The 1,2-Alternate Conformation of Calix[4]arenes: A Rare Conformation? Dynamic ^{1}H NMR Studies of Flexible Tetraalkylated Calix[4]arenes

Leo C. Groenen,[†] Jan-Dirk van Loon,[†] Willem Verboom,[†] Sybolt Harkema,[‡] Alessandro Casnati,[§] Rocco Ungaro,[§] Andrea Pochini,[§] Franco Ugozzoli,[⊥] and David N. Reinhoudt*,[†]

Contribution from the Laboratories of Organic Chemistry and Chemical Physics, University of Twente, P.O. Box 217, 7500 AE Enschede, The Netherlands, the Institutes of Organic Chemistry and Structural Chemistry, University of Parma, Viale delle Scienze, 43100 Parma, Italy, and the Centre for the Study of Structural Diffractometry C.N.R, Viale delle Scienze, 43100 Parma, Italy. *Received July 27, 1990*

Abstract: Dynamic ^{1}H NMR measurements of the tetramethyl ether of *p-tert*-butylcalix[4]arene (**2**) show for the first time that all four possible conformations of one particular calix[4]arene are present, *including the 1,2-alternate conformation.* The thermodynamically most stable partial cone conformation readily interconverts to a cone or to a 1,3-alternate conformation; the interconversion to a 1,2-alternate conformation is much slower. The 1,2-alternate conformation of **2** is the kinetically stable conformation at the ^{1}H NMR time scale. The 1,2-alternate conformation was confirmed by comparison of its ^{1}H NMR spectrum with that of the newly synthesized tetraethyl ether of *p-tert*-butylcalix[4]arene in a fixed 1,2-alternate conformation (**6**), of which the X-ray structure was determined. Partial rigidification of the calix[4]arene moiety in four different ways was achieved by replacing two of the methoxy groups of the tetramethyl ether **2** by ethoxy groups. The relative thermodynamic stabilities of the conformations of the calix[4]arene are influenced strongly by this relatively small change; in particular the 1,2-alternate conformation becomes much more stable. For the *anti*-1,3-diethyl-2,4-dimethyl ether **7b** the 1,2-alternate is even the thermodynamically most stable conformation. Molecular mechanics calculations indicate that this is caused by the combined favorable effects on the electrostatic energy of the inside orientation of the methoxy groups and the relative large distance between the two ethoxy groups. The tetraethyl ether of *p-tert*-butylcalix[4]arene is not flexible at room temperature, but it equilibrates in solution at temperatures above 100 °C to a mixture of also all the four possible conformations.

Introduction

Calix[4]arenes are molecules that are receiving increasing attention in the field of supramolecular chemistry, as they are very useful building blocks for host molecules with different properties.[1] The most pronounced features of calix[4]arenes are the relatively simple modification at both the lower rim (by reaction at the OH groups) and at the upper rim (after removal of the *tert*-butyl groups),[1] which can also be carried out with 1,3-selectivity, i.e., at the two diametrically placed phenyl rings.[2] Furthermore, the calix[4]arene moiety can exist in four different conformations (Figure 1),[3] and this offers an extra handle for directing the properties of calix[4]arenes.[4]

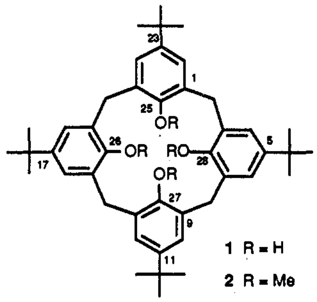
Substitution at all four phenolic oxygen atoms of a calix[4]arene generally leads to conformationally rigid products, which exist in the cone, the partial cone, the 1,3-alternate conformation, or mixtures of these, depending on the substituent and on the reaction conditions.[1]

The 1,2-alternate conformation seems to be excluded as a product of tetrasubstitution, and this might be attributed to the fact that the disubstituted intermediate is usually diametrically substituted and exists in a cone conformation,[2] so that the 1,2-alternate conformation is unattainable for further reactions. An exception might be the tetrakis(dimethylthiocarbamate) of **1**, of which the X-ray structure shows a 1,2-alternate conformation, but no details for its synthesis have been reported yet.[5]

The 1,2-alternate conformation might be observed in flexible calix[4]arenes, for which the conformations are thermodynamically controlled. The parent *p-tert*-butylcalix[4]arene **1** (Chart I) is a flexible molecule but preferably exists in the cone conformation.[6]

Gutsche has shown that the tetramethyl ether of *p-tert*-butylcalix[4]arene (**2**, Chart I) is also a flexible molecule. The ^{1}H NMR spectrum of **2**, recorded at room temperature, shows broad coalescing signals, that become sharp at lower temperature to a set of signals that was interpreted as representing two partial cone configurations.[7] The tetramethyl ether without *tert*-butyl groups behaves analogously.[7] The tetramethyl ether of *p*-nitrocalix[4]arene has been reported to exist in more than one conformation, but these have not been specified.[8] A 1,2-alternate conformation

Chart I



[†] Laboratory of Organic Chemistry.

[‡] Laboratory of Chemical Physics.

[§] Institute of Organic Chemistry.

[⊥] Institute of Structural Chemistry and the Centre for the Study of Structural Diffractometry.

(1) Gutsche, C. D. *Calixarenes*; Stoddart, F. J., Ed.; Monographs in Supramolecular Chemistry, Vol. 1; The Royal Society of Chemistry; Cambridge, 1989.

(2) (a) van Loon, J.-D.; Arduini, A.; Verboom, W.; van Hummel, G. J.; Harkema, S.; Ungaro, R.; Reinhoudt, D. N. *Tetrahedron Lett.* **1989,** *30,* 2681–2684. (b) van Loon, J.-D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1990,** *55,* 5639–5646.

(3) In this paper we use a schematic drawing of calix[4]arene in the form of a parallelogram, of which the corners represent the methylene bridges. Only the relative orientations of the alkoxy groups are shown for clarity, since the para substituents are always *tert*-butyl groups.

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(7) Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983,** *39,* 409–426.

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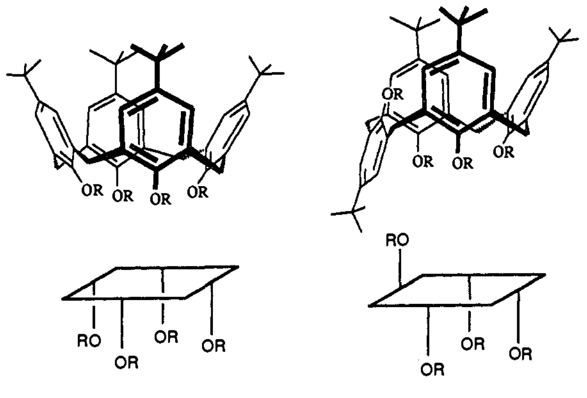


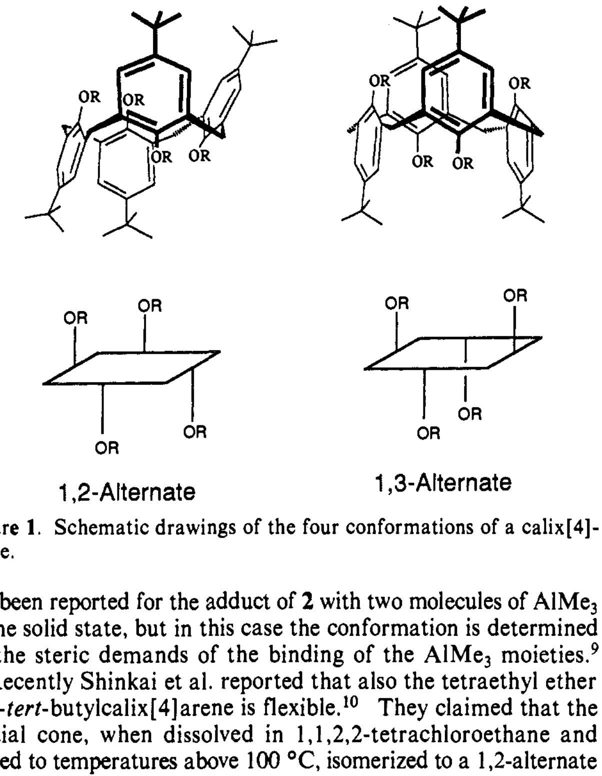


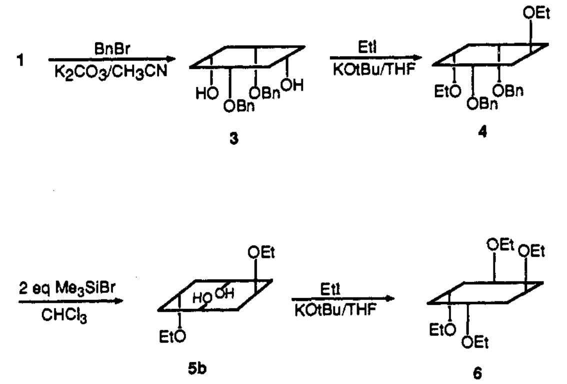
Figure 1. Schematic drawings of the four conformations of a calix[4]arene.

has been reported for the adduct of **2** with two molecules of $AlMe_3$ in the solid state, but in this case the conformation is determined by the steric demands of the binding of the $AlMe_3$ moieties.[9]

Recently Shinkai et al. reported that also the tetraethyl ether of *p-tert*-butylcalix[4]arene is flexible.[10] They claimed that the partial cone, when dissolved in 1,1,2,2-tetrachloroethane and heated to temperatures above 100 °C, isomerized to a 1,2-alternate conformation until equilibrium was reached, but no evidence for the 1,2-alternate structure was given. The ratio between partial cone and 1,2-alternate was reported to be 1.11:1 at 125 °C, implying that only a very small free energy difference ($\sim$0.09 kcal mol^{-1}) exists between these two conformations. It seems that, at least in this case, the 1,2-alternate conformation is a thermodynamically relatively stable conformation.

In the preceding paper we describe the synthesis of a series of tetramethylated upper-rim calixcrowns, which exist in three conformations, viz. the partial cone, the cone, and the 1,3-alternate.[11] For these compounds the 1,2-alternate conformation is not attainable. This result prompted us to investigate more generally the conformations of flexible and partly rigidified calix[4]arenes, and to search specifically for the 1,2-alternate conformation. The results of our investigations on tetraalkylated *p-tert*-butylcalix[4]arenes are described in this paper.

Scheme I



Results and Discussion

We started our investigations with the known tetramethyl ether **2**. The low-temperature ^1H NMR spectrum of this compound, published by Gutsche et al.,[7] already showed that there are more signals present than can be accounted for by only one partial cone conformation. Gutsche interpreted the remaining signals as corresponding to another partial cone conformation with one of the methoxy groups pointing into the cavity. On the basis of our knowledge of the conformational behavior of the upper-rim calixcrowns[11] and with the help of a 2-D EXSY NMR spectrum, we have reinterpreted this spectrum. We now believe that signals are present *corresponding to all four possible conformations, including the 1,2-alternate conformation.*

Figure 2 shows the ^1H NMR spectrum recorded at −30 °C. In the *tert*-butyl region of the spectrum three signals are present beside the three large singlets of the partial cone. These correspond to the four equivalent *tert*-butyl groups of the 1,3-alternate (δ 1.26), the 1,2-alternate (δ 1.24), and the cone (δ 1.06) conformations. The aromatic region shows in addition to the four peaks of the partial cone conformation small signals of the 1,3-alternate (singlet at δ 7.09) and the 1,2-alternate (an AB quartet with the two high peaks at δ 7.08 and 7.03) conformations. The singlet of the cone conformation cannot be identified in this spectrum as it lies under one of the signals of the partial cone at δ 6.80, but at higher temperatures this singlet shifts to higher field. The signals of the methoxy and methylene protons could be assigned as well (see Table I). The high field positions of the methoxy signals of the 1,2-alternate (δ 2.99) and the 1,3-alternate conformations (δ 2.87) and of one of the three methoxy signals of the partial cone conformation (δ 1.99) indicate that these protons are shielded by the aromatic rings. Therefore it seems likely that the corresponding methoxy groups are pointing into the cavity of the calix[4]arene.[12]

The spectra recorded at increasingly higher temperatures show that the signals start coalescing. At room temperature (RT) the spectrum shows broad peaks, but in addition to these peaks there are still sharp signals present at δ 7.05 and 7.04 (part of an ABq), 4.25 and 3.18 (ABq, J = 13.0 Hz), 3.82 (s), 3.02 (s), and 1.25 (s), most of which could already be seen in the room temperature spectrum published by Gutsche et al.[7] These signals correspond exactly to all the signals of the 1,2-alternate conformation. Only at higher temperatures do these signals coalesce with the other broad signals. This indicates that interconversions between the partial cone, the cone, and the 1,3-alternate conformations are much faster than interconversions involving the 1,2-alternate conformation. This means that the 1,2-alternate is a kinetically relatively stable conformation. This was elegantly illustrated by an EXSY NMR spectrum of **2** that was recorded at −30 °C. In this spectrum a very clear exchange pattern between the four signals of the aromatic protons of the partial cone and the singlets

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(9) Bott, S. G.; Coleman, A. W.; Atwood, J. L. *J. Inclusion Phenom.* **1987**, *5*, 747–758.

(10) Araki, K.; Iwamoto, K.; Shinkai, S.; Matsuda, T. *Chem. Lett.* **1989**, 1747–1750.

(11) van Loon, J.-D.; Groenen, L. C.; Verboom, W.; Wijmenga, S. S.; Reinhoudt, D. N. *J. Am. Chem. Soc.*, preceding paper in this issue.

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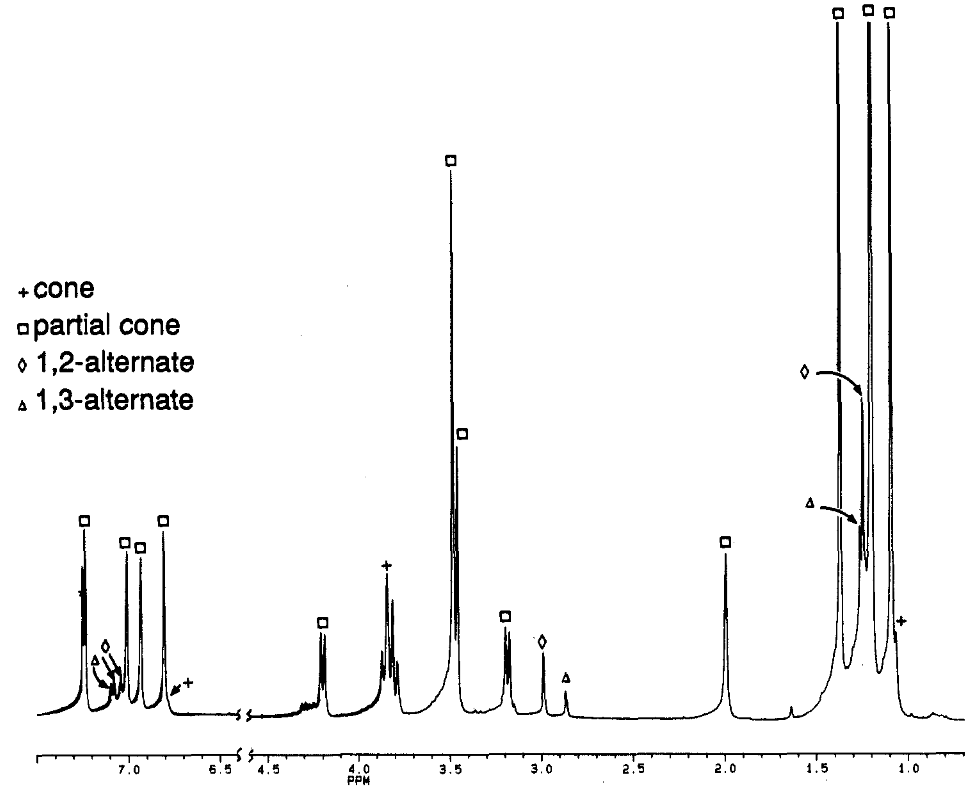


Figure 2. The 600 MHz ^{1}H NMR spectrum of compound **2** in $CDCl_3$, recorded at −30 °C.

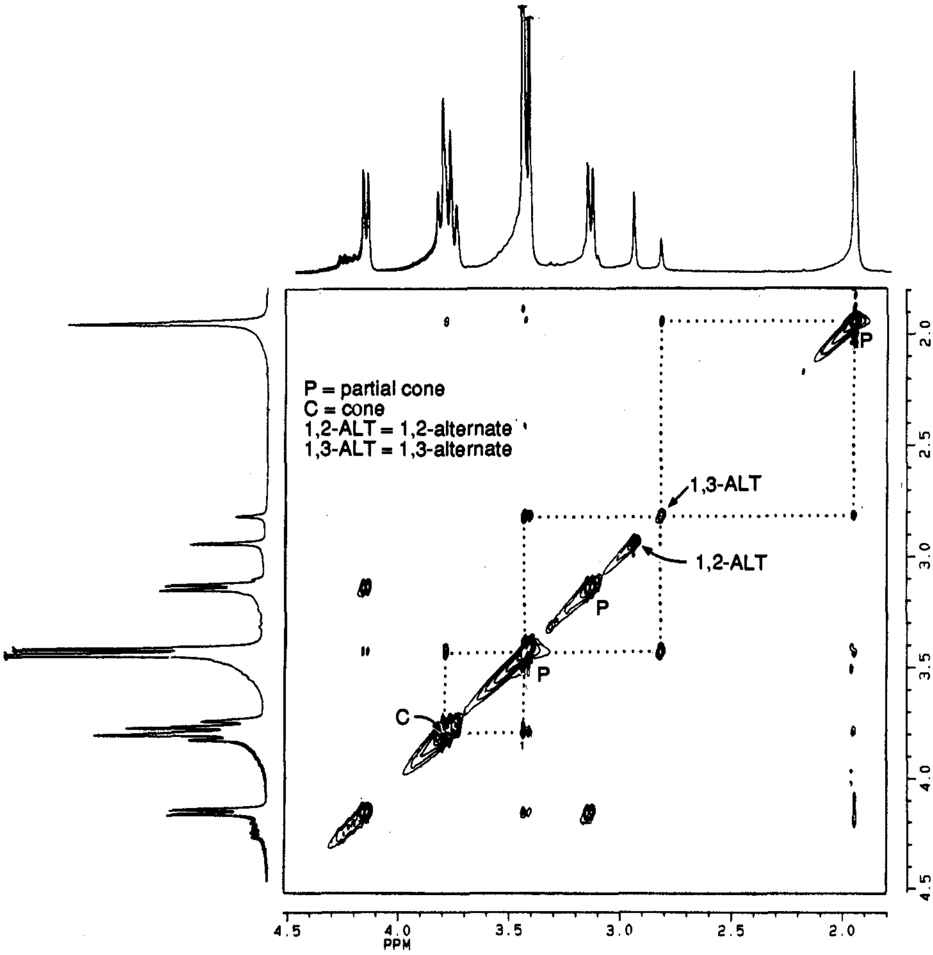
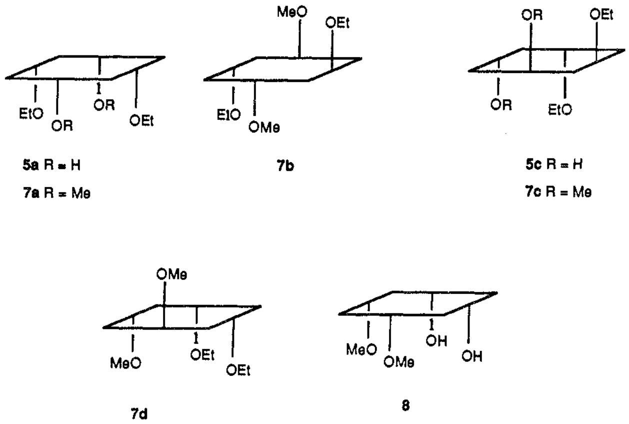


Figure 3. Part of the 600 MHz EXSY NMR spectrum (δ 4.5–1.8) of compound **2** in $CDCl_3$, recorded at −30 °C.

of the aromatic protons of both the cone and the 1,3-alternate conformations is present. A similar pattern exists between the signals of the methoxy groups (Figure 3) and, although less clearly because of T_1 noise, between the signals of the *tert*-butyl groups. No exchange peaks with signals of the 1,2-alternate conformation are present, indicating that interconversion involving this con-

Chart II



5a R = H
7a R = Me

7b

5c R = H
7c R = Me

7d

8

formation is very slow at that temperature.

So far any definite proof that the signals attributed to the 1,2-alternate conformation do indeed belong to this conformation is lacking, although it is the only remaining and unknown conformation, and the signals agree well with the expected structure. Therefore, we decided to synthesize a closely related, but nonflexible calix[4]arene in the 1,2-alternate conformation, and the tetraethyl ether of **1** (**6**) was an obvious choice (Scheme I). It is known that direct tetraethylation of **1** results in an almost quantitative yield of the partial cone conformation[7,10] and that the intermediate 1,3-diethyl ether exists in the cone conformation.[4] However, if we could start from a diametrically disubstituted calix[4]arene in which the two ethoxy groups are on different faces of the calix[4]arene (one pointing up, one pointing down as drawn for compound **5b** in Scheme I), further ethylation might lead to other conformations than the partial cone. Ethylation of the *syn*-1,3-dibenzyl ether **3**[13] in tetrahydrofuran at room temperature with potassium *tert*-butoxide as a base resulted exclusively in the dibenzyldiethyl ether **4** in a partial cone conformation as shown.[14] The two benzyl groups in **4** could be selectively removed by reaction with 2 equiv or trimethylsilyl bromide in chloroform.[15] The resulting *anti*-1,3-diethyl ether **5b** has an interesting conformation. One would expect either a partial cone or a 1,2-alternate conformation for this molecule. However, the ^{1}H NMR spectrum of **5b** shows a pattern that resembles that of a cone conformation (e.g., one AB system for the methylene bridge protons), but the chemical shifts of all the absorptions are different when compared with the ^{1}H NMR spectrum of the *syn*-1,3-diethyl ether **5a** (Chart II).[4] We propose a structure in which the two ethoxy groups are at different faces of the molecule and in which the two phenol rings are in one plane with the four methylene carbon atoms.

Ethylation of the *anti*-1,3-diethyl ether **5b** with ethyl iodide and potassium *tert*-butoxide in tetrahydrofuran at room temperature led mainly to the tetraethyl ether in the 1,2-alternate conformation (**6**), but although some partial cone was formed (the ratio 1,2-alternate/partial cone was ~11:1), the two conformational isomers could be separated by thin-layer chromatography. The ^{1}H NMR spectrum of **6** is very similar to that of the proposed 1,2-alternate conformation of the tetramethyl ether **2**, with the only difference that the methoxy signal of **2** at δ 2.99 has been replaced by a quartet at δ 3.45 and a high field shifted triplet at δ 0.60 for the ethoxy groups. The 1,2-alternate conformation was unambiguously proven by the X-ray molecular structure of a single crystal of compound **6** with two molecules of dichloromethane (see Figure 4). In the solid state the structure is not completely symmetrical. All four ethoxy groups are oriented in such a way that the CH_2 groups point outwards and the CH_3 groups inwards. The dihedral angles of the phenyl rings with the average plane of the methylene carbon atoms are 47.8, −47.5, −80.8, and 83.8°, indicating that two phenyl rings are rotated into the cavity with their oxygen substituents. This explains the upfield shift of the CH_3 protons of the ethoxy groups in the ^{1}H NMR spectrum. By rotation of the phenyl ring into the cavity the CH_3 group is brought into the shielding zone of the diametrical phenyl ring. Furthermore, there is some variation in the orientations of the *tert*-butyl groups and the ethoxy groups relative to the phenyl rings to which they are attached. In solution the structure will be rocking so that in the ^{1}H NMR spectrum only averaged signals for the ethoxy and *tert*-butyl protons are observed.

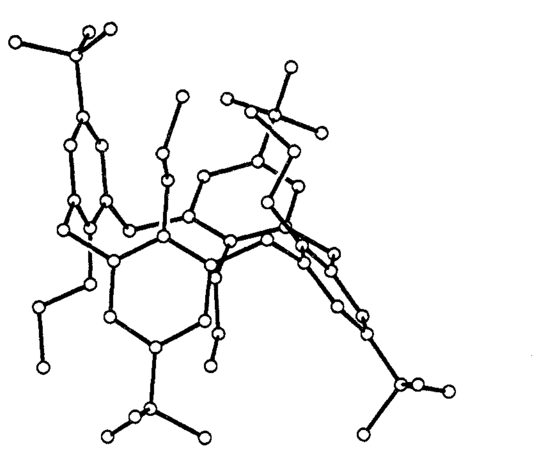


Figure 4. X-ray molecular structure of $6{\cdot}2CH_2Cl_2$ in the 1,2-alternate conformation. The dichloromethane molecules are omitted for clarity.

Now that we have shown that for a flexible calix[4]arene we can observe the four different conformations, including the rare 1,2-alternate, and have confirmed the 1,2-alternate conformation by synthesizing a fixed calix[4]arene in this conformation, it was interesting to investigate the conformations of other flexible calix[4]arenes and, in particular, to see if the 1,2-alternate conformation is present. We have synthesized the four diethyldimethyl ethers of **1** (**7a–d**), which are all partly fixed in different ways because of the ethoxy groups. Because of this partial fixation, for each of these compounds one or two of the four conformations are precluded, and this could influence the ratio of the different conformations that are present. The exclusion of certain conformations also implies the exclusion of certain pathways for interconversion between the remaining conformations, and this might affect the conformational behavior of these compounds, as would be evident from their ^{1}H NMR spectra.

The diethyldimethyl ethers **7a–c** were synthesized by methylation of the corresponding diethyl ethers **5a–c**. The synthesis of the *syn*-1,3-diethyl ether **5a** has been described previously,[4] and the synthesis of the *anti*-1,3-diethyl ether **5b** has already been discussed. The *anti*-1,2-diethyl ether **5c** was obtained by selective removal of two ethoxy groups from the tetraethyl ether of **1** in the partial cone conformation[7] by reaction with 2 equiv of trimethylsilyl iodide in chloroform,[16] and its structure could be deduced from its ^{1}H and ^{13}C NMR spectra. The spectra are different from those of the two 1,3-diethyl ethers **5a** and **5b** already synthesized, so it is definitely one of the 1,2-diethyl ethers. The ^{13}C NMR spectrum shows three signals for the methylene carbon atoms. From the methylene signals in the ^{1}H NMR spectrum it can be deduced that **5c** exists in a 1,2-alternate conformation, with one of the ethoxy groups and its neighboring hydroxy group on one face of the ring and the other ethoxy and hydroxy groups on the other face. The two methylene groups between an ethoxyphenyl ring and a phenol ring exhibit an AB quartet (δ 3.88 and 3.75, 4 H, J = 14.6 Hz), and the other methylene groups appear as two singlets (δ 3.97, 3.77, 2 H). (For the *syn*-1,2-diethyl ether a cone conformation would be expected with three AB quartets for the methylene protons.) Methylation of the diethyl ethers **5a–c** by treatment with methyl iodide in THF/DMF with

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(13) Until now an adequate nomenclature for the exact conformation of a calix[4]arene is missing. In this paper we use the prefix syn to indicate that two large O-substituents (that cannot rotate through the annulus at room temperature) are on the same face of the molecule and the prefix anti when two large O-substituents are on different faces of the molecule. The numbers 1–4 indicate the four phenyl rings of the calix[4]arene in sequential order.

(14) In tetrahydrofuran/dimethylformamide with sodium hydride as a base a 1:2 mixture of cone and partial cone was obtained.

(15) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761–3764.

Table I. Assignment of the Signals in the ^{1}H NMR Spectra of Compounds **2**, **6**, and **7a–d**, Recorded in $CDCl_3$ at −30 °C, and Relative Concentration of Each Conformation

compd		%[a]	δ Ar H[b]	δ $ArCH_2Ar$[c]	δ OMe (s)	δ OCH_2 (q)[d]	δ CH_2CH_3 (t)[d]	δ $C(CH_3)_3$ (s)
2	cone	4	6.80 (s)	4.26 and 3.19 (ABq)	3.83			1.06
	paco	85	7.24, 7.01, 6.93, 6.80 (s)	4.20 and 3.18, 3.86 and 3.80 (ABq)	2.48 (2×), 3.46, 1.99			1.37, 1.20 (2×), 1.09
	1,2-alt	8	7.08 and 7.03 (ABq)	4.30 and 3.16 (ABq), 3.81 (s)	2.99			1.24
	1,3-alt	3	7.09 (s)	*e*	2.87			1.26
7a	cone	20	7.14, 6.43 (s)	4.30 and 3.14 (ABq)	3.96	3.91	1.52	1.35, 0.80
	paco	80	7.26, 7.09 (s), 6.91, 6.58 (d)	4.06 and 3.08, 3.78 and 3.69 (ABq)	3.25, 2.97	3.65	1.42	1.41, 1.33, 1.05 (2×)
	1,3-alt	<5[f]						
7b[g]	paco	35	7.17, 6.93 (s), 6.96, 6.55 (d)	4.16 and 3.11 (ABq), 3.75 (s)	3.51	3.66, 2.88	1.33, 0.72	1.37, 1.20, 1.16 (2×)
	1,2-alt	65	7.21 and 7.07 (ABq), 7.00 (s)	4.18 and 3.16, 3.88 and 3.78 (ABq)	2.94	3.44, 3.39	0.66	1.31, 1.24
7c	paco	64	7.31 and 7.28, 7.10 and 7.08 (ABq), 6.89, 6.88, 6.56, 6.52 (d)	4.03 and 3.02, 3.73 and 3.65 (ABq)	3.22	*e*	1.42, 1.35	1.42, 1.34, 1.05, 1.02
	1,2-alt	25	7.14 and 7.03, 7.12 and 7.04 (ABq)	4.16 and 3.16 (ABq), 3.86 (s)	2.98	3.47	0.58	1.28, 1.27
	1,3-alt	11	7.13, 7.09 (s)	*e*	2.34	*e*	0.89	1.29
7d	cone	<5[f]						
	paco	76	7.19 and 7.16, 6.99 and 6.97, 6.89 and 6.71 (ABq), 7.04 (s)	4.27 and 3.17, 4.19 and 3.23 (ABq), 3.88 and 3.78 (ABq)	3.36, 1.81	4.0–3.6 (m)	1.37, 1.28	1.36, 1.23 (2×), 1.07
	1,2-alt	24	7.32, 6.84 (d), 7.10–7.02 (m)	4.43 and 3.21 (ABq), 3.82 (s)	2.97	3.4–3.3 (m)	0.52	1.29, 1.24
6[h]	cone	7	6.79 (s)	4.41 and 3.10 (ABq)		3.96	1.52	1.08
	paco	47	7.20, 7.09 (s), 6.86, 6.58 (d)	4.04 and 3.03, 3.70 and 3.62 (ABq)		3.82, 3.67 (2×), 3.58	1.42 (2×), 1.31, 1.00	1.38, 1.34, 1.04 (2×)
	1,2-alt	43	7.16 and 7.01 (ABq)	4.13 and 3.11 (ABq), 3.85 (s)		3.45	0.60	1.29
	1,3-alt	3	6.98 (s)	3.66 (s)		3.32	0.71	1.28

[a] Relative concentration. [b] J = 2.0–2.4 Hz for d and ABq. [c] J = 12.2–13.2 Hz for ABq. [d] J = 6.8–7.1 Hz. [e] Could not be located. [f] This conformation cannot be ruled out, because of the low resolution of the spectrum. [g] Recorded at 20 °C. [h] Recorded at 20 °C, after equilibration for 12 h at 132 °C in $CHCl_2CHCl_2$.

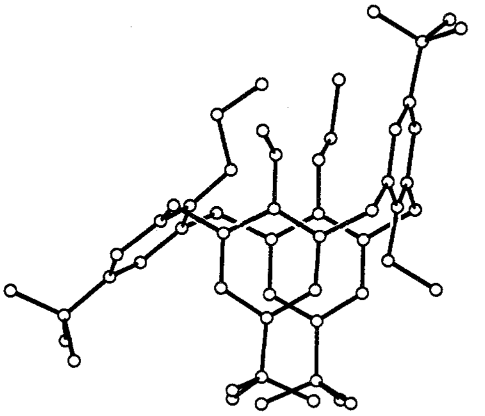

Figure 5. X-ray molecular structure of compound **7d**. Only one of the two independent molecules in the asymmetric unit is shown.

NaH as a base afforded the corresponding diethyldimethyl ethers **7a–c** in 53–72% yield.

The *syn*-1,2-diethyl-3,4-dimethyl ether **7d** was synthesized by ethylation of the 1,2-dimethyl ether **8**[17] with ethyl iodide in THF/DMF with NaH as a base. This reaction gave a 2:1 mixture of **7d** and **7c**, which could be separated by preparative thin-layer chromatography. The structure of **7d** was proved by the X-ray structure determination of a single crystal of this compound (Figure 5). It crystallizes in the monoclinic system, space group $P2_1/n$, with two independent molecules in the asymmetric unit. Both independent molecules are in the partial cone conformation with the two ethoxy groups on the same face of the calix[4]arene ring. There exist slight differences between the two independent molecules as shown by the dihedral angles between the phenolic rings with respect to the average plane of the four methylene carbon atoms. These are, starting from the rotated phenolic rings, −96.6 (−96.6), 87.2 (98.9), 41.7 (39.8), and 92.0 (89.0)° (values for the second molecule between brackets). Significant differences also exist in the orientation of the *tert*-butyl groups with respect to the planes of the phenolic rings to which they are attached. The high values of the thermal parameters for all terminal methyl groups indicate that these are mobile in the solid state.

The ^{1}H NMR spectra of the four diethyldimethyl ethers **7a–d** were recorded at different temperatures; in Table I the assigned signals are listed for the spectra recorded at −30 °C as well as the ratios of the conformations of each compound.

It is clear from this table that these ratios are strongly influenced by the substitution pattern. For all compounds **7a–d** the partial cone is less abundant than for the tetramethyl ether **2**. In some compounds the cone or the 1,3-alternate is present in higher concentration than in **2**, but it is intriguing to note that, for all compounds **7** for which the 1,2-alternate conformation is possible, this conformation is present in much higher percentage than for the tetramethyl ether **2**. For compound **7b** the 1,2-alternate is thermodynamically even more stable than the partial cone conformation.

It is further interesting to note that compound **7b** shows only sharp signals in the ^{1}H NMR spectrum that was recorded at room temperature. For the other compounds the spectra recorded at room temperature showed only broad peaks (**7a**) or broad peaks and sharp signals for the 1,2-alternate conformation (**7c** and **7d**). This is in complete agreement with the qualitative analysis of the dynamic behavior of the tetramethyl ether. Compound **7a** cannot attain a 1,2-alternate conformation, and no sharp signals are expected in the room temperature spectrum. Compound **7b** cannot attain the cone nor the 1,3-alternate conformation, which implies that the partial cone cannot interconvert by a relatively fast process to another conformation. This is the reason why sharp signals for the partial cone are present in the room temperature spectrum beside the signals of the 1,2-alternate conformation. For compounds **7c** and **7d** fast interconversion between 1,3-alternate and partial cone (**7c**) and between cone and partial cone (**7d**) is possible, so that broad coalescing signals are present in the room temperature spectra as well as sharp signals for the 1,2-alternate conformation.

The final "flexible" calix[4]arene that we want to discuss is the tetraethyl ether of **1**. This molecule, now isolated in both the partial cone[7] and in the 1,2-alternate conformation (**6**, vide supra), does not undergo any conformational change at room temperature. With all the above-mentioned results in mind we were surprised that when it was reported that also this molecule is flexible, albeit at rather high temperatures, only the partial cone and the 1,2-alternate conformations were detected.[10] Therefore, we repeated

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(16) The *anti*-1,2-diethyl ether **7c** was a quite unexpected product, that was found in a general study on the synthesis of monoalkylated calix[4]arenes starting from the corresponding tetraalkylated compounds. Casnati, A.; Arduini, A.; Ghidini, E.; Pochini, A.; Ungaro, R. *Tetrahedron*, in press.

(17) Arduini, A.; Casnati, A.; Dodi, L.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1990**, 1597–1598.

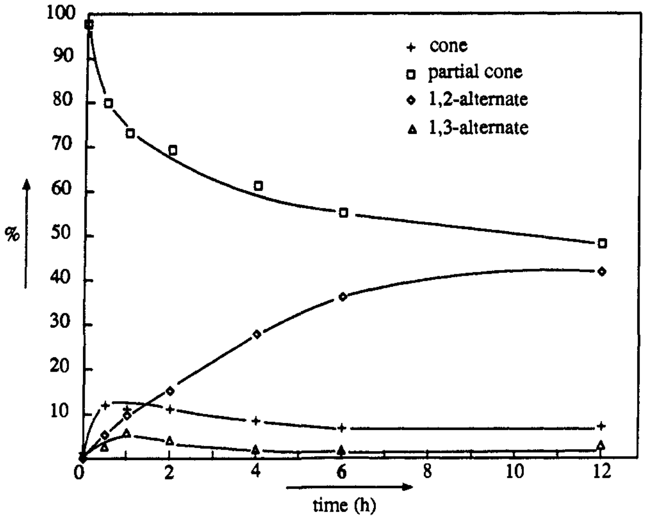

Figure 6. The relative concentration of each of the conformations of the tetraethyl ether of **1** as a function of time on heating of the starting partial cone conformation in $CHCl_2CHCl_2$ solution at 132 °C.

the reported experiment, heated the partial cone in a solution of $CHCl_2CHCl_2$ at 132 °C, and analyzed the mixtures after several time intervals by ^1H NMR spectroscopy. It was very clear from the ^1H NMR spectra that *also for this compound all four conformations are present in the mixtures* (Table I and Figure 6).

In the equilibrium mixture, after heating for 12 h, the same ratio of partial cone and 1,2-alternate was found as was reported in the literature.[10] The process as a function of time (Figure 6) can be described by a system of three interconversions of the partial cone to each of the three other conformations. After 0.5 h the equilibria between partial cone and cone and between partial cone and 1,3-alternate have already been reached. It takes about 12 h before the third equilibrium is established. In that period the amount of partial cone decreases and therefore also the amounts of cone and 1,3-alternate decrease slightly. When the composition of the mixture was measured at shorter time intervals during the first hour, we observed that the equilibrium between partial cone and 1,3-alternate was reached within 4 min and the equilibrium between partial cone and cone within 13 min. This means that also for the tetraethyl ether the partial cone to 1,3-alternate conversion is faster than the partial cone-to-cone interconversion, as we have found for the upper rim calixcrowns.[11]

In order to obtain more insight in the effects on the relative energies of the conformations on replacement of methoxy groups of **2** by ethoxy groups, we performed molecular mechanics calculations with the program QUANTA/CHARMM. We have used this program before, with slightly different parameters, in a more general computational study of the properties of calix[4]arenes, and we have found that it correctly predicted the partial cone conformation as the most stable conformation of the tetramethyl ether of *p*-methylcalix[4]arene.[18] The results for the tetramethyl, diethyldimethyl, and tetraethyl ethers of *p-tert*-butylcalix[4]arene are summarized in Table II.

For the tetramethyl ether the calculated relative energies are reasonably in line with the experimental results, except for the 1,3-alternate conformation, which has a too low energy. The differences in energy are higher than expected from the conformational distribution in solution. As to the orientation of the methoxy groups, only in the 1,2-alternate conformation is it favorable to have two diametrical methoxy groups pointing into the cavity. This considerably lowers the electrostatic energy and to a somewhat lesser extent also the van der Waals energy. The bonded energy increases slightly. For the partial cone and the 1,3-alternate conformations the inside orientation of one of the methoxy groups is not favorable because in these cases the van der Waals energy is increasing instead of decreasing. The hydrogen atoms of the inward pointing methoxy group clash with the aromatic rings that line the cavity. As the chemical shifts in the ^1H NMR spectrum do suggest an inward orientation of these methoxy groups, it seems that the van der Waals parameters for hydrogen atoms are not optimal in the QUANTA/CHARMM force field.[19]

Table II. Molecular Mechanics Energies of the Conformations of the Tetramethyl, the Diethyldimethyl, and the Tetraethyl Ethers of *p-tert*-Butylcalix[4]arene (kcal mol^{-1})

compd	cone	partial cone	1,2-alternate	1,3-alternate
2 $(OMe)_4$	70.8	64.8	68.6[a]	66.6
7a (*syn*-1,3)	47.4	36.9[b]		39.5
7b (*anti*-1,3)		46.9[b]	41.1[a]	
7c (*anti*-1,2)		38.4[b]	40.7[a]	41.5
7d (*syn*-1,2)	55.6	47.7[b]	46.3[c]	
6 $(OEt)_4$	96.6	76.0	84.8	62.5

[a] The two methoxy groups point into the cavity. [b] The methoxy group of a nonrotated phenyl ring points into the cavity. [c] One of the methoxy groups points into the cavity.

For the diethyldimethyl ethers **7a–c** the conformation with the lowest calculated energy corresponds with the thermodynamically most stable conformation in solution. Furthermore, the calculations correctly show the trend that the 1,2-alternate conformation becomes relatively more stable, although for compound **7d** it leads to the wrong order of energies for the partial cone and the 1,2-alternate conformation. This stabilization of the 1,2-alternate relative to the partial cone on going from **2** to **7b–d** is mainly due to much more favorable electrostatic interactions. The increased stability of the cone relative to the partial cone for compound **7a** was not reproduced by the calculations. The calculated energies for the 1,3-alternate conformations are generally too low, as was found for compound **2**.

The calculations for the tetraethyl ether of **1** do not reproduce the experimentally found order of stability of the conformations. The electrostatic repulsions between the methyl groups of the ethoxy substituents dominate the energy, making the 1,3-alternate the most stable conformation, as it is the only conformation in which no two ethoxy groups are close to each other.

Conclusions

We have shown for the first time, that *in solution tetrasubstituted calix[4]arenes adopt all four possible conformations, including the 1,2-alternate conformation, when these are in the thermodynamic equilibrium.* For both the tetramethyl ether and the tetraethyl ether of *p-tert*-butylcalix[4]arene the partial cone is the thermodynamically most stable conformation, followed in order of decreasing stability by the 1,2-alternate, the cone, and the 1,3-alternate conformation. Interconversion between all these conformations takes place in equilibrium, but interconversions involving the 1,2-alternate conformation are much slower than interconversions in which only the other three conformations are involved. *The 1,2-alternate is a kinetically relatively stable conformation.*

For partly rigidified calix[4]arenes, with two methoxy groups and two ethoxy groups in different substitution patterns, one or two of the conformations are precluded. This strongly influences the conformational distribution in solution. The partial cone is in all four compounds less abundant than in the tetramethyl ether **2**. *For the anti-1,3-diethyl-2,4-dimethyl ether* **7b** *the 1,2-alternate is even the thermodynamically most stable conformation.*

Molecular mechanics calculations with the QUANTA/CHARMM force field do not yet have general predictive value for the order of stability of different conformations of a tetraalkylated calix[4]arene. They do give insight in the intramolecular interactions that determine the relative stability of a certain conformation.

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(18) Grootenhuis, P. D. J.; Kollman, P. A.; Groenen, L. C.; Reinhoudt, D. N.; van Hummel, G. J.; Ugozzoli, F.; Andreetti, G. D. *J. Am. Chem. Soc.* **1990**, *112*, 4165–4176.

(19) These calculations were performed with the corrected VDW parameters for hydrogen atoms, as was suggested in a Newsletter from Polygen Corp., 1990.

Of course it should be borne in mind that the stability of a conformation in solution can be strongly influenced by its interaction with the solvent, something for which no allowance is made in these calculations.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ with Me_4Si as an internal standard. All chemicals were reagent grade and were used without further purification. Compounds **1**,[20] **2**,[7] **3**,[21] and **5a**[22] were prepared according to the literature. Tetrahydrofuran (THF) and acetonitrile were distilled and kept over molecular sieves (3Å). Dimethylformamide (DMF) was dried over molecular sieves (3Å). Petroleum ether refers to the fraction boiling at 40–60 °C. All reactions were carried out in a nitrogen atmosphere.

Unless otherwise stated, reactions were worked up in the following way. After evaporation of the solvent with a rotary evaporator, the mixture was taken up in CH_2Cl_2 (50 mL) and washed with 1 N HCl (25 mL) and with brine (25 mL). The organic layer was dried over $MgSO_4$, and the solvent was evaporated. The products were recrystallized from $CHCl_3$/MeOH, unless otherwise stated.

25,27-*anti*-5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,27-diethoxy-26,28-bis(phenylmethoxy)pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1-(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene (4), Partial Cone Conformation. To a solution of the *syn*-1,3-dibenzyl ether **3** (0.50 g, 0.6 mmol) and potassium *tert*-butoxide (KOtBu, 0.16 g, 1.3 mmol) in THF (25 mL) was added ethyl iodide (0.2 mL, 2.5 mmol). After being stirred at room temperature for 3 h the reaction was worked up. The product was obtained as a white solid: yield 90%; mp 195–198 °C; ^{1}H NMR δ 7.5–7.3 (m, 10 H, $CH_2C_6H_5$), 7.09, 6.97 (s, 2 H, Ar H), 6.88, 6.56 (d, 2 H, J = 2.4 Hz, Ar H), 4.72 and 4.61 (ABq, 4 H, J = 11.6 Hz, OCH_2Ph), 4.07 and 3.00 (ABq, 4 H, J = 13.5 Hz, $ArCH_2Ar$), 3.73, 3.43 (q, 2 H, J = 6.8 Hz, OCH_2CH_3), 3.65 (s, 4 H, $ArCH_2Ar$), 1.38, 0.60 (t, 3 H, J = 6.8 Hz, OCH_2CH_3), 1.36, 1.02 (s, 9 H, $C(CH_3)_3$), 1.08 (s, 18 H, $C(CH_3)_3$); ^{13}C NMR δ 76.8 (t, OCH_2Ph), 68.3, 67.1 (t, OCH_2CH_3), 38.0, 31.1 (t, $ArCH_2Ar$), 16.6, 16.0 (q, OCH_2CH_3); mass spectrum, *m/e* 884.586 (M^+, calcd 884.574). Anal. Calcd for $C_{62}H_{76}O_4$: C, 84.12; H, 8.65. Found: C, 83.91; H, 8.72.

26,28-*anti*-5,11,17,23-Tetrakis(1,1-dimethylethyl)-26,28-diethoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13-(27),15,17,19(26),21,23-dodecaene-25,27-diol (5b). To a refluxing solution of **4** (0.46 g, 0.52 mmol) in $CHCl_3$ (25 mL) was added Me_3SiBr (0.15 mL, 1.14 mmol). After 2 h the reaction mixture was allowed to cool to room temperature, and a few drops of water-containing methanol were added. The solvent was evaporated, and the mixture was taken up in CH_2Cl_2 (50 mL). If during the reaction the mixture had turned yellowish/brown due to the formation of Br_2, the CH_2Cl_2 layer was washed with a solution of $Na_2S_2O_3$. The organic layer was washed with H_2O (25 mL) and with brine (25 mL). After drying and evaporation of the solvent the residue was triturated with petroleum ether to yield compound **5b** as a white solid: yield 95%; mp 255–256 °C; ^{1}H NMR δ 7.16, 7.06 (s, 4 H, Ar H), 6.96 (s, 2 H, OH), 3.95 and 3.74 (ABq, 8 H, J = 15.2 Hz, $ArCH_2Ar$), 3.60 (q, 4 H, J = 7.0 Hz, OCH_2CH_3), 1.30, 1.29 (s, 18 H, $C(CH_3)_3$), 0.51 (t, 6 H, J = 7.0 Hz, OCH_2CH_3); mass spectrum, *m/e* 704.483 (M^+, calcd 704.480). Anal. Calcd for $C_{48}H_{64}O_4 \cdot 0.4CHCl_3$: C, 77.22; H, 8.62. Found: C, 77.31; H, 8.72.

27,28-*anti*-5,11,17,23-Tetrakis(1,1-dimethylethyl)-27,28-diethoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13-(27),15,17,19(26),21,23-dodecaene-25,26-diol (5c). To a solution of the tetraethyl ether of **1** in the partial cone conformation[7] (0.20 g, 0.26 mmol) in $CHCl_3$ (25 mL) was added Me_3SiI (74 μL, 0.52 mmol). After being stirred for 1 h at room temperature the reaction mixture was worked up as described for compound **5b**. Recrystallization gave **5c** as a pure white solid: yield 65%; mp 208–215 °C; ^{1}H NMR δ 8.03 (s, 2 H, OH), 7.19, 7.02 (d, 2 H, J = 2.4 Hz, Ar H), 7.04, 6.98 (d, 2 H, J = 2.3 Hz, ArH), 3.97, 3.77 (s, 2 H, $ArCH_2Ar$), 3.88 and 3.75 (ABq, 4 H, J = 14.6 Hz, $ArCH_2Ar$), 3.55–3.25 (m, 4 H, OCH_2CH_3), 1.29, 1.22 (s, 18 H, $C(CH_3)_3$), 0.38 (t, 6 H, J = 6.9 Hz, OCH_2CH_3); ^{13}C NMR δ 67.1 (t, OCH_2CH_3), 39.3, 35.3, 32.7 (t, $ArCH_2Ar$), 14.0 (q, OCH_2CH_3); mass spectrum, *m/e* 704.489 (M^+, calcd 704.480). Anal. Calcd for $C_{48}H_{64}O_4$: C, 81.77; H, 9.15. Found: C, 81.72; H, 9.38.

5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,26,27,28-tetraethoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13-(27),15,17,19(26),21,23-dodecaene (6), 1,2-Alternate Conformation. To a solution of **5b** (0.16 g, 0.23 mmol) in THF (20 mL) was added first KOtBu (58.6 mg, 0.52 mmol) and then, after being stirred for 0.5 h, ethyl iodide (0.19 mL, 2.3 mmol). After being stirred for 2 h at room temperature the reaction mixture was worked up to yield a white solid, which was a mixture of the 1,2-alternate and partial cone conformations of the tetraethyl ether. The products were separated by preparative TLC (silica gel plate, Merck 60 $F_{254+366}$, eluent CH_2Cl_2/petroleum ether 6:4) to afford 0.11 g (64%) of the tetraethyl ether in the 1,2-alternate conformation and 10 mg (6%) of the partial cone conformation. Characterization of the 1,2-alternate conformation (**6**): mp 223–228 °C (CH_2Cl_2/MeOH); ^{1}H NMR data are reported in Table I; mass spectrum, *m/e* 760.559 (M^+; calcd 760.543). Anal. Calcd for $C_{52}H_{72}O_4$: C, 82.06; H, 9.54. Found: C, 82.35; H, 9.40.

General Procedure for the Synthesis of the Diethyldimethyl Ethers 7a–c. To a suspension of the diethyl ethers **5a–c** (0.20 g, 0.28 mmol) and of NaH (1.0 g, 23 mmol, 55% suspension in oil, which was washed with petroleum ether (10 mL) before use) in THF (25 mL) and DMF (3 mL) was added methyl iodide (1.4 mL, 23 mmol). The reaction mixture was refluxed for 2 h and then allowed to cool to room temperature. The remaining NaH was destroyed with some H_2O (caution!), and then the usual workup procedure was followed. The ^{1}H NMR data are given in Table I.

25,27-*syn*-5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,27-diethoxy-26,28-dimethoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7-(28),9,11,13(27),15,17,19(26),21,23-dodecaene (7a): yield 72% of white crystals after recrystallization; mp 252–255 °C; mass spectrum, *m/e* 732.515 (M^+, calcd 732.512). Anal. Calcd for $C_{50}H_{68}O_4 \cdot 0.3CHCl_3$: C, 78.57; H, 8.95. Found: C, 78.62; H, 8.80.

25,27-*anti*-5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,27-diethoxy-26,28-dimethoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7-(28),9,11,13(27),15,17,19(26),21,23-dodecaene (7b): yield 96% of an oil; mass spectrum, *m/e* 732.513 (M^+, calcd for $C_{50}H_{68}O_4$ 732.512).

25,26-*anti*-5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,26-diethoxy-27,28-dimethoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7-(28),9,11,13(27),15,17,19(26),21,23-dodecaene (7c): yield 53% of white crystals after recrystallization; mp 235–239 °C; mass spectrum, *m/e* 732.515 (M^+, calcd 732.512). Anal. Calcd for $C_{50}H_{68}O_4 \cdot 0.1CHCl_3$: C, 80.77; H, 9.21. Found: C, 80.76; H, 9.13.

25,26-*syn*-5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,26-diethoxy-27,28-dimethoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7-(28),9,11,13(27),15,17,19(26),21,23-dodecaene (7d). To a suspension of the 1,2-dimethyl ether **8**[17] (0.15 g, 0.22 mmol) and NaH (75 mg, 1.5 mmol) in THF (20 mL) and DMF (4 mL) was added ethyl iodide (0.4 mL, 5.0 mmol). The reaction mixture was worked up as described for the methylation reactions to give a mixture of the compounds **7c** and **7d**. These were separated by preparative TLC (silica gel plate, Merck 60 $F_{254+366}$, eluent $CHCl_3$/hexane 3:4) to yield pure **7d** (85 mg, 52%) and **7c** (40 mg, 25%). Characterization of **7d**: mp 234–236 °C; ^{1}H NMR data are reported in Table I; mass spectrum, *m/e* 732.517 (M^+, calcd 732.512). Anal. Calcd for $C_{50}H_{68}O_4 \cdot 0.6CHCl_3$: C, 77.90; H, 8.87. Found: C, 77.88; H, 8.82.

2-D NMR EXSY Experiment. The proton 2-D EXSY spectrum was acquired at 600 MHz with the standard NOESYPH pulse sequence ($90°–t_1–90°–\tau_m–90°$), supplied with the Bruker software, by using time proportional phase incrementation (TPPI)[23] to obtain pure phase line shapes. The mixing time was 300 ms, and 512 t_1 increments were taken. Each FID of 2048 data points was the accumulation of 16 scans. Each scan was preceded by two dummy scans to establish steady state. The relaxation delay was chosen to be larger than $5T_1$. A $\pi/2$ shifted sine-bell window function was applied to both F_1 and F_2 domains. After zero-filling in the F_1 dimension, the final data matrix size was 1K × 1K of real data points with digital resolution of 2.6 Hz per point as the sweep width was 5263 Hz.

X-ray Structure Determination of Compounds 6·2CH$_2$Cl$_2$ and 7d. The crystal structure of **6**·2CH_2Cl_2 was determined by X-ray diffraction. Crystal data are given in Table III. Reflections were measured on an Enraf-Nonius CAD4 diffractometer, by using graphite monochromated Mo K_α radiation (λ = 0.7107 Å, $\omega/2\theta$ scan mode, scan width (ω) 0.80 + 0.34 tan θ, $3 < \theta < 25°$). The compound is unstable at room temperature, due to loss of dichloromethane. Therefore the diffraction experiments were carried out at approximately 100 K. The structure was solved by direct methods and refined with full-matrix least-squares methods. One of the chlorine atoms is disordered over two positions with relative occupancies of 75% and 25%. The number of parameters refined was 568 (scale factor, positional parameters and anisotropic thermal parameters for the non-hydrogen atoms). Hydrogen atoms of the ca-

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(20) Gutsche, C. D.; Iqbal, M.; Stewart, D. *J. Org. Chem.* **1986**, *51*, 742–745.

(21) The procedure reported in ref 12b was slightly modified by using benzyl bromide instead of benzyl tosylate as the alkylating agent.

(22) The procedure reported in ref 4 was slightly modified by using ethyl iodide instead of ethyl tosylate. This reduced the reaction time from 20 h to 5 h.

(23) Marion, D.; Wüthrich, K. *Biochem. Biophys. Res. Commun.* **1983**, *113*, 967–974.

Table III. Experimental Data for the X-ray Diffraction Studies on Compounds **6**·$2CH_2Cl_2$ and **7d**

compound	**6**·$2CH_2Cl_2$	**7d**
crystal habit and color	colorless prism	colorless flat prism
crystal dimensions, mm	0.2 × 0.3 × 0.4	0.1 × 0.5 × 0.6
formula	$C_{52}H_{72}O_4 \cdot 2CH_2Cl_2$	$C_{50}H_{68}O_4$
fw	931.02	733.09
crystal system	monoclinic	monoclinic
space group	$P2_1/c$	$P2_1/n$
T, K	100 (5)	295
cell parameters[a]		
a, Å	14.521 (5)	27.745 (3)
b, Å	29.386 (8)	20.302 (4)
c, Å	13.783 (5)	17.392 (3)
β, deg	117.25 (3)	96.35 (2)
V, Å^3	5229 (7)	9736 (3)
Z	4	8
D_{calc}, g cm^{-3}	1.188	1.000
radiation	Mo Kα	Cu Kα
μ, cm^{-1}	2.67	4.46
reflcns measd	$\pm h,k,l$	$\pm h,k,l$
unique total data	8456	10019
unique obsd data	4839 ($I \geq 3\sigma(I)$)	2647 ($I \geq 2(\sigma(I))$
agreement between equiv obsd data	*b*	0.0152
no. of variables	568	624
R	0.074	0.064
R_w	0.085	0.064
$(\Delta/\sigma)_{\max}$	0.07	0.06

[a] Unit cell parameters were obtained by least-squares analysis of the setting angles of 25–30 reflections. [b] No symmetry related reflections were measured.

lixarene and of one of the dichloromethane molecules were put in calculated positions and were treated as riding atoms in the refinements. Hydrogen atoms of the disordered dichloromethane molecule were not included. All calculations were done with SDP.[24]

For compound **7d** the single-crystal X-ray diffraction measurements were performed at room temperature on a sample sealed in a quartz capillary, with a Siemens A.E.D. diffractometer using Ni filtered Cu K_α radiation (λ = 1.54178 Å). The reflections were measured in the range $3 \leq \theta \leq 50°$ with the ω–2θ scan technique (scan speed 3–12 deg min^{-1}) with scan width from $(\theta - 0.6)°$ to $(\theta + 0.6 + \Delta\theta)°$; $\Delta\theta = [(\lambda_{\alpha 1} - \lambda_{\alpha 2})/\lambda]\tan\theta$. The most relevant data collection parameters are summarized in Table III. The intensities were calculated from profile analysis by using the Lehmann and Larsen procedure.[25] Corrections were performed for Lorentz and polarization effects.

The structure was solved by direct methods and refined with unit weights by the block full-matrix least-squares method (two blocks of 312 parameters) by using the SHELX[26] package of crystallographic computer programs. All the H atoms were taken in their calculated positions with the geometrical constraint C–H 1.08 Å, and the methyl groups were treated as rigid bodies. Parameters refined were the overall scaling factor, positional parameters, and isotropic thermal parameters for all atoms with exception of the C atoms of the methyl groups for which anisotropic thermal parameters were used. Scattering factors were taken from the literature.[27]

All calculations were performed on the GOULD 6040 Powernode of the Centro di Studio per la Strutturistica Diffrattometrica del C.N.R., Parma.

Molecular Mechanics Calculations. The calculations were performed with the program QUANTA/CHARMM, version 2.1A.[28] The first molecular structure of a calix[4]arene was built in the 2-D molecular construction mode. After minimization of this structure, other conformations were generated by changing the dihedral angles around the bonds from the aromatic rings to the methylene groups. Other orientations of the oxygen substituents were also generated by changing the concerning torsional angles. All structures were minimized until the value of "deriv" (the root-mean-square of the first derivative of the energy) was less than 0.0001 kcal mol^{-1} Å^{-1}. Of each conformation only the representative is mentioned with the lowest energy with respect to the orientation of the oxygen substituents. The *tert*-butyl groups are always placed in the same orientation, with one of the methyl groups in the plane of the phenyl ring.

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Supplementary Material Available: Tables of positional and thermal parameters, bond distances, and bond and torsional angles of the X-ray structures of **6**·$2CH_2Cl_2$ and **7d** (33 pages). Ordering information is given on any current masthead page.

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