Solvent Effects on the Conformations and Hydrogen Bond Structure of Partially Methylated *p*-*tert*-Butylcalix[4]arenes

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The effect of the solvent on the conformations of unsubstituted *p*-*tert*-butylcalix[4]arene (**1**) and its methyl ethers **2**–**6** has been investigated by ^1H NMR spectroscopy. The conformational distribution of the 1,2-dimethyl ether **4** and of the tetramethyl ether **6** is strongly influenced by the solvent used. The exact geometry of the cone conformation of the 1,3-dimethyl ether **3** and of the 1,2-dimethyl ether **4** changes from distinct C_2 symmetry in CCl_4 to close to C_4 symmetry in CS_2. It seems that inclusion of a small solvent molecule (*e.g.* CS_2) in the cone conformation can take place. Spectra recorded at temperatures up to 125 °C in $CDCl_2CDCl_2$ showed that the mono- and 1,3-di-methyl ethers are fixed in the cone conformation, whereas the unsubstituted calix[4]arene and the tetramethyl ether are flexible. These observations support a concerted mechanism for the cone-to-cone interconversion in **1**, in which two or more phenol rings rotate simultaneously.

The hydrogen bonding in partially methylated calix[4]arenes was investigated by IR spectroscopy. In all calix[4]arenes with neighbouring hydroxy groups, a strong cooperativity effect of 80% or more was observed. The exact geometry of the cone conformation affects the strength of the hydrogen bonds, because it influences the O–H···O angle in the calix[4]arene. The effect of the solvent on the geometry of the cone conformation is translated in differences of up to 79 cm^{-1} in the OH-stretch frequencies for spectra recorded in CCl_4 and in CS_2.

Calix[4]arenes are macrocyclic compounds consisting of four phenol rings that are connected at the *ortho* positions by methylene groups.[1] They are increasingly being employed as building blocks for molecules that are designed for special applications, which till now have mainly involved the complexation of cations and neutral molecules.[1,2] Their popularity is partly due to the fact that they can exist in four distinct conformations, *viz.* the cone, the partial cone, the 1,2-alternate, and the 1,3-alternate (Fig. 1).

The unsubstituted *p*-*tert*-butylcalix[4]arene (**1**) adopts in the solid state a regular cone conformation with C_4 symmetry (toluene complex).[3] At ambient temperature in solution compound **1** is flexible according to ^1H NMR spectroscopy but it is frozen out in the cone conformation upon cooling.[4] This flexibility is due to the interconversion of the two mirror-image cone conformations.[4] The cone is stabilized by an intramolecular array of very strong hydrogen bonds, as is evidenced by the very short O···O distances (2.67 Å) in the X-ray structure[3] and the very low frequency (3150 cm^{-1}) of the OH-stretch vibrations in the solid-state IR spectrum of the complex.[4a] The low frequency is indicative of a strong cooperativity effect in the hydrogen bonds.† It has been shown that in CCl_4 solution the strength of the H-bonds of calix[4]arenes that are bridged on two opposite *para* positions is considerably reduced when the C_4 symmetry of the cone is broken up to C_2 symmetry by shortening of the bridge.[5]

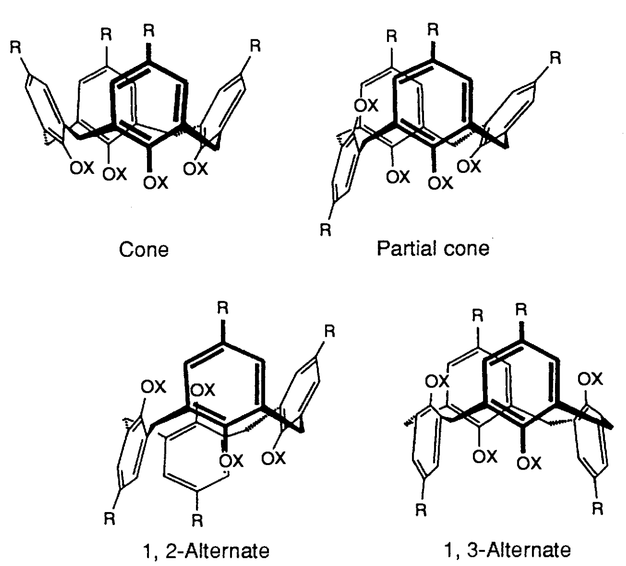

Fig. 1 The four main conformations of a calix[4]arene

When large substituents are introduced on the four oxygen atoms, the conformation of the product is fixed, *i.e.*, the isolated conformation cannot interconvert to other conformations.[6] Thus, not necessarily the thermodynamically most stable conformation is formed, but rather the conformation that is favoured by the kinetics of the substitution reaction. Only the tetramethyl ether of *p*-*tert*-butylcalix[4]arene (**6**) is conformationally flexible at ambient temperature, which indicates that the methoxy group is small enough to allow rotation of the aromatic rings to take place. At low temperature, this compound exists as a mixture of all four possible conformations, of which the partial cone is the thermodynamically most stable conformation.[7]

As for both the unsubstituted calix[4]arene **1** and the

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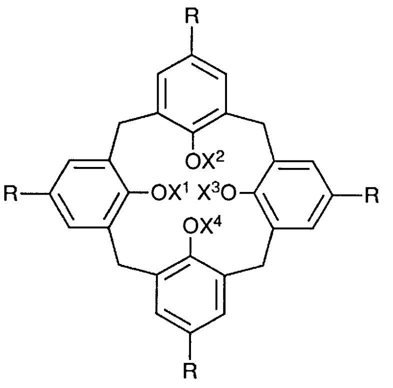
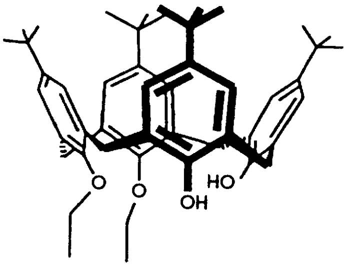
† The hydrogen bond of the first hydroxy group to a second hydroxy group will polarize the OH bond in this second hydroxy group, so that its hydrogen bond to a third oxygen atom is strengthened. For a recent article on H-bond cooperativity see ref. 16.



	R	X^1	X^2	X^3	X^4
1	Bu^t	H	H	H	H
2	Bu^t	Me	H	H	H
3	Bu^t	Me	H	Me	H
4	Bu^t	Me	Me	H	H
5	Bu^t	Me	Me	Me	H
6	Bu^t	Me	Me	Me	Me
7	H	Me	H	Me	H



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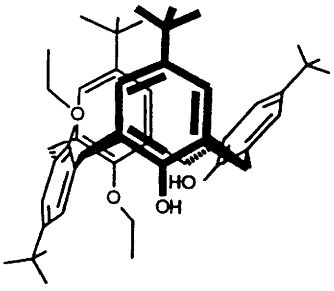

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Table 1 Band maxima in the OH- and OD-stretching regions of the IR spectra of calix[4]arenes **1**–**5** and **7**, measured in the solid phase, and in CCl_4 and CS_2 solution[a]

	Solid				Solution	
Compound	300 K		100 K		CS_2	CCl_4
1	3150		3130		3190	3140
2	OH	OD	OH	OD		
	3270	2431	(3309)	2414	3343*	3314*
	3142	2352	3249	2347	3238*	(3217)*
		2307	3129	2297	(3185)*	3180*
3	(3538)		3555		3342	(3539)*
	3456		3478			(3502)*
			(3455)*			3423*
			3435			
4	3438^+		3444^+		(3425)*	(3506)*
	3367^+		3325^+		3346*	(3453)*
					3219*	3371*
					3181*	3228*
						(3181)*
5	3452^+				3520	3522
					3375	3430
7	3384		3392		3364	(3535)
			3369			3365

[a] Solid-state spectra were recorded as KBr pellets except when bands are indicated with '$^+$', in which case the spectra were recorded as fluorolube mulls. Band maxima indicated with '*' have been obtained from the second-derivative spectra. Band maxima in parentheses are shoulders on the main peak.

tetramethyl ether **6** the thermodynamically most stable conformation can be determined (because of their flexibility); this is also possible for the partially methylated calix[4]arenes **2**–**5**. The compounds **1**–**6** are therefore valuable probes for the investigation of the thermodynamic factors that determine the conformation of a (partially substituted) calix[4]arene. In an earlier paper we have reported the results of a molecular mechanics study of compounds **1**–**7**, which were discussed together with their X-ray structures.[8] The electrostatic interactions (hydrogen bonding and oxygen–oxygen repulsion) were found to be the crucial factor for the determination of the conformation. The *para*-substituents (hydrogen or *tert*-butyl) have only a minor influence. Other authors have investigated the conformations of compounds **1**, **2**, **3** and **5** in $CDCl_3$ solution by NOE spectroscopy and concluded that all exist (mainly) in the cone conformation.[9] The OH-stretch frequencies (solid-state IR) and the OH signals (^1H NMR in $CDCl_3$) of the same compounds have been related to the acidity of the hydroxy groups.[10] Here we report the results of a detailed study of the hydrogen bonding structure and the conformations of partially methylated calix[4]arenes by IR and dynamic ^1H NMR spectroscopy, including experimental results for the 1,2-dimethyl ether **4**, which has not been studied before. Furthermore, we present experimental evidence that the solvent can have a strong influence on the conformation of a calix[4]arene.

Results

The properties of *p*-*tert*-butylcalix[4]arene (**1**) have been well established by several research groups.[3,4] We recorded the IR spectra of **1** in two different solvents and found a remarkable difference in the OH-stretch frequencies. It has been reported to be 3138 cm^{-1} in CCl_4,[11] but in CS_2 the OH-stretch vibration is found at 3190 cm^{-1} (see Table 1).

The monomethyl ether of *p*-*tert*-butylcalix[4]arene (**2**) exists in a cone conformation in $CDCl_3$ solution.[9] In the solid-state IR spectrum of **2** there are two OH bands present, a broad one at 3142 cm^{-1} and a narrower one at 3270 cm^{-1} (Table 1).[10,12] At low temperature (100 K) these bands remain essentially the same although a shoulder becomes visible at 3309 cm^{-1} (Fig. 2). The second-derivative spectrum indicates that the broad band at 3129 cm^{-1} has two maxima at 3153 and 3110 cm^{-1}. The IR spectrum of the partly deuteriated compound shows that the broad band in the OD region consists of two OD-stretch vibrations at slightly different wavenumber, as can be seen in the spectrum at 100 K (Fig. 2). In the OD region an extra

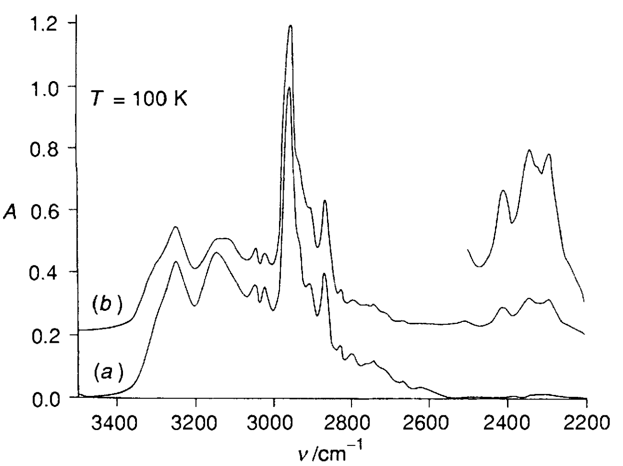

Fig. 2 Solid-state IR spectra of compound **2** at 100 K in KBr, (*a*) non-deuteriated and (*b*) partly deuteriated

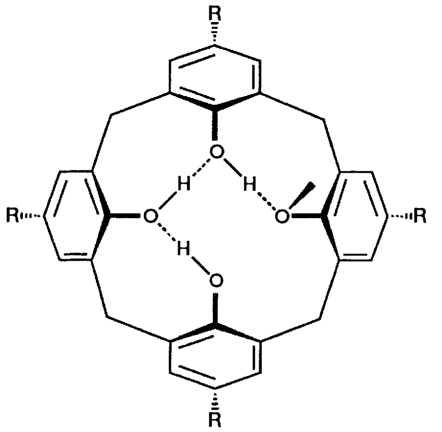

Fig. 3 The hydrogen bonding structure in the monomethyl ether **2**

shoulder at the high-frequency side is not clearly visible, but instead another shoulder is present at 2324 cm^{-1}. The isotope ratios of the three main OH-stretch vibrations are 1.34–1.35. The presence of two strong hydrogen bonds and a weaker one is commensurate with a cone conformation with cooperative hydrogen bonds (Fig. 3). The extra shoulders might indicate that another H-bonding geometry is present in the crystals. This could involve a reversal of the direction of the hydrogen bonds, which, in an asymmetrical cone like the cone predicted by molecular mechanics calculations,[8] would lead to different OH-stretch frequencies. Also in CCl_4 and in CS_2 solution three OH bands can be observed, two around 3200 cm^{-1}, of which one is a shoulder on the other, and one at 3314 and 3343 cm^{-1}, respectively.

In the ^1H NMR spectrum of **2** in $CDCl_3$ there are two OH signals at 10.13 (1 H) and 9.54 ppm (2 H).[10,12] The ^1H NMR spectra in CCl_4 and CS_2 show the same characteristic pattern for the OH signals, which seems to indicate that there is only one strong H bond and two weaker ones. This seeming discrepancy between the IR and ^1H NMR spectra can be explained from the fact that with ^1H NMR spectroscopy one looks in a different time window than with IR spectroscopy. In this case, the ^1H NMR spectrum shows the averaged signals of two equivalent conformations, *viz.* one in which the H-bonding scheme is as depicted in Fig. 3 and another in which the direction of the H bonds is reversed (flip-flop hydrogen bonding).[8] Only the proton of the middle hydroxy group is in both cases involved in a strong cooperative H bond, whereas the two outer protons form half of the time a weaker H bond. Therefore, the middle proton will be more deshielded and its signal will be found at lower field than the signals of the two outer protons.

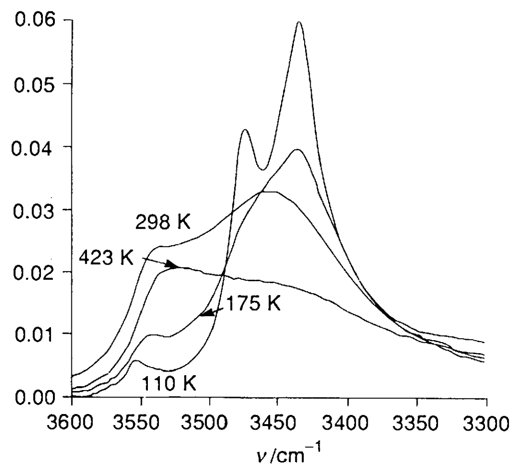

Fig. 4 Solid-state IR spectra of compound **3** in KBr at different temperatures between 100 and 500 K

The ^1H NMR spectra that were recorded at higher temperatures (up to 125 °C in $CDCl_2CDCl_2$) did not show any change in the conformation of **2**. Thus, by the introduction of just one methyl group in compound **1**, the calix[4]arene is rigidified and the direct cone-to-cone interconversion is no longer possible.

Also the 1,3-dimethyl ether **3** adopts a cone conformation, both in solution[6b,9] and in the solid state,[8] and does not show any sign of coalescence in its ^1H NMR spectrum at temperatures up to 125 °C in $CDCl_2CDCl_2$. The IR spectrum of the solid state at ambient temperature shows an OH band at 3456 cm^{-1} with a shoulder at 3538 cm^{-1}. The presence of the band at 3456 cm^{-1} indicates a rather weak hydrogen bond compared with unsubstituted calix[4]arenes.[6b,10] This is not so surprising as no cooperativity can exist in compound **3** and in fact the value of 3456 cm^{-1} is close to the value of 3470 cm^{-1} for the H-bonded hydroxy group in 2,2′-methylenebisphenol in CCl_4.[13] At low temperature the OH band at 3456 cm^{-1} is resolved into two separate bands at 3478 and 3435 cm^{-1} owing to the decrease of the half-widths (see Fig. 4). Furthermore, the second-derivative spectrum shows the presence of a shoulder at 3455 cm^{-1}. The intensities of the OH bands are very sensitive to temperature. At 100 K the band at 3538 cm^{-1} has nearly disappeared, whereas it strongly increases at the cost of the band at 3456 cm^{-1} upon heating to 500 K (Fig. 4). This phenomenon is completely reversible between 100 and 500 K. The two main OH bands at low temperature (at 3478 and 3435 cm^{-1}) belong to the two hydroxy groups in **3** that are bonded to the anisole oxygen atoms. These OH groups are not equivalent because they are involved in different $OH \cdots OCH_3$ bonds in the solid state, as is obvious from the irregular cone conformation in the X-ray structure.[8] The band at 3538 cm^{-1} (and the shoulder at 3455 cm^{-1}) might belong to a second structure in which one or two of the hydrogen bonds are reversed. As these last two bands increase gradually with increasing temperature, it seems likely that an equilibrium exists between the two H-bonded structures, and that they differ only slightly in energy.

In CCl_4 the OH band lies at 3423 cm^{-1}, but surprisingly in CS_2 this band is found at a 79 cm^{-1} lower frequency. Furthermore, in CCl_4 two shoulders can be observed at the high-frequency side at 3539 and 3502 cm^{-1}.

The solid-state IR spectrum of the 1,3-dimethyl ether of calix[4]arene (**7**) shows one OH band at 3384 cm^{-1}, a much lower frequency than for compound **3**. As for the *p-tert*-butyl analogue, this band is split in two separate bands at low temperature, in accordance with the irregular cone conformation in the X-ray structure of compound **7**.[8] The IR spectrum of **7** changes only slightly between 100 and 500 K and only at higher temperatures does an extra band at high frequency come up. The same equilibrium as for **3** might be involved but be less obvious for **7** because the energy difference between the two H-bond structures is larger. The absence of the *tert*-butyl groups in **7** also considerably reduces the solvent effect. The spectra in CCl_4 and in CS_2 show an OH band at nearly the same frequency (3365 and 3364 cm^{-1}). In CCl_4 there is again a shoulder present at 3535 cm^{-1}.

The 1,2-dimethyl ether **4** is a structural isomer of the 1,3-dimethyl ether. The ^1H NMR spectrum of **4** in $CDCl_3$ at ambient temperature shows a complex pattern of signals that cannot be assigned to one conformation. Comparison with the spectra of the *syn*-1,2-diethyl[14] and *anti*-1,2-diethyl[7] ethers of *p-tert*-butylcalix[4]arene (**8** and **9**, respectively) reveals that the spectrum of **4** can be regarded as a superposition of the spectra of compounds **8** and **9** (except for the signals of the ethyl substituents). Thus, the 1,2-dimethyl ether **4** exists in $CDCl_3$ as a mixture of the cone (the *syn* form), and of two partial cones (with an anisole ring rotated through the cavity) that interconvert rapidly on the ^1H NMR time-scale (the *anti* form).[15] The ratio between the *syn* and *anti* conformations depends strongly on the solvent. It ranges from 4.3:1 (CS_2), *via* 3.0:1 ($CDCl_3$) and 2.0:1 ($CDCl_2CDCl_2$), to 1.2:1 (CCl_4). When a sample of **4** was heated in $CDCl_2CDCl_2$, broadening of the signals started at 105 °C. This implies that the signals are starting to coalesce, owing to the interconversion of the *syn* (cone) and the *anti* (partial cone) forms.

For both the cone and the partial cone one would expect a strong and a weak hydrogen bond, as in both conformations one cooperative H bond can be formed. Indeed, four different OH bands are present in CS_2 but in CCl_4 beside these four bands an extra band at 3506 cm^{-1} is observed (Table 1). This reflects the behaviour of the *syn*- and *anti*-1,2-diethyl ethers **8** and **9**.[15] In CS_2 both compounds show only two OH bands, but in CCl_4 the *syn*-1,2-diethyl ether **8** shows two additional bands at 3525 and 3468 cm^{-1}, probably belonging to another conformation without cooperative H bonds.[15] In the solid state the IR spectrum of **4** shows only two bands at 3438 and 3367 cm^{-1}. This indicates that compound **4** crystallizes in a conformation in which two different hydrogen bonds to oxygen atoms are present, but which is not the cone or the partial cone because these would give rise to lower frequencies, as in solution. The most likely conformation is a 1,2-alternate with a hydroxy and a methoxy group on each side of the ring. Unfortunately, it has not been possible to obtain crystals suitable for X-ray crystallography in order to check this hypothesis.

The trimethyl ether **5** crystallizes in the cone conformation[8] and the solid-state IR spectrum shows one OH band at 3452 cm^{-1}, in accord with a hydrogen bond to another oxygen atom.[10] In $CDCl_3$ solution the main conformation is the cone.[9] Other conformations are present as well but these have until now not been identified with certainty. The ^1H NMR spectra that were recorded in other solvents (the same as for compound **4**) did not change the relative populations of the conformations enough to render assignment of other conformations possible. Dynamic ^1H NMR spectroscopy in $CDCl_2CDCl_2$ showed that already at 45 °C broadening of signals takes place. At 125 °C full coalescence has nearly been reached. The trimethyl ether is apparently more flexible than the 1,2-dimethyl ether.

The IR spectra in CCl_4 and CS_2 show two OH bands (see Table 1). The band at low frequency can be assigned to the cone conformation (*cf.* the solid-state spectrum), and the band at 3520 cm^{-1} probably belongs to an OH group of another conformation. Remarkable is the difference of 55 cm^{-1} between the frequencies of the low-frequency OH band in CCl_4 and in CS_2.

Table 2 Relative concentrations (in %) of the conformations of tetramethyl ether **6** in different solvents (^1H NMR, 200 MHz, −30 °C)

Solvent	Cone	Partial cone	1,2-Alternate	1,3-Alternate
$CDCl_3$	5	85	7	3
CS_2 (−15 °C)	14	81	5	<3
CCl_4	14	77	9	<3
CD_2Cl_2 (−27 °C)	18	74	8	<3

The ^1H NMR spectrum of the tetramethyl ether of *p-tert*-butylcalix[4]arene (**6**) in $CDCl_3$ at −30 °C (recorded at 600 MHz) has revealed that all four conformations are present in solution. Beside the partial cone (85%), the cone (4%), the 1,2-alternate (8%), and the 1,3-alternate (3%) are also present.[7] Spectra recorded at −30 °C at 200 MHz in several solvents showed large variations in the relative populations of the conformations (see Table 2). The spectra recorded at higher temperature (in $CDCl_2CDCl_2$) indicate that the tetramethyl ether is more flexible than the trimethyl ether. Already at 85 °C the same degree of coalescence has been reached as for the trimethyl ether at 125 °C.

Discussion

The IR spectra of the methyl ethers of *p-tert*-butylcalix[4]arene show that the cooperativity in the hydrogen bonding in calix[4]arenes is very strong. The cooperativity is often expressed as the extra shift in the frequency of an OH group that is involved in a cooperative H bond relative to the frequency shift of an OH band in a non-cooperative H bond.[16] As reference compounds 2,6-dimethyl-*p-tert*-butylphenol (3622 cm^{-1} in CCl_4 and 3611 cm^{-1} in CS_2)[13] and the trimethyl ether **5** are used. The cooperativities amount to 150, 130 and 125% in CCl_4 for calixarenes **1**, **2** and **4**, respectively, and to 80% for all three compounds in CS_2. The cooperativity is exceptionally strong compared with values given in the literature.[16] This might be due to the phenolic character of the hydroxy groups and the strict intramolecular character of the H bonds. The differences between CCl_4 and CS_2 will be discussed below.

The strength of the hydrogen bonds of the calix[4]arenes in the solid state cannot simply be correlated to the O···O distances in the crystal. The shortest O···O distances are 2.67 Å (compound **1**), 2.82 and 3.00 Å (**3**), 2.96 Å (**5**), and 2.86 and 2.90 Å (**7**).[8] Most pronounced are the discrepancies between the two 1,3-dimethyl ethers **3** and **7**. The shortest distance is found in compound **3**, but the lowest OH frequency (at 100 K) for **3** is 66 cm^{-1} higher than for **7**. This is too much to be an effect only of the different *para* substituents.* Apparently, the geometry of the H bonds plays a large role in these molecules, as has also been observed for the *para*-bridged calix[4]arenes.[5] In a symmetrical cone (with C_4 symmetry as in **1**) all four oxygen atoms lie exactly in one plane, which is parallel to the mean plane of the methylene carbon atoms.[8] In a flattened cone (with C_2 symmetry, as for **3**, **5** and **7**),[8] two opposite anisole rings are nearly perpendicular to the plane of the methylene carbon atoms and the other two aromatic rings are rotated inwards so that the dihedral angles with the methylene plane are between 35 and 50°. The oxygen atoms are not in one plane, the anisole oxygens (of **3**) lie 0.25 Å below the mean plane, and the hydroxy oxygen atoms 0.25 Å above it. For compound **7** these values are 0.20 Å. In these structures the H bonds deviate considerably

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* In CS_2 the OH-stretch frequencies for 2,6-dimethylphenol and 4-*tert*-butyl-2,6-dimethylphenol are 3610.5 cm^{-1} for both compounds. In CCl_4 the frequencies are 3621.0 and 3622.0 cm^{-1}, respectively (ref. 13).

from linearity. The deviation from linearity is more pronounced in **3** than in **7**, which may explain the stronger hydrogen bonds in **7**.

The differences between the OH-stretch frequencies in CS_2 and in CCl_4 are too large and irregular to be explained by only the intrinsic properties of the solvent. More information about the phenomena that occur in solution can be obtained from the ^1H NMR spectra. First, the solvent influences the relative amounts of the conformations of the 1,2-dimethyl ether **4** and the tetramethyl ether **6**. Unfortunately, there is not a clear trend observable. Shinkai *et al.* have suggested that for **6** a conformation with a high dipole moment (cone) is stabilized relative to the partial cone in more polar solvents.[17] However, this explanation does not cover all data presented here (*e.g.* for **6** there is more cone in CCl_4 than in $CDCl_3$, although $CDCl_3$ is the more polar solvent). Another possible explanation is that the cone can be stabilized by inclusion of a solvent molecule in the cavity. In particular, a small molecule like CS_2 can easily enter the cavity of the cone. Although no complexes of calix[4]arenes with CS_2 are known, complexes of calix[4]arenes with other solvents (*e.g.* acetonitrile, toluene and acetone) in the solid state are known,[1] as well as complexes of cone-shaped Högberg compounds with CS_2.[18] However, this effect cannot provide an explanation for all the data for compounds **4** and **6**.

An additional effect of the complexation of a solvent molecule in the cavity of a cone may be that the cone becomes more symmetrical (if it was a flattened cone before). This is apparent from the differences in the ^1H NMR spectra of compounds **3** and **4** in CCl_4 and in CS_2. The two *tert*-butyl signals of **3** are 0.46 ppm apart in CCl_4 but only 0.12 ppm in CS_2. For the cone of **4** these values are 0.08 and 0.01 ppm. Similar differences are also observed for the two aromatic signals of **3**. The degree of symmetry of the cone influences the relative positions of the oxygen atoms and thereby the strength of the H bonds (see above).

With the assumption that CS_2 can form a relatively strong complex with the cone conformation but CCl_4 cannot, many of the differences between the IR spectra in CCl_4 and in CS_2 can be explained. The simplest spectra are those of the 1,3-dimethyl ether of calix[4]arene (**7**). The OH band is not influenced by the solvent because the cone of this compound without *para*-substituents has no appreciable cavity in which complexation can take place. For the *p-tert*-butyl analogue **3** the 79 cm^{-1} difference in the OH frequencies in CCl_4 and CS_2 can now be explained by the much stronger complexation of CS_2 in the cavity of the cone. The cone in the complex is closer to C_4 symmetry than the empty cone, which has C_2 symmetry as in the X-ray structure, and this changed geometry influences the strength of the H bonds. The extra OH bands that appear in the IR spectra in CCl_4 must be due to one or more other H-bond structures. These might involve other conformations of the calixarene, or a changed geometry of the cone (*e.g.* a second 'flattened' cone in which the two phenol groups are parallel). This phenomenon will be the subject of a future research project.

Similar, but smaller, frequency shifts are apparent in the IR spectra of the 1,2-dimethyl ether **4**. The appearance of extra signals in CCl_4 also indicates for this compound the presence of other H-bond structures. Also for the trimethyl ether **5** a frequency difference is observed for the OH band that is assigned to the cone conformation. Both in CCl_4 and in CS_2 at least one other conformation is present according to the ^1H NMR spectra, which may account for the extra OH band at 3520 cm^{-1}.

Surprisingly, the situation is reversed for the unsubstituted calix[4]arene **1** and the monomethyl ether **2**, in that the OH frequencies in CS_2 are higher than in CCl_4. As there is no reason to exclude complexation in these compounds, the inclusion of a CS_2 molecule in the cavity apparently changes the cone in a way that weakens the hydrogen bonds. Possibly, the symmetry of the cone of these compounds is reduced upon complexation of CS_2. However, no indication for this was apparent from the ^1H NMR spectra of **2** in CS_2 and in CCl_4.

The differences in the cooperativity effects in CCl_4 and in CS_2 can now also be discussed. In CS_2 the cone conformations of **1**, **2**, **4** and **5** will be similar due to the complexation of a solvent molecule. The unexpected result is that maximum cooperativity is already reached when the first extra H bond is introduced. This might indicate that the geometry is not optimal for hydrogen bonding (which is obvious from the much lower frequency for **1** in CCl_4). In CCl_4, on the contrary, no complexation takes place and the strength of the H bonds is therefore also influenced by the changing geometries of the cone. Going from the trimethyl ether back to the unsubstituted calix[4]arene the cone is likely to become closer to C_4 symmetry. It is therefore difficult to assess the 'true' value of the cooperativity of the one, two or three extra H bonds in calix[4]arenes.

The dynamical behaviour of the calix[4]arenes **1**–**6** is also very intriguing. Both unsubstituted *p-tert*-butylcalix[4]arene **1** and its tetramethyl ether **6** are flexible molecules and their ^1H NMR spectra exhibit broad signals at ambient temperature (in $CDCl_3$). However, the ^1H NMR spectra of the partially methylated calix[4]arenes show only sharp signals at ambient temperature. The introduction of just one methyl group in unsubstituted *p-tert*-butylcalix[4]arene completely blocks the cone-to-cone interconversion, although this compound (**2**) can still exist in two equivalent cone conformations. Therefore, the process in **1** must involve the rotation of more than one aromatic ring at the same time. If only one aromatic ring rotated this process should also take place in **2**, because the rotation of one anisole ring at a time is possible in **6**.[7,19] Apparently, the concerted interconversion process in **1** is blocked by the methoxy group because of steric hindrance. These results are not sufficient to decide on the exact mechanism of the process, whether this involves a direct cone-to-cone interconversion,[4c] or a pathway *via* a skewed 1,2-alternate-like intermediate[4b] or even *via* a 1,3-alternate-like intermediate.[4a]

For the 1,3-dimethyl ether the cone-to-cone interconversion is blocked for the same reason as for **2**. The 1,2-dimethyl ether has two different conformations that are close in energy (*syn* and *anti*). The two equivalent partial cone conformations can interconvert fast at ambient temperature (leading to averaged signals in the ^1H NMR spectrum). This process requires the rotation of the two phenol rings so that one H bond must be broken. Interconversion between the two equivalent cone conformations does not take place. At higher temperatures broadening of the signals of cone and partial cone indicates that interconversion between cone and partial cone does take place. This would require the rotation of only one of the two anisole rings. The trimethyl ether is more flexible than the 1,2-dimethyl ether and also exists in more than one conformation. These can interconvert by the rotation of one anisole ring at a time.

Conclusions

The strength of the hydrogen bonds in partly methylated calix[4]arenes in the cone conformation is influenced not only by the number of hydroxy groups (*via* the cooperativity effect) but also by the exact geometry of the cone. The conformational distribution of calix[4]arenes that exist in more than one conformation is strongly influenced by the solvent in which they are dissolved. Inclusion of a solvent molecule in the cone conformation also changes the geometry of the cone, which can have a pronounced effect (a shift of up to 79 cm^{-1}) on the frequency of the OH bands in the IR spectra.

Also the flexibility of a calix[4]arene is strongly influenced by the number of oxygen substituents. The cone-to-cone interconversion in unsubstituted calix[4]arenes is completely blocked by the introduction of just one methyl group. As more methyl groups are introduced the calix[4]arene becomes flexible again. This lends support to a concerted mechanism for the interconversion in the unsubstituted calix[4]arene, in which two or more phenol rings rotate simultaneously, as opposed to the stepwise mechanism for the tetramethyl ether.

Experimental

The ^1H NMR spectra were recorded on a Nicolet NT 200-WB spectrometer (200 MHz). The spectra in $CDCl_2CDCl_2$ were recorded at intervals of 20 °C between 25 and 125 °C. The relative amounts of the conformations of compounds **4** and **6** in four different solvents were determined from the integrals of the methylene and methoxy signals for compound **4** and from the aromatic and methoxy signals for compound **6**. As supplementary material copies of these eight spectra are available, together with a list of the signals of the spectra of compounds **2**, **3** and **4** in CS_2, $CDCl_3$, $CDCl_2CDCl_2$ and CCl_4.*

The variable temperature solid-state IR spectra (KBr and fluorolube) were recorded on a Mattson 5020 spectrophotometer connected to a personal computer at a resolution of 2 cm^{-1} by averaging 64 scans. The IR spectra in CCl_4 and in CS_2 were recorded with a Perkin-Elmer 1720, by using 1 cm Infrasil quartz cells, at a resolution of 2 cm^{-1} by averaging 50 scans. The concentration of the samples was less than 5×10^{-3} mol dm^{-3}.

Compounds **1**,[20] **2**,[12] **3**,[6b] **6**[6b] and **7**[21] were synthesized following literature procedures. Compound **5** was synthesized by reacting **6** with one equivalent of Me_3SiI in $CHCl_3$, following the same procedure as for the synthesis of **2**.[12] Full characterization of this compound has been published by others.[10] Several methods for the synthesis of 1,2-dimethyl ether **4** have been mentioned in the literature without a description of the full experimental procedure.[14,22] One of these is described here in detail.[14]

*27,28-Dimethoxy-*p-tert*-butylcalix*[4]*arene-*25,26*-diol* **4**. A suspension of p-*tert*-butylcalix[4]arene **1** (toluene complex, 0.25 g, 0.38 mmol) and NaH (80% in oil, 0.11 g, 4.75 mmol) in DMF (10 cm^3) was stirred at room temperature for 0.5 h. The alkylating agent (0.8 mmol) was added and the reaction mixture was stirred for 16 h. The reaction was quenched by addition of HCl (1 mol dm^{-3}; 20 cm^3) and the resulting mixture was extracted with CH_2Cl_2 (2×20 cm^3). The combined organic layers were washed with HCl (1 mol dm^{-3}; 25 cm^3) and H_2O (25 cm^3), dried over $MgSO_4$, and evaporated. Purification of the crude product by taking it up in ethyl acetate and filtering off the remaining starting material, and then column chromatography [SiO_2, E. Merck, particle size 0.040–0.063 mm, 230–400 mesh, eluent CH_2Cl_2–light petroleum (b.p. 40–60 °C), 3:1] yielded **4** (34%), m.p. 222–224 °C (from hexane) (Found: C, 81.2; H, 8.75. $C_{46}H_{60}O_4$ requires C, 81.6; H, 8.93%); δ_H(250 MHz; $CDCl_3$; Me_4Si) 8.60 (2 H, s, OH, *syn*), 7.28 (2 H, s, OH, *anti*), 7.20–7.15 (4 H, m, ArH, *anti*), 7.05–6.95 (8 H, m, ArH, *syn*, and 4 H, m, ArH, *anti*), 4.39, 4.33 (1 H, d, *J* 13.5 Hz, $ArCH_2Ar$ ax, *syn*), 4.31 (2 H, d, *J* 13 Hz, $ArCH_2Ar$ ax, *syn*), 4.00 (6 H, s, OCH_3, *syn*), 3.95, 3.71 (2 H, s, $ArCH_2Ar$, *anti*), 3.87 and 3.69 (4 H, AB system, *J* 13 Hz, $ArCH_2Ar$, *anti*), 3.36 (3 H, d, *J* 13 Hz, $ArCH_2Ar$ eq, *syn*), 3.34 (1 H, d, *J* 13.5 Hz, $ArCH_2Ar$ eq, *syn*), 2.94 (6 H, s, OCH_3, *anti*), 1.30, 1.22 [18 H, s, $C(CH_3)_3$, *anti*], 1.19, 1.13 [18 H, s, $C(CH_3)_3$, *syn*]; *m*/*z* (FAB+) 677 (M^+).

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