

# Conformational interconversions of partially dehydroxylated calix[4]arenes. A molecular mechanics study<sup>1†</sup>

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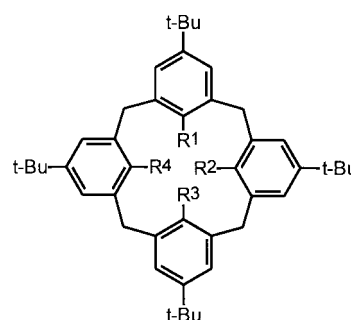
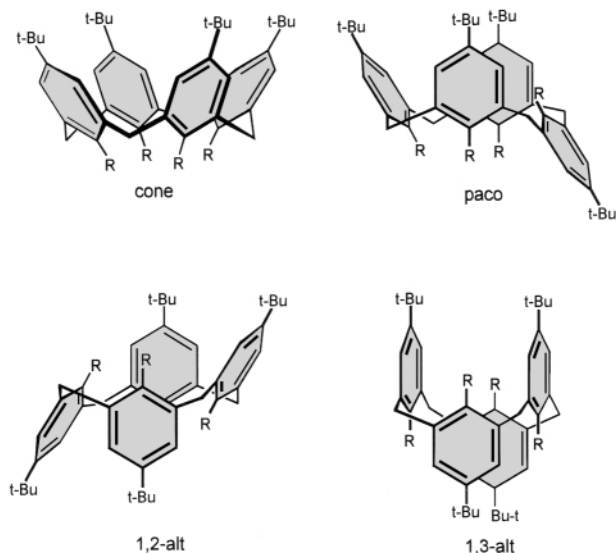
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The rotational pathways of the cone⇌cone topomerisation for a series of dehydroxylated calix[4]arenes **2–5** have been calculated using the MM3 force field. The key intermediates and rate-limiting steps have been identified and characterised. The low barriers obtained for phenyl residue rotation suggest that the compounds should be partially flexible at low temperatures. The results are discussed in relation to available experimental data.

## Introduction

Calixarenes, a well-established class of flexible macrocyclic compounds, are frequently used as building blocks for the construction of highly selective host molecules.<sup>2</sup> Among them, calix[4]arenes are of special interest due to their ability to adopt well-defined three-dimensional structures which are commonly discussed in terms of four basic conformations: cone, partial cone, 1,2- and 1,3-alternate. NMR and X-ray data indicate that



- 1  $R^1 = R^2 = R^3 = R^4 = \text{OH}$
- 2  $R^1 = R^2 = R^3 = \text{OH}, R^4 = \text{H}$
- 3  $R^1 = R^2 = \text{OH}, R^3 = R^4 = \text{H}$
- 4  $R^1 = R^3 = \text{OH}, R^2 = R^4 = \text{H}$
- 5  $R^1 = \text{OH}, R^2 = R^3 = R^4 = \text{H}$
- 6  $R^1 = R^2 = R^3 = R^4 = \text{H}$

the parent *p-tert*-butylcalix[4]arene **1** exists in solution and in the crystalline state in the cone conformation which is stabilised by a circular array of hydrogen bonds.<sup>2</sup> In solution the cone conformation interconverts with its topomerised form with a barrier of 15.7 kcal mol<sup>-1</sup> ‡ (in CDCl<sub>3</sub>).<sup>3</sup> This interconversion process involves the rotation of the four intraannular OH groups through the macrocyclic annulus and the mutual exchange of the methylene protons.

The partial or complete replacement of the OH groups by other groups or by hydrogen may alter the conformational

properties fundamentally.<sup>4</sup> By introduction of larger groups at the *endo* positions, such as CH<sub>3</sub><sup>5</sup> or SH<sup>6,7a</sup> the predominance of the cone conformation diminishes and non-cone conformations were obtained both in solution and in the crystal, *e.g.*, the 1,3-alternate conformation for the 1,3-dimethyl,<sup>5d</sup> trimercapto<sup>6d</sup> and tetramerapto<sup>6a,c</sup> *p-tert*-butylcalix[4]arene as well as tetramethylcalixarenes derived from mesitylene.<sup>5b</sup>

The replacement of the OH groups by hydrogen<sup>7</sup> not only interrupts the circular hydrogen bonding system present in **1** but also reduces the steric crowding of the substituents at the lower rim. The 1,3-didehydroxylated calixarene **4** and the fully OH-depleted metacyclophane **6** crystallise in the 1,2-alternate conformation.<sup>7c</sup> It cannot be ruled out that this conformation is stabilised by intermolecular packing interactions. § From molecular mechanics calculations Harada *et al.*<sup>7h</sup> have obtained the partial cone and cone as the preferred conformations for **4** and **6**, respectively. Their calculations also revealed that the energy differences between the cone and the other conformations substantially decrease when one or more OH groups in **1** are replaced by hydrogen. NMR spectroscopic data at low temperature indicate that **3** adopts in solution a cone or 1,2-alternate conformation,<sup>7f</sup> **4** either a 1,3-alternate<sup>7d</sup> or a mixture of 1,3-alternate and cone conformations,<sup>7h</sup> and **5** a mixture of the cone, partial cone and 1,3-alternate conformations.<sup>7h</sup> At room temperature the dehydroxylated calixarenes **2–6** are flexible on the NMR timescale and the following barriers for con-

§ **4** crystallises as a 1:1 methanol solvate in which each phenolic OH group is hydrogen bonded to a methanol molecule whereas the molecules of **6** are stapled like chairs in the crystal lattice.

<sup>†</sup> Energy contributions and geometric parameters of the transition state structures of **2–5** calculated with the MM3 force field are available as supplementary data. For direct electronic access see <http://www.rsc.org/suppdata/p2/1999/1791>, otherwise available from BLDSC (SUPPL. NO. 57575, pp. 6) or the RSC Library. See Instructions for Authors available *via* the RSC web page (<http://www.rsc.org/authors>).

<sup>‡</sup> 1 cal = 4.184 J.

**Table 1** MM3-calculated steric energies (in kcal mol<sup>-1</sup>) of the low-energy conformers of calixarenes **2–5**<sup>a</sup> (in parentheses energies relative to the most stable conformer)

Compound	cone	paco	1,2-alt	1,3-alt
<b>2</b>	23.08 (0.00)	25.51 (2.43) <sup>b</sup>	28.62 (5.54)	30.51 (7.43)
		26.74 (3.66) <sup>c</sup>		
		30.06 (6.98) <sup>d</sup>		
		29.75 (0.00) <sup>d</sup>		
<b>3</b>	27.59 (0.00)	28.01 (0.42) <sup>b</sup>	29.02 (1.44) <sup>e</sup>	30.93 (3.34)
		30.28 (2.69) <sup>f</sup>	32.73 (5.14) <sup>g</sup>	
		29.46 (1.94) <sup>b</sup>	30.56 (3.04)	
<b>4</b>	27.52 (0.00)	28.10 (0.58) <sup>f</sup>	31.76 (2.01)	30.35 (2.83)
		30.49 (0.74) <sup>f</sup>		
<b>5</b>	30.15 (0.40)	30.36 (0.59) <sup>c</sup>	31.76 (2.01)	31.39 (1.64)
		29.75 (0.00) <sup>d</sup>		
		30.49 (0.74) <sup>f</sup>		

<sup>a</sup> For the notation of conformations see text. <sup>b</sup> Paco(H) conformer. <sup>c</sup> Paco(prox) conformer. <sup>d</sup> Paco(dist) conformer. <sup>e</sup> 1,2-Alt(*syn*) conformer. <sup>f</sup> Paco(OH) conformer. <sup>g</sup> 1,2-Alt(*anti*) conformer.

formational interconversions have been determined by temperature-dependent NMR spectroscopy: 9.6 (**2**), 10.6 (**3**), 9.5 (**4**), 9.7 (**5**) and <5.9 kcal mol<sup>-1</sup> (**6**). The large difference in the free activation energies for the cone⇌cone topomerisation of **1** and **2** (6.1 kcal mol<sup>-1</sup>) reflects the replacement of the circular system of four hydrogen bonds by two acyclic ones. It is, however, not clear why the further replacement of OH groups by hydrogen in **3–5** has no effect or even leads to an increase of the energy barriers.

Molecular mechanics calculations can contribute to the understanding of the conformational behaviour of calixarenes.<sup>6d,7h,8,9</sup> As part of a program devoted to the influence of various substituents on the conformation and flexibility of calixarenes we describe in this article a detailed investigation of the pathways of conformational interconversions in **2–5**, we characterise the key intermediates and rate-limiting steps and we discuss the applicability of the MM3 force field to these compounds in relation to the available experimental data.

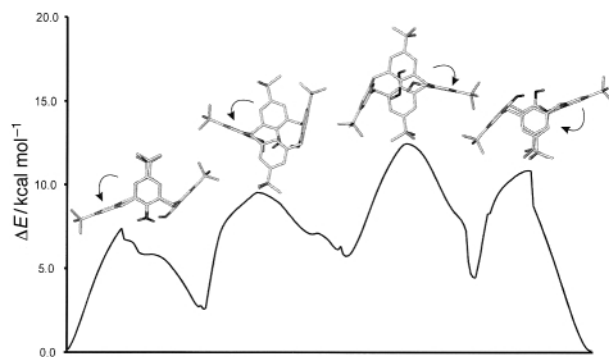
## Results and discussion

The partial replacement of OH groups in **1** by hydrogen desymmetrises the molecule and increases the number of possible conformations. For the mono- and tridehydroxylated calix[4]arenes **2** and **5** three different partial cone (paco) conformations can be distinguished in which either the non-identical ring, its neighbour or the opposite ring points in the opposite direction to the rest of the aryl residues. In the following, these conformations will be dubbed paco(OH) and paco(H) for **2** and **5**, respectively, paco(prox) and paco(dist). For the 1,2-didehydroxylated calix[4]arene **3** two partial cone conformations (paco(OH) and paco(H)) are possible and additionally two different 1,2-alternate (1,2-alt) arrangements in which the identical moieties point either in the same (1,2-alt(*syn*)) or different (1,2-alt(*anti*)) directions. Finally, for the 1,3-didehydroxylated calix[4]arene **4** again two paco conformations exist with an inverse arrangement of either a phenol (paco(OH)) or a phenyl residue (paco(H)).

Table 1 lists the steric energies of the low-energy conformers of **2–5** obtained with the stochastic search algorithm of the MM3 force field. The calculated energies are comparable to those reported by Harada *et al.*<sup>7h</sup> for calixarenes **2**, **3** and **5**. For the 1,2-dihydroxy compound **4** our calculations predict a different sequence of the energetical stabilities<sup>¶</sup> (cone > paco > 1,3-alt > 1,2-alt) due to a lower energy of the cone and 1,3-alternate forms.

Starting from the lowest energy cone conformer of each of compounds **2–5** all pathways of the stepwise rotation of the

<sup>¶</sup> The sequence reported in reference 7h is paco (28.2) > cone (28.7) > 1,2-alt (30.6) > 1,3-alt (30.9 kcal mol<sup>-1</sup>).

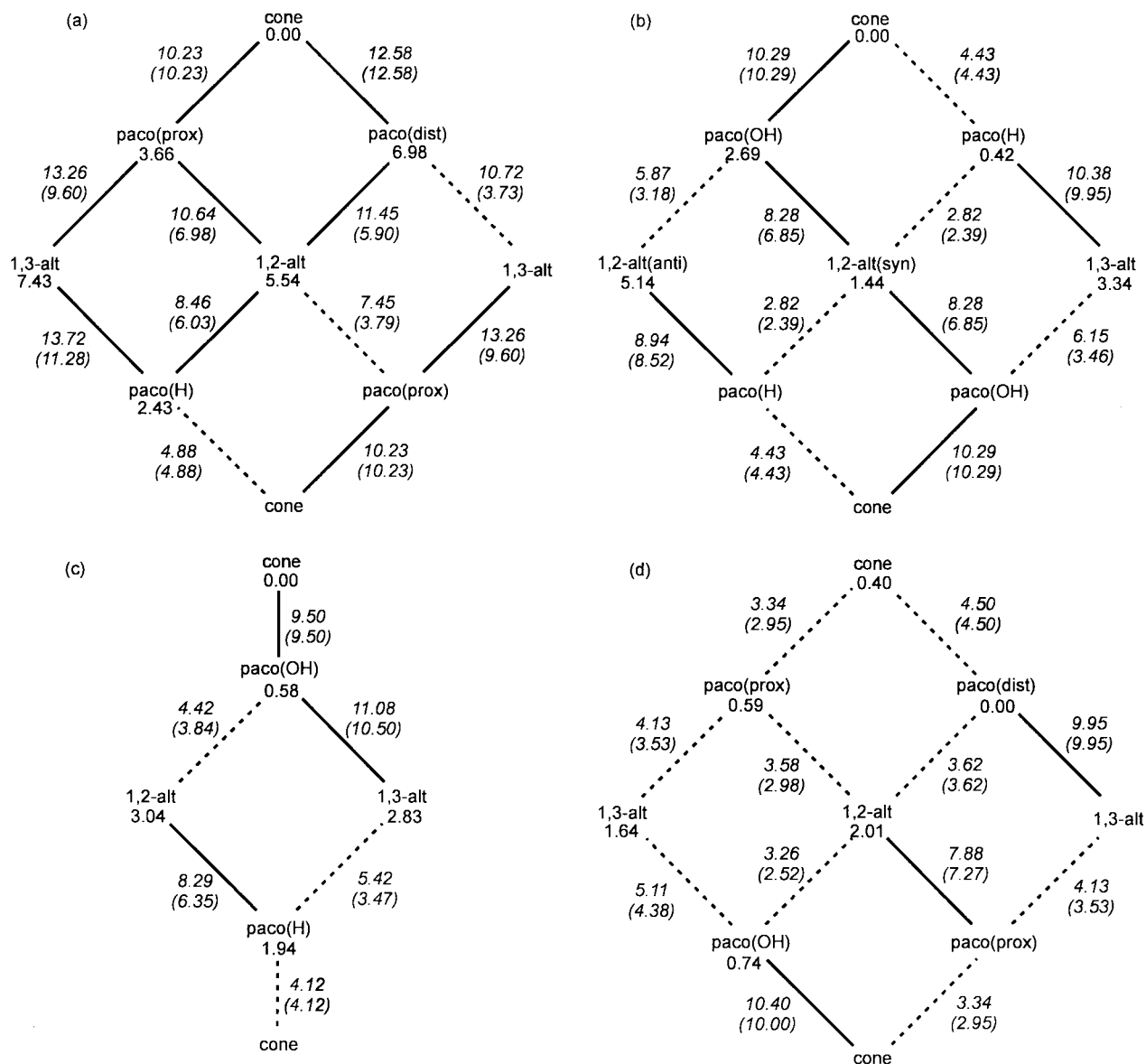


**Fig. 1** Energy profile of the cone⇌paco(H)⇌1,2-alt⇌paco(prox)⇌cone interconversion of **2** and geometries of the refined saddle points. The energies are given relative to the most stable cone conformer. Hydrogen atoms bonded to carbon are omitted. The sharp kinks result from artefacts of the calculation.

*endo*-substituents through the macrocyclic annulus leading to the topomerised cone form have been simulated using the coordinate driver method<sup>9e</sup> which is based on the standard MM3 force field.<sup>10</sup> A typical outcome of this approach together with the transition state structures is illustrated in Fig. 1 for a cone⇌cone topomerisation of **2**. The coordinate driver method locates all stationary points along the calculated pathways which are subsequently refined using the full matrix Newton–Raphson minimisation algorithm. The comparison of the refined minima with the results of the stochastic searches shows that there is virtually no difference in the calculated energies and geometries.

Fig. 2 summarises the calculated rotational pathways of **2–5**. A number of intriguing points can be raised from the calculated energies  $\Delta E^\ddagger$  and  $\Delta E_{\text{rel}}^\ddagger$  listed in these schemes. Firstly, the barriers for the rotation of phenol rings (relative to the starting conformation ( $\Delta E_{\text{rel}}^\ddagger$ )) are higher (5.90–12.58 kcal mol<sup>-1</sup>) than the barriers calculated for the rotation of phenyl residues (2.39–4.88 kcal mol<sup>-1</sup>). Since the activation energy  $\Delta E^\ddagger$  of an inversion process is the sum of the ground state energy of the starting conformer and the rotational barrier  $\Delta E_{\text{rel}}^\ddagger$ , high energies also result for phenyl ring inversions which do not involve the global minimum conformation (e.g., the paco(dist)⇌1,3-alt inversion of **2**, *cf.*, Fig. 2a), provided that the differences in the ground state energies of the basic conformations are large. However, for each interconversion between the basic conformations, *i.e.*, cone⇌partial cone, partial cone⇌1,2-alternate and partial cone⇌1,3-alternate, the overall barriers ( $\Delta E^\ddagger$ ) for phenol ring rotation are higher than the barriers for the rotation of a phenyl residue. This implies that the rate-limiting step in the topomerisation processes of **2–5** is the inversion of a phenol ring.

Secondly, for each of compounds **2–5** the partial cone⇌1,2-alternate inversions of a phenol ring possess lower rotational

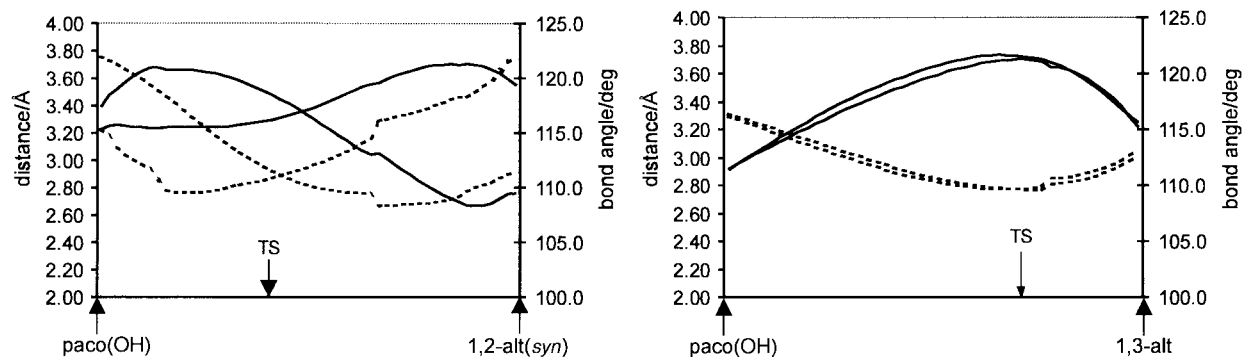


**Fig. 2** Interconversion pathways for the calixarenes **2** (a), **3** (b), **4** (c) and **5** (d). Energies (in kcal mol<sup>-1</sup>) are given relative to the most stable conformer ( $\Delta E^\ddagger$ ) and in parentheses relative to the more stable starting conformer ( $\Delta E_{rel}^\ddagger$ ). Dashed lines indicate the inversion of a phenyl residue. For the notation of conformers see text.

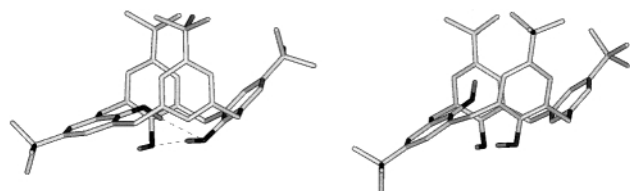
barriers ( $\Delta E_{rel}^\ddagger$ ) than the corresponding cone $\leftrightarrow$ partial cone and partial cone $\leftrightarrow$ 1,3-alternate inversions. The analysis of the calculated pathways indicated that this is caused by differences in the steric strain during the inversion processes. The rotation of an aromatic moiety forces the two adjacent rings into an almost perpendicular arrangement with respect to the mean plane of the four methylene carbon atoms. In this way, the space available for the OH group swinging through the macrocyclic annulus is smaller for the cone $\leftrightarrow$ partial cone and partial cone $\leftrightarrow$ 1,3-alternate transformations due to the almost parallel orientation of the adjoining rings than in the partial cone $\leftrightarrow$ 1,2-alternate transformations where the adjoining rings adopt an *anti*-parallel orientation. Moreover, during partial cone $\leftrightarrow$ 1,2-alternate inversion a distortion of the calixarene skeleton by a more or less pronounced deviation of the methylene carbon atoms from a mean plane (a “folded” arrangement<sup>||</sup>) is possible, which additionally increases in the space available for the *endo*-substituent. The van der Waals energy reaches a maximum

during ring inversion when the phenolic oxygen atom passes the *ortho*-carbon atoms of the adjoining rings. The repulsive contacts between these atoms cause a substantial widening of the C(*ortho*)-C(H<sub>2</sub>)-C(*ortho*) bond angles formed by the interconverting ring and its neighbouring ring(s). The oxygen and the *ortho*-carbon atoms are in closest proximity when the C(OH)-C(*ortho*)-C(H<sub>2</sub>)-C(*ortho*) torsion angles adopt an eclipsed conformation. In the course of the cone $\leftrightarrow$ partial cone and partial cone $\leftrightarrow$ 1,3-alternate inversions the *endo*-oxygen atom passes both neighbouring *ortho*-carbons simultaneously which leads to an accumulation of bond angle, torsional and non-bonding strain in the transition state (*cf.*, Fig. 3). In contrast, in the partial cone $\leftrightarrow$ 1,2-alternate inversions the *ortho*-carbon atoms of the adjoining rings are passed consecutively which means that two maxima exist for the angle bending and torsional energies (*cf.*, Fig. 3) and hence the overall steric strain during ring inversion is lower. In consequence, the 1,2-alternate conformation represents the key intermediate in the topomerisations of **2-5**. It should be noted that similar differences in the barriers ( $\Delta E_{rel}^\ddagger$ ) of the cone $\leftrightarrow$ partial cone and partial cone $\leftrightarrow$ 1,3-alternate inversions on the one hand and of the partial cone $\leftrightarrow$ 1,2-alternate inversion on the other have also been calculated for **1**,<sup>9c,e</sup> and the *p*-H-calix[4]arene<sup>9b</sup> as well as for

<sup>||</sup> A “folded” arrangement of the 1,2-alternate conformation has been found experimentally for *endo/exo*- and *exo*-calix[4]arenes<sup>8f</sup> and predicted by molecular mechanics calculations for various calixarenes lacking intraannular hydroxy groups.<sup>7h,8a,f</sup>



**Fig. 3** Evolution of the  $O \cdots C(\text{ortho})$  distances (dotted lines) and  $C(\text{ortho})-C(\text{H}_2)-C(\text{ortho})$  bond angles (solid lines) during the  $\text{paco}(\text{OH}) \rightleftharpoons 1,2\text{-alt}(\text{syn})$  inversion of **3** (left) and the  $\text{paco} \rightleftharpoons 1,3\text{-alt}$  inversion of **4** (right). The arrow (TS) indicates the position of the transition state.



**Fig. 4** Transition state structures of the  $\text{cone} \rightleftharpoons \text{paco}(\text{prox})$  (left) and  $\text{cone} \rightleftharpoons \text{paco}(\text{dist})$  (right) inversions of **2**. Dashed lines indicate hydrogen bonds. Hydrogen atoms bonded to carbon are omitted.

calix[4]arenes in which the OH groups are replaced by  $\text{CH}_3$ ,<sup>5d,9e</sup>  $\text{SH}^{9e}$  and  $\text{NH}_2$ .<sup>9e</sup>

Thirdly, the calculated barriers ( $\Delta E_{\text{rel}}^\ddagger$ ) for the  $\text{cone} \rightleftharpoons \text{partial cone}$  and  $\text{partial cone} \rightleftharpoons 1,3\text{-alternate}$  inversions of a phenol ring in **2–5** are in a relatively narrow range (9.50–10.50 kcal mol<sup>-1</sup>) with the exception of the  $\text{cone} \rightleftharpoons \text{paco}(\text{dist})$  and  $\text{paco}(\text{H}) \rightleftharpoons 1,3\text{-alt}$  inversions of **2**, which both involve the rotation of the phenol ring in a position distal to the phenyl residue. This suggests that mainly similar steric demands, as discussed above, determine the height of the rotational barriers, although one might expect that they should differ among **2–5** due to the presence or absence of intramolecular hydrogen bonds. The examination of the calculated pathways shows that the breakage of a single hydrogen bond follows upon the maximum steric strain during ring rotation, *i.e.*, a hydrogen bond present in the starting conformer is still present (but somewhat weakened) in the transition state, as in the example shown in Fig. 4 for the  $\text{cone} \rightleftharpoons \text{paco}(\text{prox})$  inversion of **2**. Thus, the energy necessary for the breakage of a single hydrogen bond does not contribute significantly to the activation energy. In contrast, in the  $\text{cone} \rightleftharpoons \text{paco}(\text{dist})$  and  $\text{paco}(\text{H}) \rightleftharpoons 1,3\text{-alt}$  inversions of **2** the two hydrogen bonds present in the cone and  $\text{paco}(\text{H})$  conformers are nearly completely broken in the transition state (*cf.*, Fig. 4) which results in high activation energies.

The rotational barriers of the  $\text{partial cone} \rightleftharpoons 1,2\text{-alternate}$  inversions of a phenol ring in **2–5** vary over a relatively wide range (5.90–8.52 kcal mol<sup>-1</sup>) owing to a complex balance of bonding and nonbonding strain as well as hydrogen bond formation and breakage, if possible, during ring inversion. For example, the lowest activation energy  $\Delta E_{\text{rel}}^\ddagger$  was calculated for the  $1,2\text{-alt} \rightleftharpoons \text{paco}(\text{dist})$  inversion of **2** (5.90 kcal mol<sup>-1</sup>, relative to the more stable 1,2-alternate conformer). This rotational barrier is surprisingly low in comparison to  $\text{partial cone} \rightleftharpoons 1,2\text{-alternate}$  inversions of **3** which likewise require the breakage of a hydrogen bond ( $1,2\text{-alt}(\text{syn}) \rightleftharpoons \text{paco}(\text{OH})$ ),  $\text{paco}(\text{H}) \rightleftharpoons 1,2\text{-alt}(\text{anti})$ ), and to the  $\text{paco}(\text{prox}) \rightleftharpoons 1,2\text{-alt}$  inversion of **2**, which involves formation and breakage of a hydrogen bond. The inspection of the transition state structure revealed that the phenolic oxygen atom of the interconverting ring is involved in two hydrogen bonds to the adjoining phenol ring and to the distal phenol ring which adopts a flattened orientation. This stabilisation of the transition state by a hydrogen

bond which is not present in the two starting conformers accounts for the low rotational barrier of the  $1,2\text{-alt} \rightleftharpoons \text{paco}(\text{dist})$  inversion.

For the monodehydroxylated calixarene **2** the cone conformation is energetically preferred which is in agreement with the experimental data.<sup>7g,h</sup> Its topomerisation requires the passage of the four *endo*-substituents through the macrocyclic annulus and the mutual exchange of the methylene protons. As discussed above, the key intermediate in the topomerisation process is the 1,2-alternate conformation, whereas rotational pathways passing the 1,3-alternate form are higher in energy (Fig. 2a). The key step in the  $\text{cone} \rightleftharpoons \text{cone}$  interconversion of **2** is the inversion of the phenol ring in a position distal to the phenyl residue. In the cone conformation it is hydrogen bonded to the two adjoining OH-groups and its inversion requires either the simultaneous ( $\text{cone} \rightleftharpoons \text{paco}(\text{dist})$ ) or consecutive breakage ( $\text{cone} \rightleftharpoons \text{paco}(\text{prox}) \rightleftharpoons 1,2\text{-alt}$ ) of the hydrogen bonds. The latter pathway is energetically preferred and thus two threshold mechanisms can be formulated for **2**:  $\text{cone} \rightleftharpoons \text{paco}(\text{prox}) \rightleftharpoons 1,2\text{-alt} \rightleftharpoons \text{paco}(\text{prox}) \rightleftharpoons \text{cone}$  and  $\text{cone} \rightleftharpoons \text{paco}(\text{H}) \rightleftharpoons 1,2\text{-alt} \rightleftharpoons \text{paco}(\text{prox}) \rightleftharpoons \text{cone}$  with an overall barrier of 10.64 kcal mol<sup>-1</sup>. The calculated barriers suggest that the  $\text{cone} \rightleftharpoons \text{paco}(\text{H})$  inversion of the phenyl residue ( $\Delta E^\ddagger = 4.88$  kcal mol<sup>-1</sup>) should not be frozen under the experimental conditions and the observed spectrum would be the weighted average of the cone and  $\text{paco}(\text{H})$  conformations.

For the 1,2-dihydroxycalixarene **3** the calculations predict that the cone conformation is most stable but its predominance diminishes compared to **2** (*cf.*, Table 1 and ref. 7h) and, according to the calculated energy differences the cone,  $\text{paco}(\text{H})$  and 1,2-alt(*syn*) conformations should be populated under experimental conditions. Biali and co-workers<sup>7f</sup> reported that the low temperature NMR spectrum of **3** is compatible with either a cone or a 1,2-alt(*syn*) conformation. The calculations suggest, however, that compound **3** should be partly flexible even at low temperatures due to the low rotational barriers for the  $\text{cone} \rightleftharpoons \text{paco}(\text{H})$  and the  $\text{paco}(\text{H}) \rightleftharpoons 1,2\text{-alt}(\text{syn})$  inversions of the phenyl residues (*cf.*, Fig. 2b) and that the observed spectrum should correspond to the weighted average of the three conformations. The key step in the  $\text{cone} \rightleftharpoons \text{cone}$  topomerisation is again the inversion of a phenol ring. Since only two phenol rings are present in **3** both can rotate *via*  $\text{partial cone} \rightleftharpoons 1,2\text{-alternate}$  which is energetically more favourable than  $\text{cone} \rightleftharpoons \text{paco}(\text{OH})$  (*cf.*, Fig. 2b). The lowest activation energy for a  $\text{partial cone} \rightleftharpoons 1,2\text{-alternate}$  inversion is 8.28 kcal mol<sup>-1</sup> ( $1,2\text{-alt}(\text{syn}) \rightleftharpoons \text{paco}(\text{OH})$ ). The threshold pathway which can be formulated for **3** must include this step twice because the other barriers for the rotation of a phenol group possess a higher energy. A  $\text{paco}(\text{OH}) \rightleftharpoons 1,2\text{-alt}(\text{anti}) \rightleftharpoons \text{paco}(\text{OH})$  interconversion exchanges the *anti*-oriented phenol ring of the  $\text{paco}(\text{OH})$  conformation and enables the energetically favourable  $\text{paco}(\text{OH}) \rightleftharpoons 1,2\text{-alt}(\text{syn})$  rotation of the second phenol ring. Thus, the lowest energy

pathway for the cone-to-cone topomerisation of **3** is cone $\rightleftharpoons$ paco(H) $\rightleftharpoons$ 1,2-alt(*syn*) $\rightleftharpoons$ paco(OH) $\rightleftharpoons$ 1,2-alt(*anti*) $\rightleftharpoons$ paco(OH) $\rightleftharpoons$ 1,2-alt(*syn*) $\rightleftharpoons$ paco(H) $\rightleftharpoons$ cone.

The most stable cone conformer of the 1,3-dihydroxycalixarene **4** is characterised by two weak hydrogen bonds (O $\cdots$ O distance 3.27 Å) between the opposite OH-groups in which each group serves both as donor and acceptor. The paco(OH) conformer is only slightly higher in energy (0.6 kcal mol<sup>-1</sup>) and, as compared to **2** and **3**, the overall energy range of the basic conformations is narrower (**2**: 7.4 kcal mol<sup>-1</sup>, **3**: 5.1 kcal mol<sup>-1</sup>, **4**: 3.1 kcal mol<sup>-1</sup>).

The rate-limiting step of the cone-to-cone topomerisation of **4** is again the most favourable rotation of a phenol group: paco(H) $\rightleftharpoons$ 1,2-alt with an energy barrier  $\Delta E^\ddagger = 8.29$  kcal mol<sup>-1</sup>. According to the calculations interconversions involving phenyl residue rotation should be possible even at low temperature (Fig. 2c) and, due to the low ground state energies of the cone and paco(OH) conformers, the observed spectrum should result from the weighted average of all conformations. Harada *et al.*<sup>7h</sup> concluded from the low-temperature ROESY spectrum of **4** that it exists as a mixture of rapidly interconverting (on the NMR timescale) cone and 1,3-alternate forms. This interconversion should proceed, as indicated by the calculations, *via* the paco(H) arrangement. The single conformer observed at low temperature<sup>7e,h</sup> might thus correspond to the weighted average of the three conformations. Hence, the calculations seem to underestimate the ground state energy of the 1,3-alternate conformer and to overestimate the stability of the paco(OH) conformation (which should be populated assuming an energy difference of 0.6 kcal mol<sup>-1</sup> to the cone conformation).

For the monohydroxycalixarene **5** the calculations predict that all conformations should be populated under experimental conditions. The lowest barrier for the rotation of a phenol ring in **5** is 7.88 kcal mol<sup>-1</sup> corresponding to the paco(prox) $\rightleftharpoons$ 1,2-alt inversion (Fig. 2d). The low barriers calculated for rotation of a phenyl residue which lie below 5.2 kcal mol<sup>-1</sup> indicate that the compound should be flexible (on the NMR timescale) even at low temperatures and that the observed spectrum should correspond to the weighted average of all conformations. This is commensurate with the experimental findings of Harada *et al.*<sup>7h</sup> who have established two types of interconversion processes on the basis of the low-temperature ROESY spectrum: exchange between cone and partial cone as well as between 1,3-alternate and partial cone. However, the calculations seem again to underestimate the stability of the 1,3-alternate conformer.

The free activation energies  $\Delta G^\ddagger$  for **2–5** determined by NMR spectroscopy vary within 1.1 kcal mol<sup>-1</sup> (see above) and do not depend on the number of intraannular OH groups. In contrast, the calculated activation energies ( $\Delta E^\ddagger$ ) for the cone $\rightleftharpoons$ cone (**2–4**) and paco(dist) $\rightleftharpoons$ paco(dist) (**5**) topomerisations decrease with the decreasing number of *endo*-OH groups: 10.64 (**2**), 8.28 (**3**), 8.29 (**4**) and 7.88 kcal mol<sup>-1</sup> (**5**) which might be ascribed to the decreasing number of hydrogen bonds and to the reduced steric strain at the lower rim. However, the rotational barriers  $\Delta E^\ddagger_{\text{rel}}$  of the calculated rate-limiting steps of the topomerisation processes in **2–5** lie within a range of 0.9 kcal mol<sup>-1</sup> indicating that the barriers are defined by similar steric interactions during ring rotation and that there is no contribution from hydrogen bonding energy. Indeed, the inspection of the rotational pathways of the paco(prox) $\rightleftharpoons$ 1,2-alt and 1,2-alt(*syn*) $\rightleftharpoons$ paco(OH) inversions of **2** and **3**, respectively, revealed that the hydrogen bonds present in the transition states are broken after reaching the maximum steric energy. Thus, it may be concluded that the differences between  $\Delta G^\ddagger$  and  $\Delta E^\ddagger$  arise mainly from the incorrect reproduction of ground state energies of the conformations of **2–5**, although it should be noted that neither the influence of the solvent nor entropic contributions have been considered in the calculations.

## Conclusions

MM3 calculations indicate that the rotational barriers of dehydroxylated calix[4]arenes **2–5** are determined by a partial cone $\rightleftharpoons$ 1,2-alternate inversion of a phenol ring. The calculations suggest that hydrogen bonding does not contribute to the activation energies for the cone $\rightleftharpoons$ cone topomerisations of **2** and **3** and that the barriers for **2–5** are determined by the steric strain resulting from unfavourable angle bending, torsional and van der Waals energies during the passage of the *endo*-OH groups through the macrocyclic annulus. This may explain the similar free activation energies obtained by NMR spectroscopy. The calculations further indicate that the dehydroxylated calix[4]arenes should be partially flexible at low temperature due to the low barriers for phenyl residue rotation and the observed spectra should correspond to the weighted average of several conformations.

## Computational details

All calculations were performed using the standard version of the MM3(92) force field<sup>11</sup> running on SGI Indigo2 workstations. The analysis and visualisation of the results were accomplished using the graphical interface of the Sybyl<sup>12</sup> molecular modelling package. Starting conformers were generated using the corresponding MM3-optimised structures of our previous calculations<sup>9c</sup> of *p-tert*-butylcalix[4]arene **1**. Low-energy conformers were obtained by exploring the potential energy hypersurface of **2–5** using the stochastic search routine of MM3. The default options of MM3 were applied to this search except for the number of pushes which was to 10000. All rotational pathways were calculated forward and backward starting from the lowest energy cone conformer and leading to its topomerised form according to the method described in ref. 9e. The conformers obtained from the stochastic search and stationary points of the rotational pathways were refined using the full matrix Newton–Raphson minimisation algorithm and characterised as minima or transition states by means of the eigenvalues of the Hessian matrix.

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