Conformation and Stereodynamics of Monodioxamethylene Calix[4]arene Derivatives

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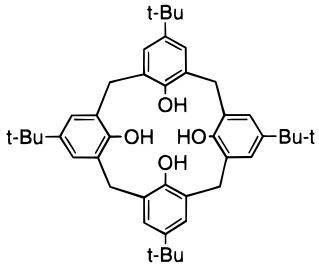
Reaction of the monospirodienone derivative of *p-tert*-butylcalix[4]arene with methylene chloride/base in the presence of a phase transfer catalyst yielded the bridged monodioxamethylene derivative **6** which was characterized by X-ray crystallography. Treatment of **6** with $NaBH_4$ resulted in *exo*-reduction of the carbonyl group and afforded the spiro alcohol **7**, which rearranged thermally to the monodioxamethylene bridged calix[4]arene **3**. Calixarene **3** exists in solution (CD_2Cl_2, 198 K) in three different conformations (a cone form with the dioxocine unit in a distorted boat conformation, and cone and partial cone forms with a boat-chair arrangement of the dioxocine) which interconvert with barriers in the 13.5−14.3 kcal mol^{-1} range. Molecular mechanics calculations indicate that the rate-limiting steps for the conformational interconversions of **3** involve transitions of the dioxocine subunit.

Introduction

The calix[*n*]arenes are synthetic molecular hosts consisting of an array of phenol and methylene groups alternately arranged within a macrocyclic ring.[1] These systems are capable to attain a large number of possible conformations. The parent *p-tert*-butylcalix[4]arene **1** exists in a cone conformation which undergoes a cone-to-cone inversion process with a barrier of 15.7 kcal mol^{-1}.[2] One strategy to limit the conformational freedom of the compounds involves bridging, i.e., interconnecting two or more atoms of the skeleton by a single atom or a group.[3] The structural constraints resulting from the introduction of a bridging group in a calix[4]arene scaffold may lead to a shift in the conformational preferences and/or to the partial or total prevention of conformational transitions in the laboratory time scale (i.e., the "rigidification" of a particular conformation). The preparation and conformational properties of the bis(dioxamethylene) calix[4]arene **2** have been described by Neri et al.[4] Calixarene **2** exists in solution as a mixture of 1,2-alternate and cone conformations, which mutually interconvert with a barrier of 18.2 kcal mol^{-1}. X-ray analysis of **2** indicates that the compound adopts in the crystal a distorted cone conformation.[4]



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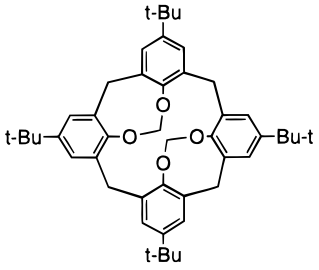

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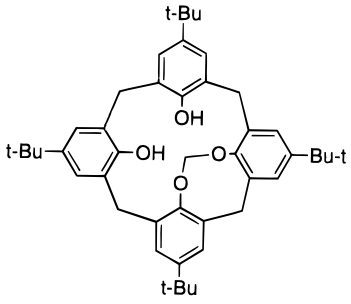
The simplest bridged calixarene is **3** in which two proximal phenol oxygens are connected to a methylene group and delimit an eight membered ring. Calixarene **3** was prepared by Böhmer and co-workers in 12% yield by reaction of **1** with 1 equiv of $BrCH_2Cl$ under basic conditions.[5] The compound was reported to exist in solution at 218 K as a conformational mixture, but no detailed stereochemical study was carried out. In this paper we describe an alternative synthesis of **3** and an experimental and computational study of the conformation and stereodynamics of the system.



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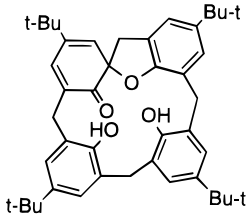

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Results and Discussion

Monospirodienone Derivatives as Starting Materials for the Preparation of Proximally Derivatized Calixarenes. Oxidation of **1** with tetraalkylammonium tribromide/base affords the monospirodienone calixarene **4**[6a] or a mixture of bis(spirodienone) derivatives (**5A**, **5A′**, and **5B**).[6b,7] Since a spirodienone group

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[‡] Hebrew University of Jerusalem.

(1) For reviews on calixarenes see: (a) Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989. (b) *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds., Kluwer: Dordrecht, 1991. (c) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713. (d) Gutsche, C. D. *Aldrichimica Acta* **1995**, *28*, 1.

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

(3) For a recent example of a bridged calixarene see: Saiki, T.; Goto, K.; Tokitoh, N.; Goto, M.; Okazaki, R. *Tetrahedron Lett.* **1996**, *37*, 4039.

(4) Neri, P.; Ferguson, G.; Gallagher, J. F.; Pappalardo, S. *Tetrahedron Lett.* **1992**, *33*, 7403.

(5) Kraft, D.; Böhmer, V.; Vogt, W.; Ferguson, G.; Gallagher, J. F. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1221.

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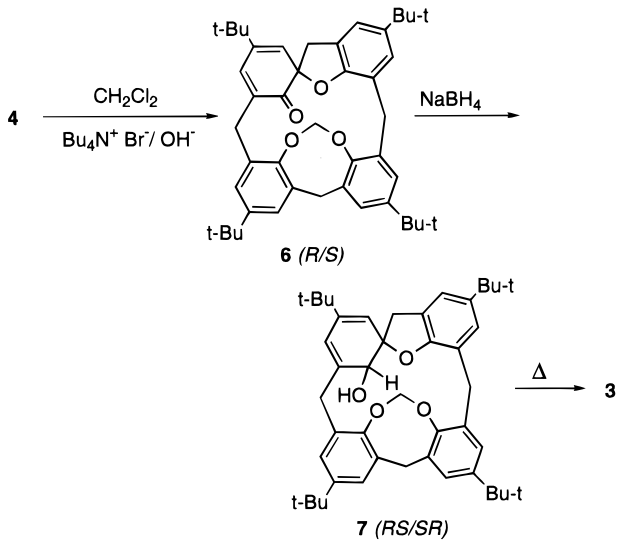
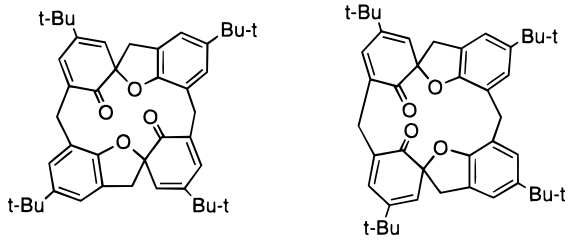
Scheme 1



is derived from two adjacent phenyl groups and may be reduced back to phenols, **4** can be used as a synthetic intermediate for the preparation of selectively derivatized calixarene systems. For example, a proximal dehydroxylated calixarene was prepared by phosphorylation of the free hydroxyls of **4** followed by reductive cleavage (K/NH_3) of the phosphate and spiro groups.[6a]



Dioxamethylene Intrabridged Spirodienone Derivatives. Notably, although CH_2Cl_2 is not a good alkylating agent, treatment of **4** with CH_2Cl_2/aq NaOH (30%) in the presence of $Bu_4N^+Br^-$ as a phase transfer catalyst yielded the bridged monospirodienone **6** (Scheme 1). Under the same reaction conditions no alkylation of **1** was observed.

The ^1H NMR spectrum of **6** displays four singlets for the *t*-Bu groups, ten doublets for the methylene groups (2.96, 3.23, 3.32, 3.61, 3.68, 3.78, 4.17, 4.72, 5.42, 5.62 ppm, the last two doublets resembling the dioxamethylene signals reported by Neri et al. for **2**),[4] two doublets for the vinyl protons, several overlapping aromatic signals in the 6.98−7.05 ppm region, and a doublet at 7.21 ppm. The ^{13}C NMR displays three distinctive signals at δ 83.34, 103.08, and 195.48 ppm, which can be assigned to the spiro, dioxamethylene, and carbonyl carbons, respectively.

(6) (a) Aleksiuk, O.; Grynszpan, F.; Biali, S. E. *J. Chem. Soc., Chem. Commun.* **1993**, 11. (b) Litwak, A. M.; Grynszpan, F.; Aleksiuk, O.; Cohen, S.; Biali, S. E. *J. Org. Chem.* **1993**, *58*, 393.

(7) For a review on spirodienone calixarene derivatives see: Aleksiuk, O.; Grynszpan, F.; Litwak, M. A.; Biali, S. E. *New J. Chem.* **1996**, *20*, 473.

(8) Van Gelder, J. M., Brenn, J., Thondorf, I.; Biali, S. E. *J. Org. Chem.* **1997**, *62*, 3511.

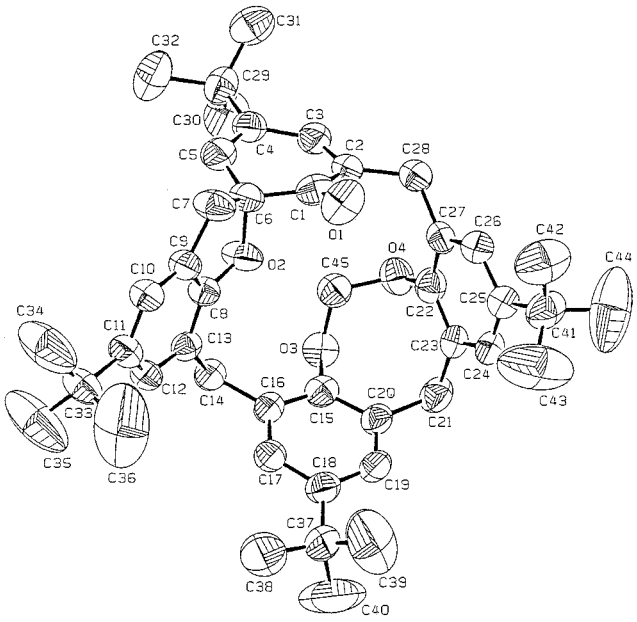


Figure 1. Numbering scheme of **6**.

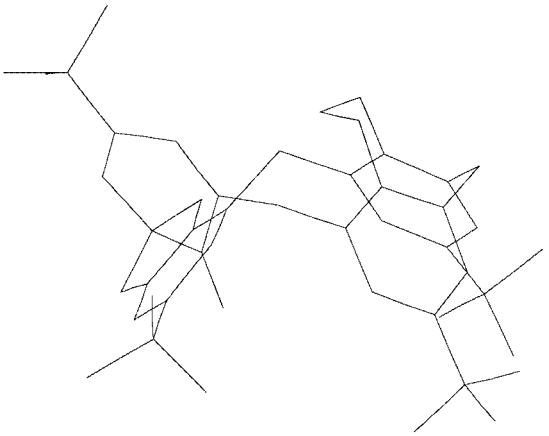
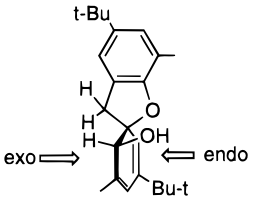


Figure 2. Side view of the X-ray structure of **6**.

A single crystal of **6** grown from $CHCl_3$/MeCN was submitted for X-ray analysis. Calixarene **6** exists in the solid state in a distorted partial cone conformation in which the phenoxy rings are pointing to the same side of the molecular mean plane (Figures1 and 2). The system crystallized with a disordered molecule of MeCN which is located in the cavity defined by the three phenoxy rings. The eight-membered dioxocine subunit exists in a boat-chair conformation (see below).

Reduction of the Monospirodienone Derivative. The nucleophilic addition of MeLi to the carbonyl groups of the bis(spirodienone) calixarene derivatives is stereospecific, and in the case of **5B**, X-ray analysis indicated that the product derives from the attack to the carbonyl face anti to the spiro oxygen.[8] Reaction of a (racemic) solution of **6** in THF with $NaBH_4$ proceeded rapidly, and the yellow color of the solution (typical of the spirodienone derivatives) was discharged in minutes yielding **7**. The hydride addition creates a new stereocenter and therefore both the *RR*/*SS* and *RS*/*SR* products could be expected. However, only a single diastereomeric form was obtained, indicating that the addition of the hydride ion to the carbonyl group proceeded in a stereoselective manner.

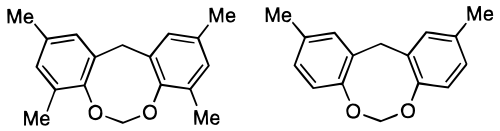
Scheme 2



The complete assignment of all the signals of the ^{1}H NMR spectrum of **7** in $CDCl_3$ to the individual protons was achieved by NOESY and COSY-DQF spectra. The NOESY cross-peaks are in agreement with a syn orientation of the three aromatic rings and an anti arrangement of the cyclohexadienol relative to these rings. The coupling constant ^3J for the H−C−O−H fragment (12.3 Hz) indicates an anti H−C−O−H torsional angle. The NOE cross-peaks involving the methine signal (at 4.42 ppm) and the dihydrofuran methylene protons indicate that these protons are in steric proximity and therefore that **7** derives from the attack of the hydride to the less hindered *exo* face of the carbonyl group (cf. Scheme 2). The configurations of the two chiral centers in the racemic **7** obtained are *RS*/*SR*. The spirodienol hydroxyl group is pointing into the intramolecular cavity, its high field shift (0.85 ppm) caused by the shielding effect of the ring currents of the three adjacent aromatic rings.

Thermal rearrangement of **7** under vacuum at 493 K lead to **3** (Scheme 1).

Molecular Modeling Investigations. Conformations and Conformational Transitions of Dibenzo[*d*,*g*][1,3]dioxocines. A 6*H*,12*H*-dibenzo[*d*,*g*][1,3]dioxocine system may adopt a rigid boat-chair conformation (BC) of C_s symmetry as well as flexible twist-boat (TB), distorted boat (DB), and twist (T) conformations of C_2 or C_1 symmetries, respectively (Figure 3). The solution and/or crystal structures of a number of dioxocines (e.g., **9**) are known,[9−12] and thus we performed computational investigations of **8** and **9** as model systems for the dioxocine subunit of the calixarene **3** in order to test the applicability of force field methods to this class of compounds.



8 **9**

The results of the conformational studies performed with the RANDOMSEARCH method[13] of Sybyl[14a] (Tripos force field[14b]) and the stochastic search routine[15] of MM3(94)[16] are summarized in Table 1. For both compounds the force field calculations predict the BC structure as the lowest energy conformation, in agreement with the experimental results available for **9**. However, the Tripos calculations seem to underestimate the energy gaps between the different conformations. The comparison of the basic conformations of **8** and **9** reveals that the additional methyl group in **8** has no influence on either the energies or geometries. The calculated geometry of **9** is in good agreement with the crystal structure[11] as indicated by the low root-mean-square (rms) deviations obtained from superposition of the heavy atoms of the crystal and optimized structures: 0.04 Å (MM3) and 0.20 Å (Tripos), and by the deviations of the torsional angles t_1−t_6: ±2° (MM3) and ±5° (Tripos).

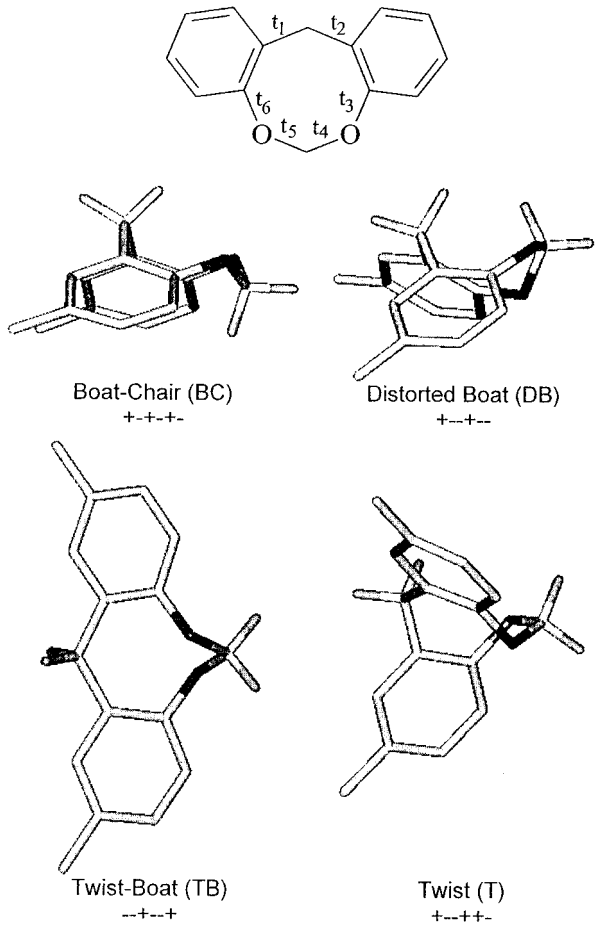


Figure 3. Basic conformations of the dibenzo[*d*,*g*][1,3]-dioxocine core of **9**, together with the signs of the torsional angles t_1−t_6 used for the characterization of the conformations.

Table 1. Calculated and Experimentally Estimated Relative Energies (in kcal mol^{-1}) of the Basic Conformations of 8 and 9

compound	method	BC	TB	DB	*T*
8	MM3	0.0	6.0	3.9	3.4
	TRIPOS	0.0	−	3.2	1.9
9	MM3	0.0	5.5	3.6	3.3
	TRIPOS	0.0	1.0	3.2	0.9
	exp[9]	0.0		>3.0[a]	

[a] Only one conformation was observed in solution, and therefore a lower limit of 3.0 kcal mol^{-1} was estimated for the energy gap.

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Table 2. Calculated (MM3(94)) Relative Steric Energies (in kcal mol^{-1}) of the Conformers of 3

conformer	relative energy
cone/BC	2.6
cone/DB	0.0
paco/BC	2.4
paco-prox/DB	4.1
paco-dist/DB	3.9
paco-dist/T	7.0
1,2-alt/BC	3.8
1,2-alt/DB	3.4
1,2-alt/T	2.8

The activation energies for the mutual interconversion between the BC and the lowest energy nonchair conformation and between the two enantiomeric DB forms (labeled DB and DB*) for compounds **8** and **9** were calculated using the dihedral angle driver procedure of the MM3(94) force field. Following earlier investigations[17−19] on similar compounds, the torsion angle t_5 was chosen as the reaction coordinate.

The transitions between a nonchair conformation and the BC form proceed via a half-chair like transition state with a near zero t_5 angle. The main structural feature of the transition state is the widening of all bond angles. Consequently, the main contribution to the activation energy originates from the angle bending term. The barriers calculated for **8** and **9** (14.0 and 13.2 kcal mol^{-1}) are larger than the one measured in **2** for the DB/BC interconversion in the 1,2-alternate conformation but smaller than in dibenzo[*a*,*d*]cyclooctane.[19] This is reasonable since the incorporation of oxygen atoms into such ring systems should result in more flexible forms.

The transition state of the interconversion between the enantiomeric DB forms is a C_s symmetric boat−boat conformation. The calculated barriers for the DB ⇄ DB* enantiomerization are smaller than 7.0 kcal mol^{-1} and point to the large flexibility of these conformations as postulated by other authors.[20]

Low-Energy Conformations of the Dioxamethylene Calix[4]arene 3. In principle, the dioxamethylene calix[4]arene **3** can adopt the cone, 1,2-alternate (1,2-alt), and partial cone (paco) conformations, whereas structures with an anti arrangement of the bridged aryl rings (e.g., an 1,3-alternate conformation) are unlikely. Conformations of **3** were generated using the stochastic search routine of the MM3 force field. The results of the calculations are summarized in Table 2.

In general, structures with DB conformations of the dioxocine showed a "flattened" arrangement of one of the bridged aromatic rings. Two distinct paco conformations were found differing in the position of the flattened ring (proximal or distal relative to the unique aryl ring pointing in the opposite direction to the rest). These two forms will be dubbed "paco-prox" and "paco-dist". According to the calculations, the lowest energy form corresponds to the cone/DB conformation.

Conformational Interconversions of 3. Two kinds of dynamic processes are possible for **3**: (i) those involving the passage of phenyl rings through the annulus of the macrocycle (a ring "flip"); (ii) those involving a conformational transition of the dioxocine moiety. The passage of one of the phenyl rings through the macrocycle was achieved by using the coordinate driver procedure[21] based on the MM3 force field. The attempted cone/DB ⇄ paco-prox/DB interconversion could not be achieved with this method due to strong repulsions between the hydroxyl group of the rotating phenol and one of the oxygens of the dioxocine. The results of the MM3 calculations are summarized in Figure 4.

In general, ring flip processes starting from a DB structure possess relatively low barriers. For all three transitions a significant widening of the C−C−C bond angles of the Ar−CH_2−Ar bonds was observed. The aryl ring flips involving a BC structure of the dioxocine subunit afforded the highest activation energies. This may be caused by the orientation of the O−CH_2−O group toward the interior of the macrocycle which leads to close van der Waals contacts to the phenolic hydroxyl groups during ring inversion.

The barriers for the BC ⇄ DB transitions relative to the particular BC conformation are similar to those found for **8** and **9**. The enantiomerizations of the C_1 symmetrical cone/DB and 1,2-alt/DB to their enantiomeric cone/DB* or 1,2-alt/DB* proceed through transition states with a C_s symmetric boat−boat conformation of the dioxocine. The barriers for these processes are 1.7 kcal mol^{-1} and 5.1 kcal mol^{-1}, respectively (relative to the starting DB conformation). Thus, it can be concluded that there is no significant influence of the calixarene backbone on the dynamics of the dioxocine ring system.

The cone/DB ⇄ 1,2-alt/DB interconversion and the topomerization of the paco-dist/DB and paco-prox/DB forms could proceed via the concerted movement of the two bridged aromatic rings through the macrocyclic annulus. The topomerization leads to a paco* conformation with the originally anti-oriented phenol ring taking a syn orientation and vice versa. The activation energies of the cone/DB → 1,2-alt/DB, paco-prox/DB → paco-prox/DB*, paco-dist/DB → paco-dist/DB* transitions were calculated as 14.8, 10.6, and 17.1 kcal mol^{-1}, respectively. In all the transition states calculated for these concerted movements a TB conformation of the dioxocine ring was found.

From the calculations it can be concluded that conformational transitions of the calixarene scaffold possess relatively low barriers when the dioxocine is in a flexible nonchair conformation. These transitions involve either rotations of the phenol rings or the concerted movement of two rings of the dioxocine. In contrast, the BC conformation of the dioxocine unit is rigid and induces high activation energies for the passage of aromatic rings through the macrocyclic annulus.

Solution Conformation. Two conformations were observed for the macrocyclic skeleton of **2**: the 1,2-alternate (the preferred conformation) and the cone conformation. In the cone form both dioxocine subunits possess a DB conformation whereas in the 1,2-alt conformation one dioxocine system exists in a DB while the second adopts a BC conformation.[4]

The 400 MHz ^{1}H NMR spectra of **3** were recorded in CD_2Cl_2 and $CDCl_2CDCl_2$ in the temperature ranges 198 K−rt and room temperature−393 K, respectively. Whereas the spectrum at 393 K displays sharp signals for the

(17) Anet, F. A. L.; Yavari, I. *J. Am. Chem. Soc.* **1977**, *99*, 6986.
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(21) Thondorf, I.; Brenn, J. *J. Mol. Struct. (THEOCHEM)* **1997**, *398−399*, 307.

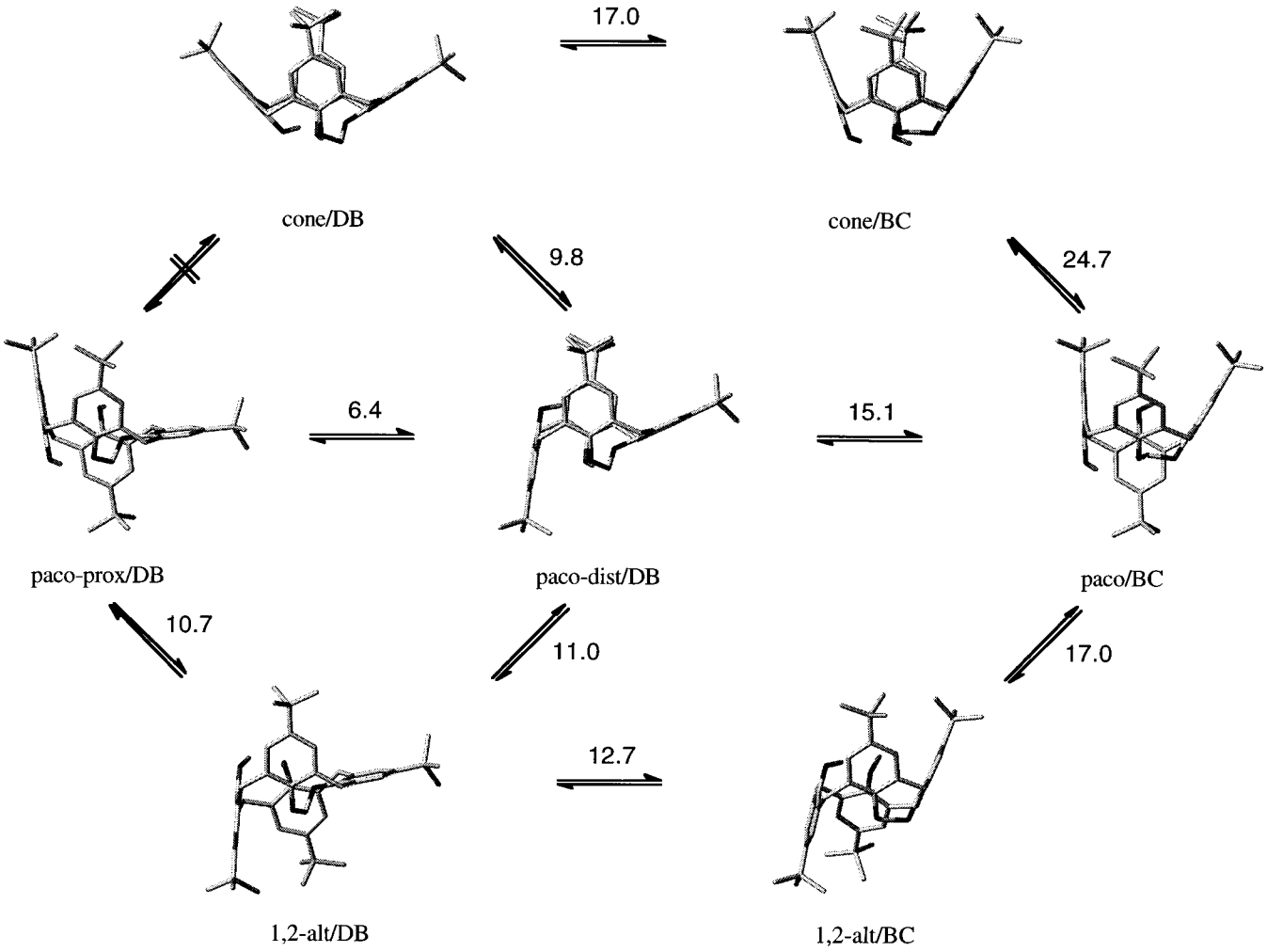


Figure 4. Calculated (MM3) relative steric energies of the conformational transitions of **3** (in kcal mol^{-1}). The energies are relative to the most stable conformer.

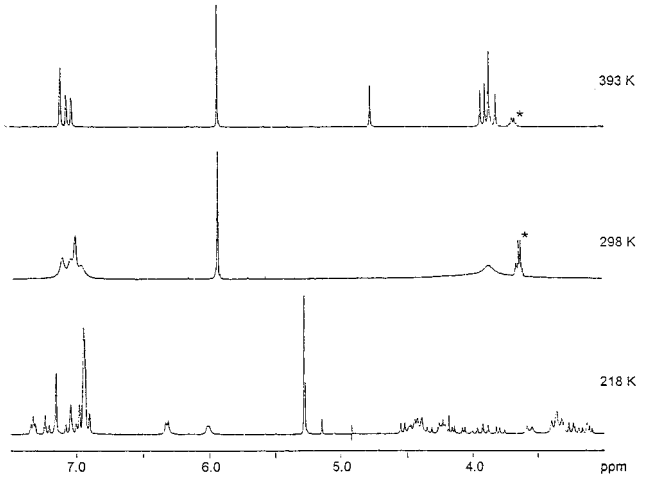


Figure 5. 400 MHz ^{1}H NMR spectra of the aromatic and methylene region of **3** at 393 and 298 K (in $C_2D_2Cl_4$) and at 218 K (in CD_2Cl_2). The signals marked with an asterisk correspond to an impurity.

aromatic, *tert*-butyl, and methylene groups, upon lowering the temperature the signals broadened and decoalesced into a complex pattern (Figure 5). The low-temperature spectrum displays three sets of signals, which are labeled 1, 2, and 3 according to their decreasing intensities (Figure 6). The first two sets display four aromatic signals whereas set 3 displays eight aromatic signals. Precluding accidental isochrony, the signal pattern suggests that sets 1 and 2 correspond to conformers of effective C_s symmetry whereas the third set corresponds to a structure of C_1 symmetry.

The assignment of the signals to the individual protons of three conformers was carried out by means of DQF−COSY, ^{13}C HMQC, and NOESY experiments.

Set 1. The signals at 6.02 and 6.32 ppm were assigned to the protons of the O−CH_2−O group on the basis of their chemical shifts and their smaller geminal coupling constant (J = 7.5 Hz)[22] as well as by the downfield chemical shift of the attached carbon (93.0 ppm). The chemical shifts differences ($\Delta\delta$) of ca. 0.8, 0.9, and 1.0 ppm for the protons of the Ar−CH_2−Ar methylenes are consistent with a syn arrangement of all the aromatic rings, i.e., a cone conformation. The conformation of the dioxocine could be derived from a NOE cross-peak between the OCH_2O proton at 6.02 ppm and the axial methylene proton of the dioxocine (4.47 ppm) which is consistent with a DB conformation of the cyclic acetal. Although this form is asymmetric, fast conformational averaging between the two enantiomeric DB conformers on the NMR time scale (without concomitant macrocyclic

(22) Electronegative α substituents decrease the absolute value of the ^2J coupling constant of a methylene group: Günther, H. *NMR Spectroscopy*; Wiley: Chichester, NY, 1980; p 101.

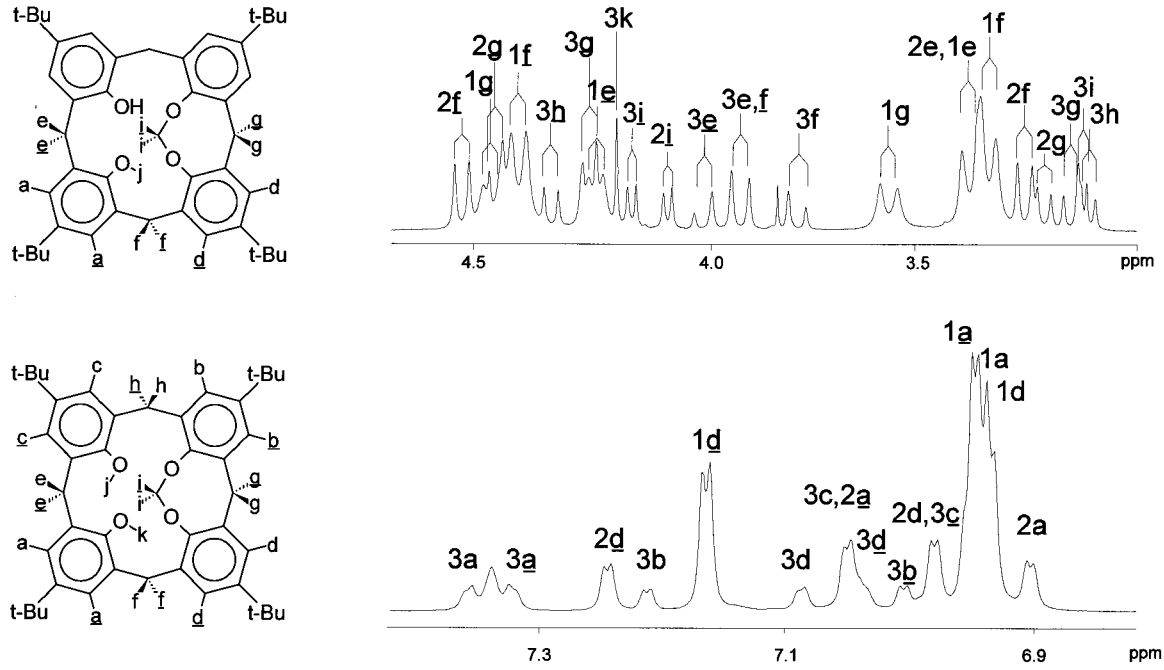
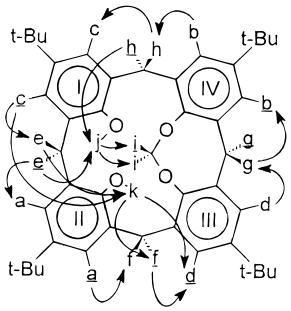


Figure 6. Left: Numbering schemes for conformers of C_2 (top) and C_s (bottom) symmetry. Right: Methylene (top) and aromatic (bottom) region of the ^{1}H NMR spectrum of **3** at 218 K in CD_2Cl_2. The signals are assigned to the sets 1, 2, and 3. The singlet at 7.32 ppm corresponds to the OH signal of set 2.

Scheme 3



ring inversion) should lead to effective C_s symmetry, without mutually exchanging the axial and equatorial methylene protons. Indeed, calculations of **3** (see above) indicate that the barrier for the process is for the cone form only 1.7 kcal mol^{-1}.

Set 2. This set displays signals at 3.26 and 4.54 ppm for the methylene protons f and f, their large chemical shift difference suggesting a syn arrangement of the neighboring rings. NOE's were observed between signal f and the aromatic signals a and d, as well as between a and d and the equatorial (upfield) methylene signals e and g, respectively, in agreement with a cone conformation of the macrocyclic ring. The $\Delta\delta$ value for the dioxamethylene protons ($\Delta\delta$ = 2.25 ppm) is remarkably larger than in the sets 1 ($\Delta\delta$ = 0.3 ppm) and 3 ($\Delta\delta$ = 1.03 ppm). This suggests a cone/BC conformation because only in this conformation is one bridging methylene proton spatially close to the centers of two aromatic rings whereas the other one is deshielded by its proximity to the hydroxyl groups of the phenol rings.

Set 3. The NOE interactions observed for this set are depicted in Scheme 3. The cross-peaks between d and g and b and g as well as between b and h and c and h are consistent with a syn arrangement of the three aromatic rings I, III, and IV, but ring II is in an anti orientation toward these three rings as evidenced by the NOE's of protons a and d as well as a and c to different methylene protons of the same pair (f and f and e and e, respectively).[23] Furthermore NOE's from the hydroxyl signal k to d and c were observed. Signal set 3 can be therefore ascribed to a paco conformation of C_1 symmetry. The anti orientation of ring II is further supported by the small chemical shifts differences found for the two methylene proton pairs f/f ($\Delta\delta$ = 0.13 ppm) and e/e ($\Delta\delta$ = 0.09 ppm) compared with g/g ($\Delta\delta$ = 1.10 ppm) and h/h ($\Delta\delta$ = 1.22 ppm). Notably, NOESY cross-peaks were observed between the hydroxyl protons j and both O−CH_2−O protons. Inspection of molecular models suggests that this is in agreement with a BC conformation of the dioxocine subunit. Moreover, the chemical shifts of the O−CH_2−O protons which are at a higher field (δ 3.13 and 4.16 ppm) than in set 1 (6.02 and 6.32 ppm) further support the presence of a paco/BC conformation since only in this conformation are both protons close enough to the centers of the aromatic rings to be influenced by their shielding effects.

de Mendoza and co-workers reported that the methylene groups in calix[4]arenes resonate at 30−33 ppm when the adjacent rings are oriented syn and at 36−38 ppm when the rings are oriented anti.[24] ^{13}C-HMQC NMR data of **3** indicate that the methylene carbons attached to the protons f, h, and e appear in the 28−32 ppm region for both sets 1 and 2, in agreement with syn orientations of the adjacent rings (i.e., cone conformations). In contrast, the carbons attached to e and f of set 3 appear in the 36−37 region, in agreement with a paco conformation. The empirical rule fails for the dioxocine rings of set 1 since although the dioxamethylene bridge precludes an anti arrangement, the methylene carbon attached to g resonates at 38.2 ppm.

(23) For identification purposes, pairs of signals on the same ring or methylene group are labeled with the same letter (i.e., a and a), with the underline denoting the signal resonating at a lower field.

(24) Jaime, C.; de Mendoza, J.; Prados, P.; Nieto, P. M.; Sanchez, C. *J. Org. Chem.* **1991**, *56*, 3372.

Table 3. Experimental (NMR) Molar Fractions and Relative Free Energies (in kcal mol^{-1}, shown in parentheses) of the Three Conformers of 3 in CD_2Cl_2 at Different Temperatures

conformer	temperature				
	198 K	208 K	218 K	225 K	229 K
cone/DB	0.55(0.0)	0.53(0.0)	0.55(0.0)	0.55(0.0)	0.56(0.0)
cone/BC	0.34(0.19)	0.32(0.21)	0.27(0.31)	0.24(0.37)	0.24(0.39)
paco/BC	0.11(0.63)	0.15(0.52)	0.18(0.48)	0.21(0.43)	0.20(0.47)

Relative Energies of the Conformers of 3. The relative free energies ($\Delta G°$) of the conformers of **3** were calculated at different temperatures (Table 3) from their population ratio in CD_2Cl_2. The MM3 calculations correctly predict the three lowest energy conformations and their stability order, but overestimate the relative energies of the cone/BC and paco/BC forms. The temperature dependence of the free energies estimated from the integrals of the ^{1}H NMR spectra indicate an entropic contribution to the relative free energies (Table 3) which is neglected by force field calculations.[25]

Conformational Interconversions in 3. Neri et al. have shown that the barrier for the cone → 1,2-alt interconversion of **2** is 18.2 kcal mol^{-1} (a value higher than the barrier for the cone-to-cone* inversion of **1**) while the BC−DB transition of the dioxocine in the 1,2-alt conformation has a barrier of 12.4 kcal mol^{-1}. An even higher conformational flexibility should be expected for the single methylene bridged calixarene **3**.

Chemical exchange[26] cross-peaks were observed in the NOESY (EXSY) spectrum between the sets 1 and 2 as well as between 1 and 3, indicating cone/DB ⇄ cone/BC and cone/DB ⇄ paco/BC interconversions. The exchange cross-peaks between the signal sets 2 and 3 were of lower intensity. Thus, the interconversion between the cone/BC and the paco/BC conformers is either much slower than the other interconversions or it does proceed via one of the other populated conformations as an intermediate (indirect exchange). The latter is in agreement with the molecular mechanics calculations (see above).

Self-exchange cross-peaks were observed between the axial and equatorial methylene protons of set 1 indicating a cone-to-cone* inversion process of the cone/DB conformation. These cross-peaks displayed considerable intensities even after the mixing time used for the NOESY spectrum was reduced. Therefore, it can be concluded that the cone-to-cone* inversion process does not involve any of the other two populated conformers as intermediates since such a hypothetical indirect exchange should manifest in an increase of the intensities of the cross-peaks between sets 1 and 2 (and/or 1 and 3) with a concomitant decrease of the self-exchange cross-peaks. However, a rotational pathway proceeding via a low populated paco/DB or 1,2-alt/DB conformers would be in agreement with the observed cross-peak intensities. The relatively large intensities of the self-exchange cross-peaks for set 1 indicate that the rate of the cone-to-cone* inversion process is higher than the rest of the processes detected by the NOESY spectrum. This is further supported by the ^{1}H NMR spectrum of **3** at 253 K in which the methylene protons of set 1 are strongly broadened whereas the rest of the signals are relatively narrow.

Self-exchange cross-peaks were observed between the aromatic signals a and c, a and c, b and d, b and d as well as between the methylene signals f and h and f and h of set 3, in agreement with a topomerization process of the paco/BC conformation. Two indirect pathways involving low populated conformers and one indirect pathway involving the cone/DB conformation are possible for this topomerization. The presence of intense exchange cross-peaks at 150 ms mixing time supports the first alternative.

The rate constants for the cone/BC → cone/DB, cone/DB → paco/BC transitions and the topomerization of the paco/BC conformation were calculated from the integrals of the signals of the NOESY spectrum recorded with a mixing time of 0.5 s using the "initial rate approximation".[25−27] All nonoverlapping diagonal and cross-peaks were integrated. All diagonal peaks belonging to the same signal set and all exchange cross-peaks pertinent to the same exchange process were averaged. The rate constants and rotational barriers at 218 K for the conformational interconversions observed are listed in Table 4.[28,29] Ideally, the differences between the experimental free energies of activation of the forward and reverse processes ($\Delta\Delta G^{\ddagger}$) should be equal to the free energy difference ($\Delta G°$) between the conformers. However, deviations of up to 0.3 kcal mol^{-1} were observed indicating the limited precision of the approximations used. Notwithstanding that the MM3 force field overestimates the relative energies of the solution conformers, the agreement of the experimental barriers with the calculated ones is remarkably good (Table 4). For the interconversion paco/BC ⇄ cone/BC rate constants of 0.007 s^{-1} and 0.003 s^{-1} were estimated. These rates are one order of magnitude lower than the slowest step of a stepwise pathway cone/BC → cone/DB → paco/BC. Thus it seems likely that these two rate constants are not first order, but are due to an indirect exchange process as deduced from the small intensities of the exchange cross-peaks for this process.

The rate constant of the cone-to-cone* inversion of the cone/DB conformation was estimated from the integrals of the diagonal signals of the protons of the dioxamethylene bridge and their exchange cross-peaks. Since both diagonal signals show only cross-peaks of extremely small intensities with the signals of the dioxamethylene protons of other conformations, a model for the exchange of two equally populated sites could be used.[29] Using mixing times of 0.15 and 0.5 s rate constants of 6.1 and 16.6 s^{-1} were calculated which afforded free energies of activation of 11.8 and 11.4 kcal mol^{-1}, respectively.[30] The barrier of the cone-to-cone* inversion is nearly 2 kcal mol^{-1} lower

(25) Preliminary ^{1}H NMR experiments indicate that in CD_3COCD_3 the most populated conformer of **3** is the cone/BC.

(26) For a review see: Perrin, C. L.; Dwyer, T. J. *Chem. Rev.* **1990**, *90*, 935. For examples of the determination of the kinetics of the interconversions of the conformers of calixarene derivatives by 2D-EXSY spectroscopy see: (a) Blixt, J.; Detellier, C. *J. Am. Chem. Soc.* **1994**, *116*, 11957. (b) van Loon, J.-D.; Groenen, L. C.; Wijmenga, S. S.; Verboom, W.; Reinhoudt, D. N.; *J. Am. Chem. Soc.* **1991**, *113*, 2378.

(27) Kumar, A.; Wagner, G.; Ernst, R. R.; Wüthrich, K. J. *J. Am. Chem. Soc.* **1981**, *103*, 3654.

(28) The rate constants were derived using the equation $I_{ij} = k_{ji}\tau_m Mj°$.

(29) Wöhnert, J. Diplomarbeit, Martin-Luther-Universität, Halle-Wittenberg, 1996.

(30) The intensity of the exchange cross-peaks between the two dioxamethylene signals are influenced also by the mutual NOE effects which have an opposite sign to the magnetization transfer effects due to the dynamic process. These NOE effects should not contribute significantly to the cross-peak intensities at the small mixing times used, but strictly the values obtained for the barrier represent only an upper limit.

Table 4. Experimental Rate Constants (in s^{-1}) at 219 K and Experimental and Calculated (MM3) Barriers (in kcal mol^{-1}) for the Conformational Transitions Cone/DB → Cone/BC, Cone/DB → Paco/BC and the Topomerization of the Paco/BC Conformation

process	k	$\Delta G^{\ddagger}$	calcd[a]	rotational process
cone/DB → cone/BC	0.02	14.3	17.0	cone/DB → cone/BC
cone/BC → cone/DB	0.08	13.7	14.4	cone/BC → cone/DB
cone/DB → paco/BC	0.02	14.3	15.1	cone/DB → paco-dist/DB → paco/BC
paco/BC → cone/DB	0.14	13.5	12.7	paco/BC → paco-dist/DB → cone/DB
paco/BC →paco/BC*	0.14	13.5	12.7	paco/BC → paco-dist/DB → paco-prox/DB → paco-prox/DB* → paco-dist/DB* → paco/BC*

[a] Energy barriers relative to the initial conformer.

than for the other transitions involving a BC−DB interconversion of the dioxocine system.

The lowest energy pathway for the cone-to-cone* inversion of the cone/DB form calculated by MM3 proceeds via the intermediates paco-dist/DB → paco-prox/DB → paco-prox/DB* → paco-dist/DB* conformations with a total barrier of 10.6 kcal mol^{-1}.

Conclusions. Three low energy conformers of **3** exist in CD_2Cl_2, a cone conformation with its dioxocine unit in a distorted boat conformation (cone/DB), and cone and partial cone conformations with a boat-chair arrangement of the dioxocine. Molecular mechanics calculations are in reasonable agreement with the experimental data and indicate that the rate-limiting steps for the conformational interconversions of **3** are the transitions of the dioxocine system. The dynamic behavior of the dioxocine is not altered by introducing it into the calixarene framework.

Experimental Section

Molecular Modeling. All molecular modeling calculations were done using the SYBYL 6.2 software including the RANDOMSEARCH procedure and with the MM3(94) force field. Rotations around all C−C and C−O bonds were allowed in the RANDOMSEARCH procedure for the eight-membered ring compounds. An upper limit of 70000 search cycles was used. Conformations with an energy <15 kcal mol^{-1} relative to the conformation with the lowest energy were saved. The SEARCH was finished when all conformations were found at least six times due to a 99% probability to find all possible minima. For all energy minimizations using the TRIPOS force field, the calixarene parameters previously described were used.[31] All calculations were done with a distance dependent dielectric constant $\epsilon = 1$ using Gasteiger−Hückel charges[32] and the Powell minimization algorithm with a maximum of 3000 minimization cycles.

The MM3 calculations were carried out using the standard parameter set. Missing torsional parameters for the O−Csp^3−O−Csp^2 fragment were generated with the MM3 parameter estimator and used without further modification. The stochastic search routine of MM3 was employed for the generation of conformers using the default values for the input parameters except for the number of pushes, which was set to 10000. The torsion angle used as the reaction coordinate was changed in 10° steps during the dihedral angle driver calculations and the structure of the maximum energy along the reaction pathway saved. In a range of 20° around this structure the torsion angle was modified in 1° steps. The conformational transitions of the dioxamethylene calixarene were simulated with the coordinate driver method[21] using the phenolic *p*-carbon atoms as moving atoms and a stepwidth of 0.1 Å. The concerted movements of the dioxocine unit were achieved by gradual modification of the *z*-coordinate of the dioxamethylene carbon atom in steps of 0.01 Å. The transition states were obtained by refining the conformer of maximum energy using the full matrix Newton−Raphson minimization method followed by checking that there is one negative eigenvalue in the Hessian matrix.

Crystallography. X-ray diffraction data were measured by with an ENRAF-NONIUS CAD-4 automatic diffractometer. Cu Kα (λ = 1.54178 Å) radiation with a graphite crystal monochromator in the incident beam was used, respectively. The crystallographic computing was done on a VAX 9000 computer using the TEXSAN structure analysis software.

Crystal data for **6**: $C_{45}H_{54}O_4 \cdot CH_3CN$, space group *C*2/*c*, a = 25.677(4) Å, b = 10.265(3) Å, c = 34.484(7) Å, β = 97.03(3)°, V = 8286(2) $Å^3$, z = 2, ρ_{calc} = 1.12 g cm^{-3}, μ(Cu Kα): 5.15 cm^{-1}, no. of unique reflections: 6354, no. of reflections with $I \geq 3\sigma_I$: 3650, R: 0.072, R_w: 0.098.

NMR Spectroscopy. The ^{1}H NMR spectra and COSY-DQF and NOESY spectra were recorded with a Bruker Avance DRX 400 and Varian Unity 500 MHz spectrometer. For the NOESY spectra, 1024 increments for T_1 with 2048 complex data points were recorded using a spectral width of 3063.726 Hz and two scans per increment. Zero-filling to 2048 complex data points was done in the F_1-dimension. A relaxation delay of two seconds between the experiments and mixing times of 150 and 500 ms were utilized for the NOESY experiments. "Shifted" sine functions were applied as window-functions in order to improve the signal-to-noise ratio. The integration of the signals in the NOESY spectra for the calculation of the rate constants was done using the TRIAD software.

For the ^{13}C-HMQC spectrum 128 increments with 96 scans per increment were recorded in the F_1 dimension using a spectral width of 16970 Hz. Sine (F_2) and squared sine functions (F_1) were applied as window functions.

Preparation of the Dioxamethylene Spirodienone Derivative of *p-t*-Bu-calix[4]arene (6). A 600 mg (0.9 mmol) amount of **4**[11b] and 540 mg (5.6 mmol) of tetrabutylammonium bromide were dissolved in 300 mL of CH_2Cl_2, and a 30% NaOH solution was added. After 18 h of reflux, 100 mL of water was added, and the organic phase was separated, washed with water until neutrality, dried ($MgSO_4$), and evaporated. The solid yellow residue was purified by column chromatography (silica gel, eluent: chloroform). The first yellow fraction was collected to give 314 mg (0.47 mmol, 52.3%) of **6**. Pure **6** (mp: 194−196 °C) was obtained by recrystallization from $CHCl_3$/MeCN. ^{1}H NMR (400 MHz, $CDCl_3$, rt) δ 7.21 (d, broad, 1H, ArH), 7.05−6.98 (overlapping doublets, 5H, ArH), 6.96 (d, 1H, J = 2.3 Hz, CH), 6.02 (d, 1H, J = 2.0 Hz, CH), 5.62 (d, 1H, J = 7.7 Hz, O−CH_2−O), 5.42 (d, 1H, J = 7.7 Hz, O−CH_2−O), 4.72 (d, 1H, J = 11.8 Hz, CH_2), 4.17 (d, 1H, J = 15.6 Hz, CH_2), 3.78 (d, 1H, J = 15.8 Hz, CH_2), 3.68 (d, 1H, J = 14.8 Hz, CH_2), 3.61 (d, 1H, J = 14.7 Hz, CH_2), 3.32 (d, 1H, J = 13.6 Hz, CH_2), 3.23 (d, 1H, J = 11.9 Hz, CH_2), 2.96 (d, 1H, J = 15.9 Hz, CH_2), 1.28 (s, 9H, t-Bu), 1.21 (s, 9H, t-Bu), 1.17 (s, 9H, t-Bu), 1.15 (s, 9H, t-Bu) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, rt) δ 195.48 (C=O), 152.74, 151.63, 150.90, 147.38, 147.15, 146.78, 144.26, 138.70, 138.43, 137.93, 135.47, 131.16, 129.24, 128.15, 128.06, 127.07, 125.19, 125.07, 124.62, 123.36, 123.08, 120.26, 103.08 (O−CH_2−O), 83.34 (C−O), 37.02, 35.34, 34.74, 34.53, 34.29, 34.18, 31.89, 31.38, 31.19, 28.85, 28.37 ppm. IR: ν 1698.1 cm^{-1} (C=O). CI MS: m/z 659.4 (MH^+).

(31) Thondorf, I.; Hillig, G.; Brandt, W.; Brenn, J.; Barth, A.; Böhmer, V. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2259.

(32) Gasteiger, J.; Marsili, M. *Tetrahedron* **1980**, *30*, 3219.

Dioxamethylene Monospirodienol Calix[4]arene (7). A 250 mg (0.38 mmol) amount of dioxamethylene monospirodienone calix[4]arene was dissolved in 150 mL of tetrahydrofuran. A 400 mg (10.6 mmol) amount of $NaBH_4$ was added while stirring, and after 5 min of reflux the yellow color of the solution disappeared. A 100 mL volume of EtOH was then added, and the stirring was continued for an additional 1 h. The solvent was evaporated, and the solid residue was redissolved in 50 mL of CH_2Cl_2 and washed three times with 50 mL of water. The organic phase was separated, dried, and evaporated. The white solid was recrystallized from 100 mL of acetonitrile to give 112 mg (0.17 mmol or 45%) of colorless needles of **7**, mp 206−207 °C. ^{1}H NMR: (400.133 MHz, rt, $CDCl_3$) δ 7.16 (d, J = 1.3 Hz, ArH, 1H), 7.09 (d, J = 2.3 Hz, ArH, 1H), 7.03 (d, J = 2.3 Hz, ArH, 1H), 7.02 (s, ArH, 1H), 7.00 (d, J = 2.3 Hz, ArH, 1H), 6.95 (d, J = 2.1 Hz, ArH, 1H), 6.2 (s, C═CH, 1H), 5.90 (d, J = 8.0 Hz, OCH_2O, 1H), 5.68 (s, C═CH, 1H), 5.51 (d, J = 8.0 Hz, OCH_2O, 1H), 4.83 (d, J = 11.8 Hz, CH_2, 1H), 4.39 (d, J = 11.8 Hz, H−C(OH), 1H), 4.11 (d, J = 13.8 Hz, CH_2, 1H), 3.84 (d, J = 14.2 Hz, CH_2, 1H), 3.49 (d, J = 14.1 Hz, CH_2, 1H), 3.42 (d, J = 15.5 Hz, CH_2, 1H), 3.31 (d, J = 13.8 Hz, CH_2, 1H), 3.28 (d, J = 12.8 Hz, CH_2, 1H), 2.95 (d, J = 15.6 Hz, CH_2, 1H), 1.28 (s, t-Bu, 9H), 1.19 (s, t-Bu, 9H), 1.14 (s, t-Bu, 9H), 1.09 (s, t-Bu, 9H), 0.87 (d, J = 12.0 Hz, CHO*H*, 1H). ^{13}C NMR: (100.4 MHz, rt, $CDCl_3$) 154.0, 152.7, 150.6, 148.1, 147.6, 147.2, 143.6, 141.2, 139.6, 139.3, 131.2, 130.5, 128.3, 126.9, 125.5, 124.9, 124.5, 123.5, 123.1, 122.7, 120.6, 120.3 ppm, 102.3 (OCH_2O), 88.8 (Csp^3), 76.45 (HCOH), 40.5, 37.5, 35.4, 34.3 (2C), 34.2 (2C), 31.8, 31.3, 31.1, 29.4, 28.6 ppm. CI MS: m/z 661.4 (MH^+). Anal. Calcd for $C_{45}O_4H_{56}$: C, 81.78; H, 8.54. Found: C, 81.73; H, 8.57.

Dioxamethylene Calix[4]arene 3. A 130 mg (0.2 mmol) amount of **7** was heated under vacuum for 5 min at 220 °C. The product was purified by preparative TLC (eluent: CH_2Cl_2). The fraction with R_f = 0.15 was nearly pure product containing traces of **1** which were removed by trituration of the product with ethanol and filtration. The ethanolic solution was evaporated, and the residue was recrystallized from *n*-hexane, giving 40 mg (31%) of **3**, mp 221 °C (lit.[5] 247−249 °C). ^{1}H NMR: (400.133 MHz, 393 K, $C_2D_2Cl_4$) δ 7.13 (d, J = 2.0 Hz, ArH, 4H), 7.08 (d, J = 2.3 Hz, ArH, 2H), 7.04 (d, J = 2.2 Hz, ArH, 2H), 4.8 (s, OH, 2H), 3.95 (s, CH_2, 2H), 3.92 (s, CH_2, 2H), 3.89 (s, CH_2, 4H), 3.84 (s, CH_2, 2H), 1.32 (s, t-Bu, 18H), 1.25 (s, t-Bu, 18H) CI MS m/z 661.1 (MH^+), 660.1 (M^-). Anal. Calcd for $C_{45}O_4H_{56}$: C, 81.78; H, 8.54. Found: C, 82.01; H, 8.84.

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Supporting Information Available: ^{1}H and COSY NMR of **6**, copies of the NOESY and the ^{13}C-HMQC spectra of **3**, and chemical shifts of the three conformers of **3** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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