Spectroscopic studies of hydrogen-bond structures and dynamics of partially methylated *p-tert*-butylcalix[6]arenes

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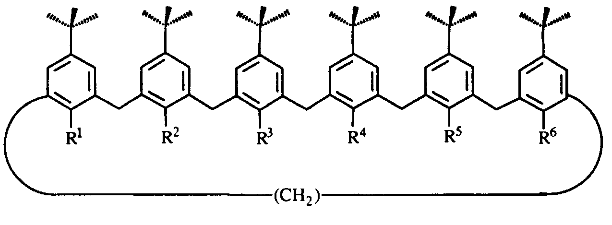
Hydrogen-bond structures of partially methylated *p-tert*-butylcalix[6]arenes were investigated both in solution and the solid state by Fourier transform infrared spectroscopy (FTIR). The hydrogen bonds in these macrocycles are preferentially of the three-centred and cooperative types. The dynamic behaviour of these calix[6]arenes is characterized by fast rearrangement of the methoxy groups in the calix[6]arene annulus and was investigated by means of 2D NMR spectroscopy. The conformational behaviour is primarily dominated by an interplay of favourable hydrogen-bond formation and the tendency of 'self-inclusion' of the methoxy groups.

Introduction

The modular approach for the design of large molecular assemblies is a well-established methodology in supramolecular chemistry and has been applied by us, for example, in the synthesis of calixspherands,[1] calixcrowns,[2] water-soluble cyclodextrin–calix[4]arene host molecules,[3] holands[4] and anion receptors.[5] Among the different building blocks, calix[4]arenes[6] are frequently used, because of their well-known chemical and physical properties. In order to expand the scope of calixarene chemistry, we focused attention on the calix[6]arenes and in collaboration with the groups of Ungaro and de Mendoza we investigated selective lower[7] and upper rim functionalization.[8] Calix[6]arenes are more flexible than calix[4]arenes and in the case of C_{3v} calix[6]arenes, which are alternately substituted with small alkyl and other (bulkier) substituents, we demonstrated that the conformations are stabilized by self-inclusion of the alkyl substituents.[9] The more complex dynamics between the flattened cone and the 1,2,3-alternate conformations present was confirmed by the existence of two macrocyclic ring interconversion mechanisms.[9] The conformational flexibility of calix[6]arenes has also been reduced by (*e.g.* three-point) capping of either the lower or the upper rim.[10] Recently, we successfully quantified all dynamic processes in selectively phosphorylated calix[6]arenes by performing 2D NMR spectroscopy.[11]

Hydrogen bonding is an important driving force which governs the conformation and dynamics of partially substituted calix[*n*]arenes in general[6] and also plays an important role in the stabilization of deprotonated intermediates in alkylation and acylation reactions.[12] Therefore, it is of the utmost importance to analyse the hydrogen-bond structures of calix[6]arenes.



	R¹	R²	R³	R⁴	R⁵	R⁶
1	OH	OH	OH	OH	OH	OH
2	OMe	OH	OH	OH	OH	OH
3	OMe	OMe	OH	OH	OH	OH
4	OMe	OH	OMe	OH	OH	OH
5	OMe	OH	OH	OMe	OH	OH
6	OMe	OMe	OMe	OH	OH	OH
7	OMe	OH	OMe	OH	OMe	OH
8	OMe	OMe	OH	OMe	OH	OH
9	OMe	OMe	OMe	OMe	OH	OH
10	OMe	OMe	OMe	OH	OMe	OH
11	OMe	OMe	OH	OMe	OMe	OH
12	OMe	OMe	OMe	OMe	OMe	OH
13	OMe	OMe	OMe	OMe	OMe	OMe

The partially methylated *p-tert*-butylcalix[6]arenes **2**–**12** are the most simple functionalized calix[6]arenes, which are not hampered by complicated interactions between substituents.[7] These derivatives are flexible at room temperature and exhibit fast interconversion on the chemical-shift timescale. Hydrogen-bond geometries can be investigated with both ^1H NMR spectroscopy and IR spectroscopy. Owing to the six orders of magnitude faster time window of IR spectroscopy, different bond geometries with a very short lifetime up to 10^{-13} s can be observed. ^1H NMR spectroscopy reflects the conformation of a molecule in a time window of 10^{-3}–10^{-6} s. The band maximum of the OH-stretching mode varies from 3650–3100 cm^{-1} and is very sensitive to different hydrogen-bond geometries in which an OH group may be involved. Consequently, this spectral range contains information about the hydrogen-bond structure(s) in each conformation present. In earlier investigations on calix[4]arenes, Groenen *et al.*[13] have shown a nice experimental correlation between the OH-stretching frequency and the ^1H NMR chemical shift. Recently, we were able to characterize the different types of hydrogen-bond structures of a series of acyclic oligomeric phenol condensates and to characterize them by the specific OH stretching frequency.[14] In this paper, we present the results of an FTIR spectroscopic study on the hydrogen-bond structures, which exist in partially methylated calix[6]arenes. In addition the dynamic behaviour of these calixarenes was investigated by means of 2D NMR spectroscopy. Together with our previous studies,[9,11] these results complete the conformational and dynamic model of calix[6]arenes.

Results and discussion

IR spectra of partially methylated *p-tert*-butylcalix[6]arenes **2–4**, **6–8** and **10–12** were recorded both in solution and in the solid state. The absorption bands in the OH-stretching region of dilute solutions in CCl_4 and CS_2 are broader than in the solid state. This is attributed to conformational flexibility, *i.e.* reorientational relaxation broadening. Owing to the reduced HBWs (half bandwidth) of individual bands in the solid state, the overall band shape shows more details. The low temperature solid-state spectra exhibit enhanced resolution and these were subjected to detailed analysis. The maxima of individual bands were determined interactively by second derivative, curve fit, and Fourier self-deconvolution procedures.

Coupling interactions often give rise to distortion of the bandshape of OH-stretching modes in intra- or inter-molecular bonded systems. For the series of calix[6]arenes studied a characteristic spectral phenomenon is observed at *ca.* 3200 cm^{-1} mostly present as a hole in the broad hydrogen-bond absorption. The origin of this phenomenon has been described by Evans,[15] who showed that mixing of wavefunctions of fundamental and overtone or combination vibrations of equal symmetry create a hole, now called an Evans hole, in a broad fundamental band. This spectral artefact might erroneously be interpreted in terms of additional conformers or hydrogen bonds.

Variable-temperature NMR spectra of partially methylated *p-tert*-butylcalix[6]arenes **2–4**, **6–8**, **10** and **12** were recorded between 206–296 K in CD_2Cl_2 solution on a 500 MHz NMR spectrometer, while monomethylated- **2** 1,3,5-trimethylated- **7** and 1,2,3,5-tetramethylated-calix[6]arene **10** were also recorded in CD_2Cl_2 solution at 188 K on a 400 MHz NMR spectrometer. All ^1H NMR spectra, which are sharp at room temperature, broaden upon lowering the temperature, and from the coalescence temperatures, which vary between 230–250 K, an upper limit for the activation Gibbs free energy of 42–46 kJ mol^{-1} was estimated for the interconversion process with the highest energy barrier.

For the discussion of the results, the different calix[6]arenes have been divided into two classes, *viz.* in a series of partially methylated calix[6]arenes with isolated hydroxy groups† and a series with proximal‡ hydroxy groups.

Partially methylated *p-tert*-butylcalix[6]arenes with isolated hydroxy groups

IR spectroscopy of dilute solutions. As reported for *p-tert*-butylcalix[6]arene **1**,[14] the OH stretching mode of partially methylated calix[6]arenes is far less affected by the nature of the solvent compared with partially methylated *p-tert*-butylcalix[4]arenes[13] since solvent molecules do not exactly fit in the less preorganized structures of calix[6]arenes.

The IR spectrum of pentamethylated calix[6]arene **12** measured in dilute CCl_4 solution exhibits two maxima and a shoulder in the OH region. The band at 3358 cm^{-1} is dominant, while absorptions at 3621 and 3510 cm^{-1} are very weak (Table 1). The latter are assigned to a free OH group and OH ··· π bond, respectively. The band at 3358 is 72 cm^{-1} red shifted compared with isolated OH ··· OMe bands, previously observed in related acyclic model compounds.[14] In our opinion, this large red shift can be assigned to a different H-bond geometry possibly due to favourable interaction of the OH group with more than one OMe group.

The structure of 1,2,4,5-tetramethylated calix[6]arene **11** differs from pentamethylated **12** in that the distally positioned methoxy group is replaced by an OH group. Similar band maxima at 3346 and 3358 cm^{-1} were observed for calix[6]arene **11** in dilute CCl_4 and CS_2 solution, respectively (Table 1). Both pentamethylated **12** and 1,2,4,5-tetramethylated-calix[6]arene **11** render the same structural feature that each OH group shares two proximal OMe groups, and most likely the interactions between OH groups and the OMe groups are similar in both calixarenes. In our opinion, in both cases three-centred hydrogen bonds§ between an OH group and two proximal OMe groups are formed. This type of hydrogen bond gives a relatively unstrained molecular geometry and the observed band maxima nicely agree with those observed for three-centred hydrogen bonds in the previously investigated acyclic model compounds.[14]

The OH spectral region of 1,2,3,5-tetramethylated calix[6]arene **10** in dilute CCl_4 and CS_2 solution is similar to the previously discussed spectra of pentamethylated **12** and 1,2,4,5-tetramethylated-calix[6]arene **11**, and exhibit band maxima at 3355 and 3345 cm^{-1}, respectively (Table 1). However, the formation of three-centred hydrogen bonds with exclusively proximal OMe groups is not possible as it forces one OMe group to accept two hydrogen bonds simultaneously. Therefore, also the existence of three-centred hydrogen bonds between an OH group and a proximal and a medially positioned OMe group is postulated for these cyclic calix[6]arene systems, contradictory to its absence in acyclic oligomeric condensates.¶,[14] Structure elucidation by means of dynamic ^1H NMR spectroscopy (see below) reveals that two OMe groups are alternately positioned in the annulus of the calix[6]arene. This conformational feature allows the formation of three-centred OH ··· (OMe,OMe) hydrogen bonds between proximally and medially positioned OMe groups without forcing too much strain on the molecular geometry. The IR spectrum of 1,3,5-trimethylated calix[6]arene **7** in dilute CCl_4 solution shows, apart from the major band at 3350 cm^{-1} assigned to the three-centred hydrogen-bond geometry, an additional band at *ca.* 3400 cm^{-1}, which has been assigned to an isolated (two-centred) OH ··· OMe hydrogen bond. The red shift of 20–30 cm^{-1} for this hydrogen bond[14] may be assigned to the cyclic structure of the calix[6]arene skeleton.

IR spectroscopy of solid-state samples. The OH-stretching region in the solid state IR spectrum of pentamethylated calix[6]arene **12** at 110 K is similarly shaped as its spectrum in solution and exhibits a band maximum at 3391 cm^{-1} (Table 2). The blue shift of 33 cm^{-1} compared with the value observed in solution points to a somewhat different hydrogen-bond geometry. The band position is intermediate to that of the reference value in solution of a two-centred (OH ··· OMe) bond and the value observed (see above) for the three-centred (OH ··· OMe,OMe) hydrogen bond. Apparently, molecular packing in the solid state favours a two-centred geometry over the three-centred one. Moreover, the weak band at 3627 cm^{-1} is assigned to a free OH group.

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† Hydroxy groups are isolated, when they do not have other neighbouring (proximal) hydroxy groups.

‡ The calix[6]arene skeleton is schematically depicted as a hexagon, in which each corner represents a phenolic moiety. 'Proximal' are two aromatic moieties, which are connected *via* a methylene bridge; 'medial' are two aromatic moieties, which are separated by one aromatic moiety; 'distal' are two aromatic moieties, which are separated by two aromatic moieties.

§ In the literature the terms 'three-centred' and 'bifurcated' are sometimes confused. In a three-centred hydrogen bond, one hydrogen bond donor is bound to two (hydrogen bond) acceptors, while in a bifurcated hydrogen bond, one hydrogen bond acceptor binds two hydrogen-bond donors simultaneously; ref. 22(*c*).

¶ Recently, X-ray diffraction data of calix[6]arene thiophosphates provided clear evidence for the existence of such hydrogen bonds for this class of functionalized calix[6]arenes; see ref. 11.

Table 1 IR spectral data (ν/cm^{-1}) of partially methylated *p-tert*-butylcalix[6]arenes with 'isolated' OH groups in dilute solution (T = 295 K)

Compound	OH ··· (OMe, OMe)	OH ··· OMe	OH ··· π	OH$_{free}$
7	3350^a	~3400^a (sh)	3550^a (sh)	
(1,3,5)	3330^b	~3400^b (sh)	3550^b (sh)	
10	3355^a		3510^a (sh)	
(1,2,3,5)	3345^b		3510^b (sh)	
11	3346^a		3520^a (sh)	
(1,2,4,5)	3338^b		3520^b (sh)	
12	3358^a		3510^a (sh)	3621^a (w)
(penta)	3350^b		3500^b (sh)	3600^b (w)

^{a} Recorded in CCl_4 solution. ^{b} Recorded in CS_2 solution. sh = shoulder. w = weak intensity.

Table 2 IR spectral data (ν/cm^{-1}) of partially methylated *p-tert*-butylcalix[6]arenes with isolated OH groups in the solid state (T = 110 K)

Compound	OH ··· (OMe, OMe)	OH ··· OMe OH ··· OH	OH ··· π	OH$_{free}$
7	3325, 3290^c		3505^c	
(1,3,5)	[3326^a]	[Asym]	[3520]	
10	3258^b	3350	3510 (sh)	
(1,2,3,5)	[3310]	[3370]	[3500]	
11	3330, 3295, 3260^b (sh)			
(1,2,4,5)	[3328]			
12		3391		
(penta)		[3395]	[3500]	3627^c

^{a} [ ] data at 295 K. ^{b} Data obtained *via* second derivative. ^{c} Curve-fit results.

Upon cooling more spectral details are recognized in the OH-stretching region of 1,2,4,5-tetramethylated calix[6]arene **11**. The best curve fit result is obtained with three bands at 3330, 3295 and 3260 cm^{-1}, respectively. Obviously each band reflects the presence of a three-centred hydrogen bond, albeit that the maxima are red-shifted if compared with solution data. Apparently, molecular packing in the crystalline phase yields shorter O ··· O distances reflecting stronger hydrogen bonds.

In the low-temperature solid-state spectrum of 1,2,3,5-tetramethylated calix[6]arene **10** again a more complex pattern is observed compared to the solution phase (Table 2). The band at 3350 cm^{-1} is assigned to an isolated two-centred (OH ··· OMe) hydrogen bond with slightly shorter O ··· O distances than those of pentamethylated calix[6]arene **12**, while the red-shifted band at 3258 cm^{-1} most likely agrees with a cooperative three-centred hydrogen bond *i.e.* the OH acting as an acceptor and twice as a donor.[‖] Accordingly the 3350 cm^{-1} band may be assigned to an isolated medial OH ··· OH interaction, although the involvement of the intermediate methoxy group cannot be excluded. Similar observations as for 1,2,4,5-tetramethylated calix[6]arene **11** were made for 1,3,5-trimethylated calix[6]arene **7**. The solid-state spectrum at 300 K exhibits a broad asymmetric band with a maximum at 3326 and a shoulder at 3500 cm^{-1}, which upon cooling to −165 °C splits into bands at 3505, 3325 and 3290 cm^{-1} (Table 2) (Fig. 1). The bands at 3325 and 3290 cm^{-1} are assigned to a three-centred hydrogen bond with slightly different geometry. With the exception of the low-intensity broad band at *ca.* 3450 cm^{-1} (HBW > 150 cm^{-1}) in the spectrum of 1,2,4,5-tetramethylated calix[6]arene **11**, which originates from residual adsorbed water, OH ··· π hydrogen bonding was recognized for all other compounds; a characteristic absorption between 3500 and 3520 cm^{-1} being the criterion (Table 2).

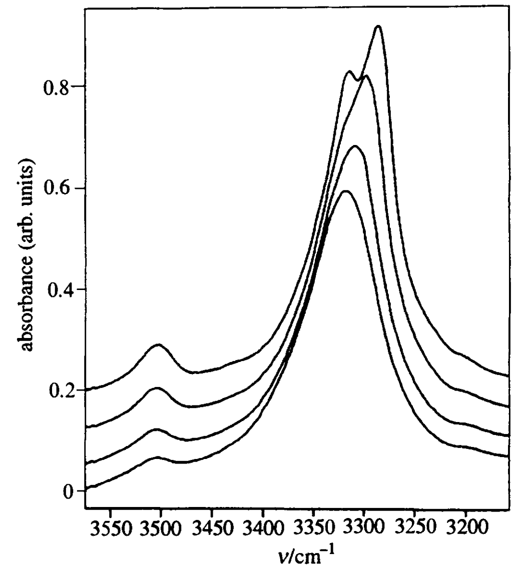

Fig. 1 OH-stretching region of 1,3,5-trimethylated *p-tert*-butylcalix[6]arene **7** in the solid state (KBr) at 300 (lower spectrum), 230, 150 and 110 K (upper spectrum)

From observations in solution as well as in the solid state we conclude that typical three-centred hydrogen bonds occur for all partially methylated calix[6]arenes with only isolated OH groups. The only exception is pentamethylated calix[6]arene **12** where the isolated OH ··· OMe hydrogen bond seems favoured in the solid state whereas in solution the three-centred hydrogen-bond geometry is predominant. Apparently, molecular packing effects dominate here. In the solid state the three-centred hydrogen-bond geometry is (slightly) different from solution due to reduction of the conformational mobility as a result of molecular packing. Shorter O ··· O contacts are correlated with red-shifts of the OH band maxima.

Variable-temperature NMR spectroscopy. The ^{1}H NMR spectrum of pentamethylated calix[6]arene **12** exhibits very broad resonances at 206 K. In accordance with the single strong IR band maximum both in solution and in the solid state, a single OH resonance is present both at room temperature and 206 K at 7.34 and 8.5 ppm, respectively. 1,2,3,5-Tetramethylated

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[‖] In a three-centred hydrogen bond one OH donor interacts with two hydrogen-bond acceptors. In fact, the OH proton is surrounded by three more or less attractive atoms. An initial OH group in a cooperative chain differs from a terminal one by its unique donor function only; this initial OH oxygen does not act as an acceptor at the same time. A terminal OH is bifunctional *e.g.* both an acceptor and a donor.

calix[6]arene **10** exhibits roughly the same behaviour. At 188 K the conformational interconversion rate has decreased to such an extent that the signals of the ^1H NMR spectrum are sharp. This spectrum exhibits three AX spin systems for the methylene bridges, three signals for the OMe groups in the ratio 2 : 1 : 1 and four signals for the *tert*-butyl groups in the ratio 1 : 1 : 2 : 2. Strong connectivities between the signals of the equatorial (upfield) protons of the methylene bridges and the signals of the aromatic protons as well as between the signals of the aromatic protons in a NOESY spectrum, point to a *syn*-arrangement of all aromatic moieties.

The signals of two OMe groups have been shifted extraordinarily upfield compared with the shifts of other methylated derivatives (Table 3), which points to a strong ring-current effect of the aromatic moieties. Because of the observed signal pattern the conformation should have a plane of symmetry with the upfield shifted OMe groups located in this plane. Both OMe groups show strong connectivities with each other, with the signals of the axial (downfield) protons of the methylene bridges, and with signals of aromatic protons. These spectral features indicate that these OMe groups are deeply embedded in the annulus of the calix[6]arene. The OMe groups at 2.0 and 1.4 ppm clearly exhibit an exchange connectivity with a weak signal at 3.8 and 4.0 ppm, respectively. The OMe group at 4.0 ppm shows a strong exchange connectivity with a weak signal at 1.8 ppm (Fig. 2). Additionally, the OH resonance has a strong exchange connectivity with a weaker OH resonance, which is slightly shifted upfield. These exchange connectivities indicate that the major *syn*-conformer interconverts rapidly with a conformer present in low concentration (minor conformer). This process maintains the plane of symmetry and reorients the OMe groups from inside to outside the cavity (schematically depicted in Fig. 3).

Upon cooling to 206 K the OH resonance of 1,3,5-trimethylated calix[6]arene **7** decoalesces in two resonances in the ratio 2 : 1, while in addition broad multiple resonances for the *tert*-butyl groups are observed. Upon further cooling to 188 K both the *tert*-butyl and the OMe resonances appear as three signals of equal intensity. Only one OMe group has shifted upfield (1.8 ppm), which indicates that it is located in the cavity of the calix[6]arene. The NOESY spectrum at 188 K exhibits a strong exchange connectivity between the signals of the OH groups, while a strong and a weak exchange connectivity were observed between the upfield- and both downfield-positioned OMe groups. These data match a three-site exchange process with fast flipping of two methoxy groups (*a*) and slow pinched-conformer interconversion (*b*) (Fig. 4).** Superposition of both dynamic processes gives the observed averaged (pseudo) C_{3v} symmetric conformation at room temperature. Whereas in the solid state the pinched conformer interconversion is unlikely, the splitting of the IR band at low temperature in two band maxima indicates that at least two different conformations must be present under these conditions.††

Partially methylated *p-tert*-butylcalix[6]arenes with proximal hydroxy groups

Based on the fact that cooperative H-bonding is energetically more favourable than 'isolated' donor–acceptor interaction, methylated calix[6]arenes with proximal OH groups are expected to give different H-bond geometries compared with the calix[6]arene derivatives discussed above.

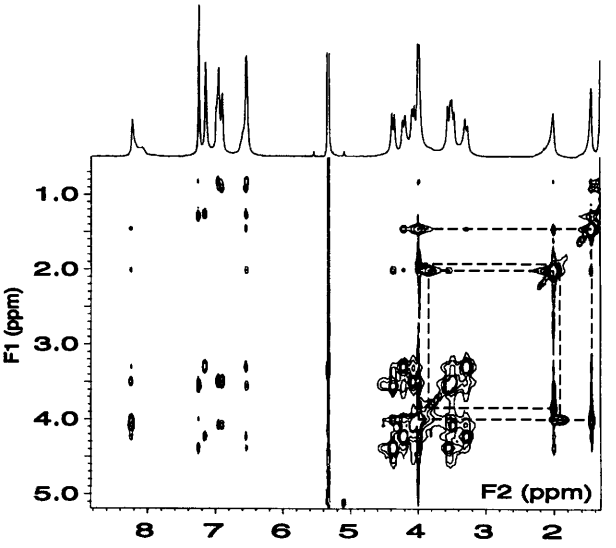

Fig. 2 Part of the NOESY spectrum of 1,2,3,5-tetramethylated *p-tert*-butylcalix[6]arene **10** recorded at 188 K in CD_2Cl_2

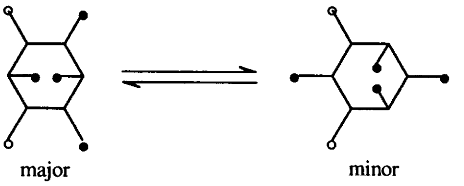

Fig. 3 Dynamic exchange of methoxy groups in 1,2,3,5-tetramethylated *p-tert*-butylcalix[6]arene **10**; primed and open dots refer to methoxy and hydroxy groups, respectively

Table 3 Positions of hydroxy and methoxy resonances (δ) in the ^1H NMR spectra of *p-tert*-butylcalix[6]arenes **2**–**13**[a]

Compound	ArOH	OMe
2	9.79, 9.55, 8.78 (2 : 1 : 2)	4.00
3	8.55, 8.20 (1 : 1)	3.80
4	8.65, 8.05, 6.90 (1 : 2 : 1)	3.73
5	8.26	3.70
6	8.29, 7.56 (2 : 1)	3.90, 2.91 (2 : 1)
7	6.77	3.46
8	8.29, 7.66, 7.05 (1 : 1 : 1)	3.33, 3.28, 3.11 (1 : 1 : 1)
9[b]	9.03, 7.66 (1 : 1)	3.71, 3.17 (1 : 1)
10	7.63	3.97, 2.58, 2.21 (2 : 1 : 1)
11	8.03	3.14
12	7.34	3.50, 3.06, 3.05 (1 : 2 : 2)
13		3.00

[a] Relative intensities of integrals is placed between brackets. [b] Values taken from ref. 23.

IR spectroscopy of dilute solutions. The OH absorptions in the spectra of monomethylated calix[6]arene **2** in solution are very broad. Three maxima at 3315, 3227 and 3200 cm^{-1} in CCl_4 and 3330, 3229 and 3200 cm^{-1} in CS_2 could be distinguished (Table 4). In both solvents the splitting of the bands at 3227/3200 and 3229/3200 cm^{-1} is assigned to an overtone interference creating an Evans hole at *ca.* 3200 cm^{-1} (see above). The 'real' band maxima are positioned at *ca.* 3210 cm^{-1}, between both maxima, and these were assigned to OH groups involved in a cooperative hydrogen bond. The weaker bands at 3315 and 3330 cm^{-1} correspond with a three-centred hydrogen bond.

The IR spectra of 1,2-dimethylated- **3**, 1,3-dimethylated- **4** and 1,2,3-trimethylated-calix[6]arenes **6** clearly show strong red-shifted bands compared with the series with isolated hydroxy groups, which indicates that these calix[6]arenes exhibit cooperative type hydrogen bonding. In all compounds listed in Table 4 a band between 3300–3360 cm^{-1} was observed, which may originate from OH groups involved in either three-

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** For a detailed discussion of pinched structures and pseudo-rotation see ref. 11.

†† Although comparison of intensity ratios needs correction for the differences in absorption coefficients, the introduced error is supposed to be small, because all hydroxy groups are involved in comparable types of hydrogen bonding, and consequently frequency differences will be small.

Table 4 IR spectral data (ν/cm^{-1}) of partially methylated *p-tert*-butylcalix[6]arenes with proximal OH groups in dilute solution (T = 295 K)

Compound	OH $\cdots$ (OH,OH) OH $\cdots$ (OMe,OMe) OH $\cdots$ (OH,OMe)/ OH $\cdots$ OMe	OH $\cdots$ (OH) $\cdots$ O (cooperative)	OH $\cdots$ π
2	3315^{a} (sh)	(3227, 3200)^{a,c}	~3500^{a}
(mono)	3330^{b} (sh)	(3229, 3200)^{b,c}	~3500^{b}
3	3310 (sh)^{a}	3265^{a}	
(1,2)	3310 (sh)^{b}	3260 (sh)^{b}	~3470^{b}
4	3330^{a}	3200^{a} (sh)	~3510^{a}
(1,3)	3325^{b}	3200^{b} (sh)	~3510^{b}
6	3340^{a}	~3250^{a} (sh)	
(1,2,3)	3330^{b}	~3250^{b} (sh)	
8	3360^{a}	~3250^{a} (sh)	
(1,2,4)	3355^{b}	~3250^{b} (sh)	

^{a} Recorded in CCl$_4$ solution. ^{b} Recorded in CS$_2$ solution. ^{c} Splitting due to Fermi resonance (Evans hole).

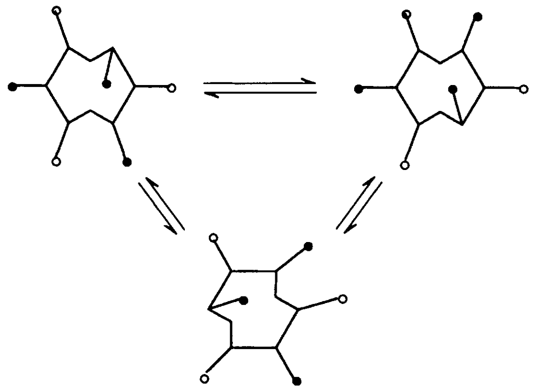

Fig. 4 Dynamic exchange of methoxy groups in 1,3,5-trimethylated *p-tert*-butylcalix[6]arene **7**; primed and open dots refer to methoxy and hydroxy groups, respectively

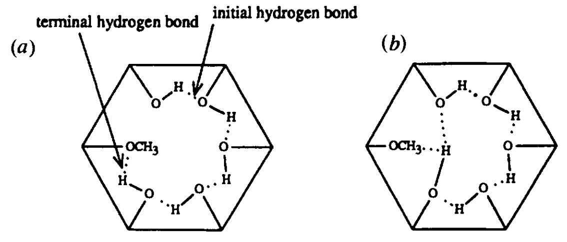

Fig. 5 (*a*) Hydrogen-bond array terminated by a single (OH $\cdots$ OMe) hydrogen bond; (*b*) hydrogen-bond array terminated by a three-centred (OH $\cdots$ OH,OMe) hydrogen bond in monomethylated *p-tert*-butylcalix[6]arene **2**

centred or OH $\cdots$ OMe hydrogen bond geometries and at the same time take part in cooperative H-bonding. In the latter case the OH stretching frequencies are red shifted, which can be satisfactorily explained if the OH acts as both a donor and acceptor. In the spectra of monomethylated- **2**, 1,2-dimethylated- **3** and 1,3-dimethylated-calix[6]arene **4** a weak band at *ca.* 3500 cm^{-1} was observed. These bands have been assigned to OH groups involved in OH $\cdots$ π hydrogen bonding, based on previous assignments in the series of calix[6]arenes with isolated OH groups. The small red-shift of these bands could be related to the effect of cooperativity as well (*i.e.* OH $\cdots$ OH $\cdots$ π).[14b]

IR spectroscopy of solid-state samples. If geometric and steric restrictions are not taken into account all OH groups of monomethylated calix[6]arene **2** are considered to participate in a cooperative hydrogen-bond array (Fig. 5). As cooperativity has been recognized to increase the strength of hydrogen bonds involved, it is expected that in IR a red shift of the OH absorptions occurs. The solid-state spectrum at 110 K [Fig. 6(*a*), Table 5] shows a very complex band with three separate maxima at 3380, 3317 and 3240 cm^{-1}. Reasonable curve-fit results were obtained when introducing at least six bands, however, care should be taken in the interpretation of these results. Considering the frequency of the bands at 3240 and 3165 cm^{-1} both have to be assigned to OH groups participating in cooperative hydrogen bonds. Obviously, the initial OH group in the hydrogen-bond array will withdraw the least (or no) cooperativity increase. Concomitantly the band at 3380 cm^{-1} is assigned to the initial OH group in the hydrogen-bond array [Fig. 5(*a*)]. For the array displayed in Fig. 5(*b*), where all OH groups are participating in a circular cooperative hydrogen bond, the assignment must be related to hydrogen-bond geometries, where steric effects are factors determining full cooperativity. At this point, the 3317 cm^{-1} band can best be assigned to a terminal three-centred hydrogen bond. Coupling effects, in the solid phase, are frequently recognized to cause temperature-sensitive broad side bands next to fundamental ones, these bands originate from low frequency ($<$ 100 cm^{-1}) modes.[16]

The spectrum of 1,2-dimethylated calix[6]arene **3** at 110 K exhibits similar spectral features to those observed for monomethylated calix[6]arene **2**; both red-shifted bands at 3292 and 3237 cm^{-1} (Table 5) are assigned to cooperative hydrogen bonds. In agreement with the expectation that when less OH groups participate in the hydrogen-bond array the cooperative effect is weaker, it explains the reduced cooperativity, *i.e.* strength of the hydrogen bonds, in **3**. The band at 3348 cm^{-1} is assigned to a three-centred hydrogen bond, most likely initial as its position nicely matches with the previously made assignments in the series of partially methylated *p-tert*-butylcalix[6]arenes with isolated OH groups (see above). The position of the band at 3446 cm^{-1} is too high to allow assignment to an OH group which initiates the hydrogen-bond array. Alternatively, it may be assigned to a terminal OH $\cdots$ π interaction present in a cooperative $\cdots$ O–H $\cdots$ O–H $\cdots$ π chain, which explains the red shift.

A somewhat different spectrum in the OH stretching region, compared with **2** and **3**, is observed for 1,2,3-trimethylated calix[6]arene **6** [Fig. 6(*b*)]. In line with previous assignments the maximum at 3347 cm^{-1} is attributed to an OH group involved in a three-centred initial hydrogen bond. The splitting of the band at about 3200 cm^{-1}, causing maxima at 3213 and 3188 cm^{-1}, originates from Fermi resonance creating an Evans hole in the band shape.

The OH-stretching region of 1,3-dimethylated- **4** and 1,2,4-trimethylated calix[6]arene **8** at 110 K both exhibit a strong absorption at *ca.* 3335 cm^{-1}. In accordance with the assignment in **3** and **6**, this band is assigned to a three-centred hydrogen-bond geometry. In both spectra, evidence is found for a cooperative hydrogen bond; the broad band at 3195 cm^{-1} with Evans interference for compound **4** and a blue-shifted one at 3245 cm^{-1} for compound **8**. Again, it follows that structural possibilities for increased cooperativity

Table 5 IR spectral data (ν/cm^{-1}) of partially methylated *p*-*tert*-butylcalix[6]arenes with proximal OH groups in the solid state (T = 110 K)

Compound	OH • • • (OH) • • • O (cooperative)	OH • • • (OH,OH) OH • • • (OH,OMe) OH • • • (OMe,OMe)	OH • • • O (isolated)	OH • • • π
2	(3240, 3165)^{c,d}	3317^{b}	3380^{b}	
(mono)	[3260]	[3322]	[3381]	
3	3292, 3237^{b}	3348^{b}		3446^{b}
(1,2)	[3260]	[3310]		[3440]
4	3195^{c}	3338^{c}		3510^{c}
(1,3)		[3370]		[3520 (sh)]
6	(3213, 3188)^{c,d}	3347^{c}		
(1,2,3)	[(3220, 3195)^{d}]	[3367]		
8	3240^{c}	3335^{c}		3496^{c}
(1,2,4)	[3255]	[3360]		[3494]

[a] [ ] data at 295 K. [b] Data obtained by Fourier self deconvolution. [c] Curve-fit results. [d] Splitting due to Fermi resonance (Evans hole).

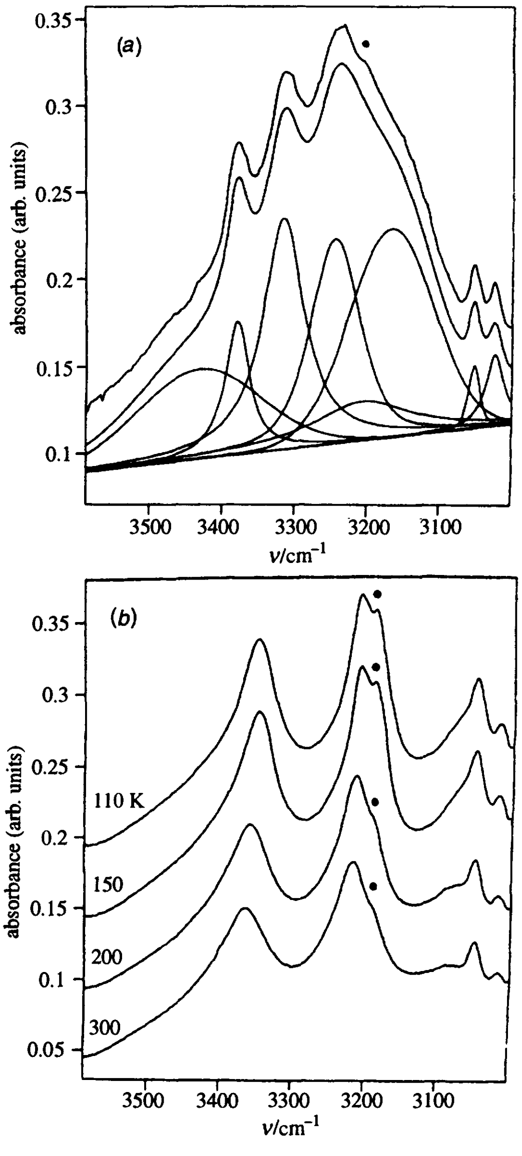

Fig. 6 (*a*) The OH-stretching region of monomethylated *p*-*tert*-butylcalix[6]arene **2** in the solid state (KBr) at 110 K and (*b*) a series of variable-temperature spectra of 1,2,3-trimethylated *p*-*tert*-butylcalix[6]arene **6**. The positions of the Evans holes are denoted with markers.

provide stronger hydrogen bonds. For both calix[6]arenes **4** and **8** the absorption at *ca.* 3500 cm^{-1} is assigned to an OH • • • π bond.

From Table 5 it follows that all calix[6]arenes with proximal OH groups show (*i*) hydroxy groups present in a cooperative chain and (*ii*) an initial three-centred hydrogen bond. For monomethylated calix[6]arene **2** the position of the three-centred bond is red shifted compared with calix[6]arenes **3**, **4**, **6** and **8**, and an additional band at 3380 cm^{-1} is observed. An alternative interpretation is needed to explain these phenomena; most likely some geometric irregularity in the cooperative chain affects the 'initial' three-centred bond, which is possibly participating in the cooperative chain. The presence of two different conformations in the solid state may be an alternative explanation.

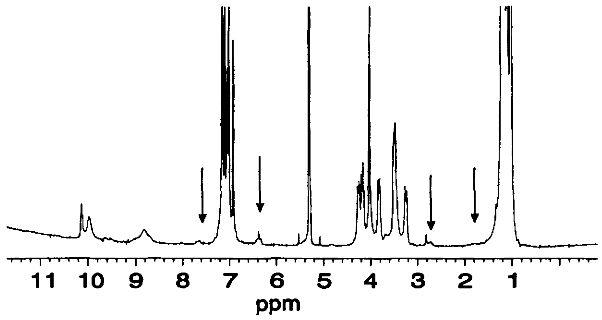

Fig. 7 ^{1}H NMR spectrum of monomethylated *p*-*tert*-butylcalix[6]arene **2** recorded at 188 K in CD_2Cl_2. The markers indicate signals of a minor conformer.

Variable-temperature NMR spectroscopy. Upon cooling the ^{1}H NMR spectrum of monomethylated calix[6]arene **2** resolves in a spectrum (Fig. 7) which shares several features with that of 1,2,3,5-tetramethylated calix[6]arene **10**. At 188 K the methylene protons exhibit three AX spin systems, and an analysis of NOE connectivities shows that the conformation has a *syn*-arrangement. The ^{1}H NMR OH resonances are present as three singlets in the ratio 1 : 2 : 2 (from down- to upfield).

In the IR spectra different maxima are observed (see above) and the difference can be explained by reversal of the hydrogen bond array.‡‡ This dynamic feature, which is slow on the IR timescale but fast on the NMR timescale leads to coalescence of four NMR signals to two averaged ones. The NOESY spectrum also exhibits quite strong exchange connectivities between the major signals and very weak signals in the baseline. From this it can be deduced that the major *syn*-conformer interconverts, as observed for 1,2,3,5-tetramethylated calix[6]arene **10**, with a minor conformer that has an estimated higher free energy of 7 kJ mol^{-1}. Most likely these conformers differ with respect to the location of pinched methylene bridges.[11]

1,2-Dimethylated calix[6]arene **3** exhibits roughly the same

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‡‡ The stronger a hydrogen bond, the more electron density is distributed over both the donor and acceptor nucleus. This results in stronger deshielding of the proton and a subsequent downfield shift of its ^{1}H NMR signal. Due to anisotropy of a hydrogen bond this rule of thumb is only valid for one set of donor and acceptor atoms involved in one covalent geometry: see ref. 22.

behaviour as monomethylated calix[6]arene **2**. However, upon cooling two decoalescence temperatures at 233 and 206 K were observed. Down to 250 K two OH resonances are observed, while the arrangement of the other signals points to a conformation having a (pseudo) plane of symmetry. However, at 188 K both OH signals decoalesce in a broad set of multiple resonances, while the other signals become very broad. This means that in solution, 1,2-dimethylated calix[6]arene **3** exhibits a complicated conformational behaviour. The ^{1}H NMR spectrum of 1,2,3-trimethylated calix[6]arene **6** at room temperature exhibits two singlets for the three OH groups. The upfield shifted singlet has half the intensity of the downfield shifted singlet (Table 3), which is opposite to the spectral features of monomethylated- **2** and 1,2-dimethylated-calix-[6]arene **3**. ^{1}H NMR spectroscopy thus confirms the different hydrogen-bond structure of 1,2,3-trimethylated calix[6]arene **6** compared with monomethylated- **2** and 1,2-dimethylated-calix[6]arene **3** as was demonstrated by IR spectroscopy. 1,3-Dimethylated- **4** and 1,2,4-trimethylated-calix[6]arene **8** show similar spectral features as monomethylated calix[6]arene **2**. For 1,3-dimethylated calix[6]arene **4** also signals were observed, which point to the existence of a small amount of a minor conformer.

Conclusions

The spectral patterns in the OH-stretching region show strong similarities between solid-state and solution data. This points to the absence (or minimal effect) of intermolecular interactions for partially methylated *p-tert*-butylcalix[6]arenes. The conformational distribution of this class of compounds is mainly governed by favourable hydrogen-bond formation. The OH groups of partially methylated *p-tert*-butylcalix[6]arenes may form three-centred hydrogen bonds with proximally and medially positioned OH and OMe groups. Proximal OH groups tend to form hydrogen-bond arrays with a strongly cooperative character and in some cases there are indications that these arrays have a cyclic nature. Based on NMR spectroscopy inclusion of the OMe group also occurs, but the importance in terms of energetic contributions is small. The flexibility of the partially methylated *p-tert*-butylcalix[6]arenes should not only be interpreted in terms of fast-ring interconversion, but also in terms of fast reorientation of the OMe groups in the annulus of the calix[6]arene. These features rationalize the conformational behaviour of partially alkylated calix[6]arenes and serve as a basis to a more general understanding of these macrocycles.

Experimental

General

For the synthesis of the partially methylated calix[6]arenes see refs. 7(*a*) and 23.

IR measurements

Solution spectra in CCl_4 (Merck p.a.) and CS_2 (Aldrich 99^+) were run in 10 or 50 mm Infrasil cells on a Perkin-Elmer 1800 or 2000 FTIR spectrometer. The concentrations varied between 10^{-2} to 10^{-4} M. Scanning parameters: resolution 2 cm^{-1}. Accuracy of peak maxima is for sharp peaks 1 cm^{-1} and for broader bands better than 10 cm^{-1}. Solid samples were prepared as KBr (Merck) pellets at 10 ton cm^{-2}. Solid-state spectra were recorded on a Mattson RS-5 FTIR spectrometer equipped with a DTGS detector. Scanning parameters: resolution 2 cm^{-1}, apodization triangular, number of accumulated scans between 16 and 400. Accuracy for sharp peaks is 1 cm^{-1} and for broader bands better than 10 cm^{-1}. For variable-temperature experiments an evacuable Specac P/N 21000 cell connected to a West M2071 microprocessor-based controller was used with boiling liquid nitrogen as a cooling agent. Accuracy for the temperature is 2 K for measurements at 420, 300 and 110 K, and better than 4 K for intermediate temperatures. Galactic GRAMS (version 3.0 software) has been applied for spectral data manipulation *viz.* second-derivative spectroscopy and curve-fitting techniques. Residual water or polymorphicity influenced the reproducibility of variable-temperature solid-state spectra in a negative sense. Improved reproducibility was obtained when the samples, pressed in KBr pellets, were dried over silica and spectra were recorded, over a standard temperature trajectory starting at room temperature, heating to ± 170 °C and cooling to − 165 °C (liquid N_2).§§

NMR measurements

NMR measurements were performed at 400 and 500 MHz on Varian Unity 400WB and Bruker AM500 spectrometers, respectively. $SiMe_4$ was used as internal standard for ^{1}H NMR spectroscopy. NOESY,[17,18] ROESY[19] and TOCSY (MLEV17)[20] were performed using standard Varian pulse programs. All TOCSY (MLEV17) experiments were performed with mixing times of 30 ms. The mixing times of the NOESY experiments ranged from 100 to 700 ms. The mixing time of the ROESY experiments consisted of a spin lock pulse of 2 kHz field strength with a duration of 300 ms. All 2D experiments performed on the Unity 400WB were collected, using 2D hypercomplex data.[21] Data were Fourier transformed in the phase-sensitive mode after weighting with shifted square sine-bells of shifted Gaussian functions. NMR data were either processed by the standard Varian VnmrS/VnmrX software packages installed on the Unity 400WB spectrometer host computer (SUN Sparc 10) or by the NMRi package installed on a SUN4 computer. Thermodynamic parameters (ΔG°) were calculated from equilibrium constants, which could be derived from signal integrals in 1D ^{1}H NMR spectra recorded at 400 MHz. $\Delta G^\ddagger$ values were calculated from interconversion rate constants, which were determined by integration of exchange peaks in EXSY/NOESY experiments.

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§§ In the solution studies the possible presence of water did not influence the spectroscopic data and the dynamics of the system. The presence of bound water was not observed with NMR and IR spectroscopy. In this case separate signals for 'free' and 'bound water' are expected.

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