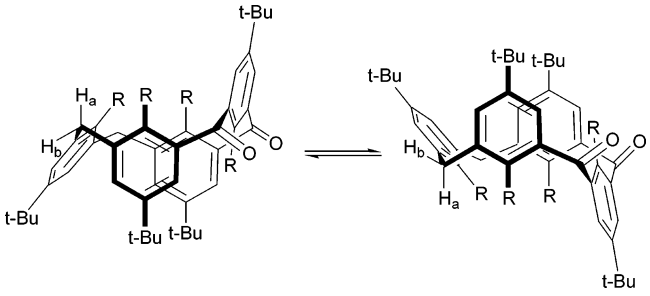


FIGURE 4. X-ray structure of dioxocalixarene **9**. The disordered phenolic OH protons are ommited. The macrocycle adopts the 1,2-alternate conformation.

SCHEME 7



The low temperature (240 K) ^{1}H NMR spectrum of **9** displayed for the aromatic, methylene, and *tert*-butyl groups a signal pattern almost identical to that of **8.** This signal pattern is consistent only with a conformation of C_{2v} or C_{2h} symmetry, i.e., with a cone or 1,2-alternate conformation. On the basis of the similarity between the spectra of **9** and **8**, and since the chemical shift of the OH protons in $CHCl_3$ (δ 7.07 ppm) is inconsistent with a circular array of hydrogen bonds, we ascribe to **9** a preferred 1,2-alternate conformation.

Topomerization Barriers of 7 and 9. Topomerization of the diastereotopic methylene protons of **7** or **9** requires that all rings rotate through the annulus of the macrocycle. The topomerization of tetrahydroxy dioxocalixarene **7** is schematically depicted in Scheme 7. From the chemical shift difference between the methylene protons under slow exchange conditions ($\Delta\delta$ = 253.7 Hz), the value of the geminal coupling constant (J = 13.9 Hz) and the coalescence temperature of the signals (T_c = 280.6 K), a barrier of 12.8 kcal mol^{-1} was calculated for the partial cone to partial cone inversion of **7**.[14] Similarly, from the coalescence data for the methylene protons of **9** ($\Delta\delta$ = 192.8 Hz, J = 14.1 Hz, T_c = 291.9 K) a barrier of 13.6 kcal mol^{-1} was determined. The value of these barriers is intermediate between those determined for

TABLE 1. MM3 Calculated Relative Energies (kcal mol^{-1}) of Dioxocalixarene 7[a]

	ΔE	E_{bs}	E_{ab}	E_{tors}	ΣE_{cross}	ΣE_{bond}	E_{14vdw}	E_{vdw}	E_{dipole}	$\Sigma E_{nonbond}$
cone	0.0	4.9	9.0	−14.9	−0.6	−1.6	41.1	−15.6	6.7	32.2
paco (a)	2.8	5.3	10.4	−22.8	−0.3	−7.4	41.1	−6.7	6.5	40.9
paco (c)[b]	3.7	5.0	8.9	−15.7	−0.5	−2.3	41.2	−11.1	6.6	36.7
paco (b)	3.9	5.1	8.9	−15.0	−0.6	−1.6	41.4	−11.9	6.6	36.1
1,2-alt	4.0	5.2	9.4	−19.5	−0.5	−5.4	41.4	−8.2	6.9	40.1
1,3-alt	8.0	5.1	10.0	−20.5	−0.3	−5.7	41.2	−3.3	6.4	44.3

[a] E_{bs}, bond stretching energy; E_{ab}, angle bending energy; E_{tors}, torsional energy; ΣE_{cross}, energy associated with bend−stretch, stretch−stretch, and torsion−stretch cross terms; ΣE_{bond}, sum of bonded energy terms; E_{14vdw}, energy associated with 1,4-van der Waals interactions; E_{vdw}, van der Waals energy; E_{dipole}, dipole interaction energy; $\Sigma E_{nonbond}$, sum of nonbonded energy terms. [b] Paco conformer in which rings B or D point in the opposite direction to the rest.

TABLE 2. MM3 Calculated Relative Energies (kcal mol^{-1}) of Dioxocalixarene 9[a]

	ΔE	E_{bs}	E_{ab}	E_{tors}	ΣE_{cross}	ΣE_{bond}	E_{14vdw}	E_{vdw}	E_{dipole}	$\Sigma E_{nonbond}$
cone	0.0	5.0	9.3	−15.4	−0.6	−1.7	41.2	−16.3	5.8	30.7
1,2-alt (a)	1.8	5.2	10.2	−25.9	−0.2	−10.7	41.4	−5.5	5.6	41.5
paco	4.2	5.0	8.8	−16.7	−0.5	−3.4	41.2	−10.5	5.9	36.6
1,2-alt (b)	7.0	4.9	9.8	−15.4	−0.5	−1.2	41.8	−10.7	6.0	37.1
1,3-alt	10.4	4.9	9.0	−15.2	−0.4	−1.7	40.6	−5.1	5.4	40.9

[a] For abbreviations see footnote a in Table 1.

the monooxocalixarene **4** (10.6 kcal mol^{-1})[5] and the tetraoxocalixarene derivative **3** (15.2 kcal mol^{-1}).[4]

MM3 Calculations. Molecular mechanics calculations (MM3(96))[15,16] were conducted for the two dioxocalixarenes **7** and **9** bearing free OH groups in order to estimate the relative energies of the different conformations (Tables 1 and 2). In contrast to the experiment, the calculations predict that both compounds should exist almost exclusively in the cone conformation. Although the stability of the paco (a) and 1,2-alt (a) conformers is underestimated, the calculations reproduce the general trend that the replacement of two methylene groups in the parent *p-tert*-butylcalixarene **1** by carbonyl groups results in a destabilization of the cone compared with the other conformations.[17] Analysis of the energy components reveals that this destabilization comes mostly from unfavorable torsional energies that are, however, compensated by attractive nonbonding interactions. The geometry of the structures found in the crystal is well reproduced by the calculations as indicated by rms values of 0.23 Å for the paco (a) conformers of **7** and of 0.19 Å for the 1,2-alt (a) conformers of **9**.

Syn vs Anti Arrangements of Pairs of Geminal Rings. CrO_3 oxidation of the atropisomers of **2** occurs preferably at the methylene groups connected to pairs of rings oriented anti. In the preferred conformation of oxocalixarenes **3**, **7**, and **9**, pairs of rings connected to a given carbonyl prefer an anti orientation. It seems likely that both observations are connected. An anti arrangement of a pair of geminal rings may allow for a better conjugation between the rings and the carbonyl connected to them, as suggested by the lower E_{tors} terms in the MM3 calculations of the paco (a) and 1,2-alt (a) conformations of **7** and **9**, respectively. Similar conjugation effects may be responsible for the lower activation energy for the oxidation of methylenes connected to geminal rings oriented anti, resulting in the regioselectivity observed.

Experimental Section

MM3 Calculations. A conformational search was performed for **7** and **9** with the stochastic search routine of the standard MM3(96) force field using the default parameters except for the number of pushes, which was set to 10 000. Missing torsional parameters were taken from the parameter estimator without further modification. Subsequently, all conformers were re-optimized with the MM3(96) force field using the block-diagonal Newton−Raphson algorithm followed by the full matrix Newton−Raphson algorithm and identified as energy minima by means of the eigenvalues of the Hessian matrix. The analysis and visualization of the calculated structures was carried out using the Sybyl software.

X-ray Crystallography. Crystal data for 2: $C_{56}H_{62}N_2O_{12}$, FW = 955.11 g mol^{-1}, space group $P2_1/c$, a = 15.40(1) Å, b =12.935(4) Å, c = 27.73(1) Å, β = 105.76(5); V = 5317(4) Å^3, Z = 4, T = 293 K, ρ_{calc} = 1.193 g cm^{-3}, μ(CuKα) = 0.684 mm^{-1}, no. of unique reflections = 7062, no. of reflections with $I \geq 2\sigma(I)$ = 3771, R = 0.0890, R_w = 0.1250.

Crystal data for 7: $C_{44}H_{52}O_6$ (2 $C_4H_8O_2$), FW = 853.10 g mol^{-1}, space group $P\bar{1}$, a = 11.84 (1) Å, b =18.897(5) Å, c = 11.573(3) Å, α = 104.16 (3)°, β = 96.25 (5)°, γ = 82.52 (5)°, V = 2481(2) Å^3, Z = 2, T = 293 K, ρ_{calc} = 1.142 g cm^{-3}, μ(Cu Kα) = 0.627 mm^{-1}, no. of unique reflections = 6197, no. of reflections with $I \geq 2\sigma(I)$ = 4811, R = 0.077, R_w = 0.118.

Crystal data for 9: $C_{44}H_{52}O_6 \cdot 0.68H_2O$, FW = 689.13 g mol^{-1}, space group $P2_1/n$, a = 8.607 (2) Å, b =14.920 (3) Å, c = 14.587 (3) Å, β = 93.004 (3)°, V = 1870.6(6) Å^3, Z = 2, T = 100.0(2) K, ρ_{calc} = 1.216 g cm^{-3}, μ(Mo Kα) = 0.080 mm^{-1}, no. of unique reflections = 3299, no. of reflections with $I \geq 2\sigma(I)$ = 2936, R = 0.057, R_w = 0.143.

Oxidation of Atropisomeric Mixture of 2. A 2.4 g portion of a mixture of atropisomeric forms of **2** (mainly a 1:1 mixture of the $\mathbf{2}^{paco}$ and $\mathbf{2}^{1,3-alt}$) was dissolved in 140 mL of acetic anhydride, and to the solution was added 7 g of CrO_3 dissolved in 30 mL acetic anhydride and 10 mL acetic acid. The mixture was slowly heated and then refluxed for 2 h. During the

(14) The exchange rates at the coalescence temperatures (k_c) were estimated using the equations $k_c = 2.22\,(\Delta\nu^2 + 6J^2)^{1/2}$. See: E. Juaristi *Stereochemistry and Conformational Analysis*; Wiley: New York, 1991; pp 253−254.

(15) MM3(96) is included in the Sybyl 6.9 program package (Tripos Assoc., Inc., St. Louis, MO 63144).

(16) (a) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551. (b) Lii, J.-H.; Allinger, N. L. *J. Am. Chem. Soc.* **1989**, *111*, 8566. (c) Lii, J.-H.; Allinger, N. L. *J. Am. Chem. Soc.* **1989**, *111*, 8576.

(17) The order of the relative stabilities obtained from MM3(96) calculations on the *p-tert*-butylcalix[4]arene **1** are cone (0.0) > paco (5.6) > 1,2-alt (7.2) > 1,3-alt (10.8 kcal mol^{-1}). (Thondorf, I. Unpublished results.)

heating period the solution color changes from dark red to green. Water and $CHCl_3$ were added, and the organic phase was separated and evaporated. The residue was recrystallized from a minimum amount of chloroform/ethanol. The first fraction consisted of 0.8 g of **6**[3] (34%), and the second fraction consisted of 0.5 g of **5** (22%), mp 290 °C.

Spectroscopic data for 5: ^{1}H NMR ($CDCl_3$, 300 MHz, rt) δ 8.05, (s, 2H, Ar−H), 7.63 (d, J = 2.1 Hz, 2H, Ar−H), 7.31 (d, J = 2.2 Hz, 2H, Ar−H), 7.26 (s, 2H, Ar−H), 3.97 (d, J = 12.9 Hz, 2H, CH_2), 3.54 (d, J = 12.9 Hz, 2H, CH_2), 2.26 (s, 3H, MeCO), 2.00 (s, 6H, MeCO), 1.42 (s, 9H, *t*-Bu), 1.28 (s, 18H, *t*-Bu), 1.18 (s, 9H, *t*-Bu), −0.38 (s, 3H, *t*-Bu) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, rt) δ 191.5, 170.1, 169.5, 168.2, 150.0, 149.7, 149.1, 145.0, 143.9, 142.9, 134.3, 133.7, 132.9, 132.3, 130.5, 125.4, 125.1, 35.0, 34.7, 34.3, 31.28, 31.2, 30.7, 21.0, 20.9, 16.9 ppm; CI MS (−DCI) m/z 844.2 (M^-).

Oxidation of $2^{1,3-alt}$. A 0.5 g (0.6 mmol) portion of $2^{1,3-alt}$ was dissolved in 80 mL of acetic anhydride and 2 mL AcOH, and to the solution was added CrO_3 (1.6 g, 16 mmol). After 2 h of reflux, water and $CHCl_3$ were added to the green mixture. After phase separation, the organic phase was evaporated, and the residue was recrystallized from $CHCl_3$/MeOH, yielding 360 mg (88%) of essentially pure $6^{1,3-alt}$.[3]

Hydrolysis of 5. A mixture of dioxocalixarene tetraacetate **5** (0.5 g, 0.6 mmol), 70 mL of 1 N aq NaOH, and 30 mL of methanol was refluxed during 1 h. After acidification (neutralization) with concentrated HCl, the precipitate formed was filtrated, yielding 0.40 g (98%) of tetrahydroxydioxocalixarene **7**, mp 259 °C (dec):^{1}H NMR ($CDCl_3$, 300 MHz, rt) δ 7.95 (s, 2H), 7.49 (d, J = 2.4 Hz, 2H), 7.48 (d, J = 2.4 Hz, 2H), 7.12 (s, 2H), 3.90 (br s, 4H), 1.41 (s, 9H), 1.29 (s, 18H), 1.26 (s, 9H) ppm; ^{1}H NMR ($CDCl_3$, 400 MHz, 220 K) δ 8.98 (br s, 1H), 8.20 (br s, 2H), 7.98 (s, 2H), 7.50 (br d, 2H), 7.47 (br d, 2H), 7.14 (s, 2H), 5.76 (s, 1H). 4.24 (d, J = 13.9 Hz, 2H), 3.60 (d, J = 13.9 Hz, 2H), 1.42 (s, 9H), 1.28 (s, 18H), 1.26 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$, rt) δ 191.9, 151.4, 150.0, 145.6, 145.4, 145.2, 145.0, 133.0, 132.9, 129.4, 127.6, 127.6, 126.4, 125.6. 125.4, 34.6, 34.3, 34.1, 31.9, 31.4, 31.3 ppm. IR (KBr) ν 3471, 3249 (OH), 1647 (C=O) cm^{-1}; CI MS (+DCI) m/z 677.2 (MH^+).

Oxidation of $2^{1,2-alt}$. A 9:1 mixture of $2^{1,2-alt}$ and $2^{1,3-alt}$ (350 mg, 0.42 mmol) dissolved in 80 mL of acetic anhydride and 1.5 mL of acetic acid was oxidized with 1 g of CrO_3 (10 mmol) as described for 2^{paco}. Fractional crystallization from $CHCl_3$/MeOH afforded 30 mg of **6** (first fraction) and 100 mg of **8** (second fraction), mp 340 °C (dec): ^{1}H NMR ($CDCl_3$, 400 MHz, rt) δ 7.63 (d, J = 2.2 Hz, 4H), 7.56 (d, J = 2.2 Hz, 4H), 3.71 (d, J = 13.4 Hz, 2H), 3.44 (d, J = 13.5 Hz, 2H), 1.41 (s, 12H), 1.36 (s, 36 H); ^{13}C NMR (100.6 MHz, $CDCl_3$, rt) δ 193.3, 168.6, 149.3, 144.0, 134.1, 132.6, 131.1, 124.8, 34.7, 31.3, 30.0, 20.1 ppm; CI MS (+DCI) m/z 846.3 (MH^+).

Hydrolysis of $8^{1,2-alt}$. A mixture of 25 mg (0.03 mmol) of $8^{1,2-alt}$, 1.5 mL of MeOH, and 4 mL of 1 N aqueous NaOH was refluxed for 7 h. After acidification a precipitate formed that was filtered, yielding 15 mg (76%) of **9**, mp 360 °C (dec): ^{1}H NMR (400 MHz, $CDCl_3$, 240 K) δ 7.60 (d, J = 2.4 Hz, 2H), 7.57 (d, J = 2.3 Hz, 2H), 7.07 (4H), 4.05 (d, J = 14.1 Hz, 2H), 3.58 (d, J = 14.1 Hz, 2H), 1.37 (s, 36H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, rt) δ 192.7, 149.6, 145.2, 132.7, 128.1, 126.8, 125.5, 34.4, 31.3, 31.1 ppm; CI MS (+DCI) m/z 677.3 (MH^+).

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Supporting Information Available: Crystallographic data for **6**, **7**, and **9** (in CIF format); NMR spectra of **5**, **7**, **8**, and **9**; and minimized coordinates (MM3) of the conformers of **7** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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