JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
*J. Phys. Org. Chem.* 2004; **17:** 752–759
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/poc.791

# Conformational analysis of calixarene derivatives substituted at the methylene bridges†

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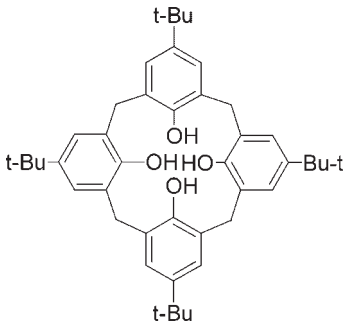
ABSTRACT: The conformation of tetrahydroxycalix[4]arene derivatives substituted at two opposite methylene bridges or at a single bridge by an alkyl or aryl group is reviewed. The cone form with an equatorial substituent is the lowest energy conformation of calixarenes possessing one bridge substituted by an alkyl group, whereas both the axial and equatorial conformers are similarly populated if the substituent is an aryl group. In the *cone* conformation of calixarenes possessing two opposite bridges substituted in *trans* fashion by a pair of groups, one group must necessarily be located in an axial position. The steric interactions ensuing from the presence of an axial group destabilize the *cone* conformation, rendering the *1,2-alternate* form the lowest energy conformation in some derivatives. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: calixarenes; macrocycles; conformation; stereochemistry; NMR; rotational barriers; axial; equatorial

## INTRODUCTION

Calix[*n*]arenes are synthetic macrocycles consisting of *n* phenolic rings interconnected by methylene groups.[1] Several conformations are possible for the parent compound, *p-tert*-butylcalix[4]arene (**1**) resulting from the different arrangements of the phenolic rings. In general, the conformation of calix[4]arenes is analyzed in terms of the four basic arrangements resulting from the different 'up' or 'down' orientations of the phenol rings relative to the mean macrocyclic plane passing through the four methylene carbons. Following Gutsche, these arrangements are usually designated '*cone*', '*partial cone*', '*1,3-alternate*' and '*1,2-alternate*' (Fig. 1).[1]

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The parent *p-tert*-butylcalix[4]arene adopts in solution and solid state a *cone* conformation stabilized by a circular array of hydrogen bonds between the four phenolic OH groups. The compound is conformationally flexible and undergoes a dynamic process involving rotation around the $H_2C—Ar$ bonds. In this process, the intra-annular atoms pass through the cavity annulus (a *cone*-to-*cone* inversion process, Scheme 1) with a barrier of 15.7 kcal mol$^{-1}$ (1 kcal = 4.184 kJ) in $CDCl_3$[2] (for a review on the conformation and stereodynamics of calixarenes, see Ref. 2b).

The effect of the substituents on the rings, derivatization of the OH groups (e.g. alkylation, acylation) and, to a lesser extent, replacement of the hydroxyls by another group (e.g. H, SH, $NH_2$) on the conformation and/or rigidity of the calixarenes have been the subject of key reviews and monographs.[1] Comparatively, the study of the conformational consequences of the formal introduction of substituents on the bridges has lagged behind, most likely due to the lack of synthetic methods for the preparation of such compounds; however, the development of synthetic routes for the formal incorporation of substituents into the bridges of the calixarene scaffold makes these studies possible.[3–5] In this paper, we review the conformational consequences of the formal incorporation of an alkyl or aryl substituent into one or two bridges of the calix[4]arene scaffold.

## AXIAL, EQUATORIAL AND ISOCLINAL PROTONS IN THE CALIX[4]ARENE SKELETON

Different steric environments may surround a substituent attached to a calixarene methylene group, depending on the conformation of the macrocycle. In the *partial cone* and *1,2-alternate* forms, two different types of methylene

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†Dedicated to Professor Kurt Mislow on the occasion of his 80th birthday.

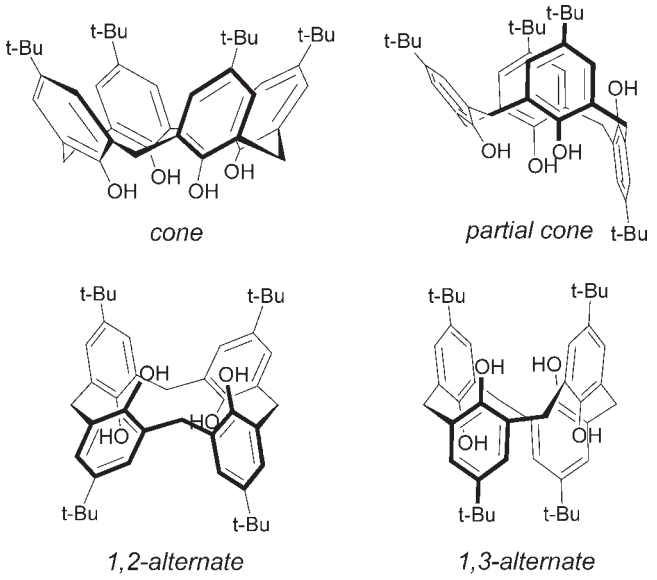
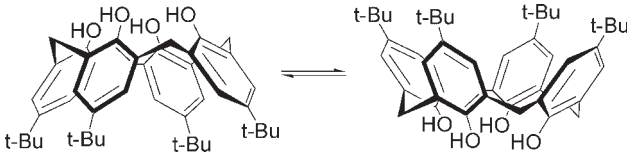
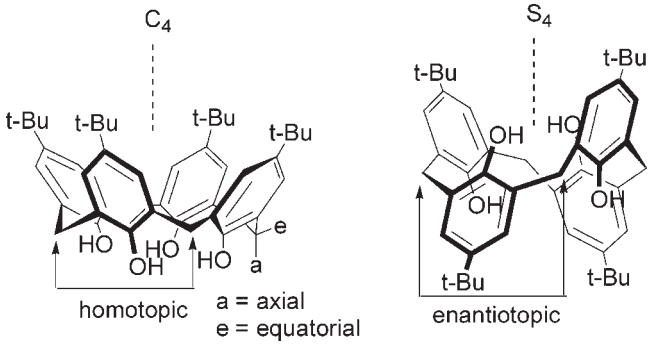



**Figure 1.** The four basic 'up--down' conformations of *p-tert*-butylcalix[4]arene



**Scheme 1**




**Scheme 2**

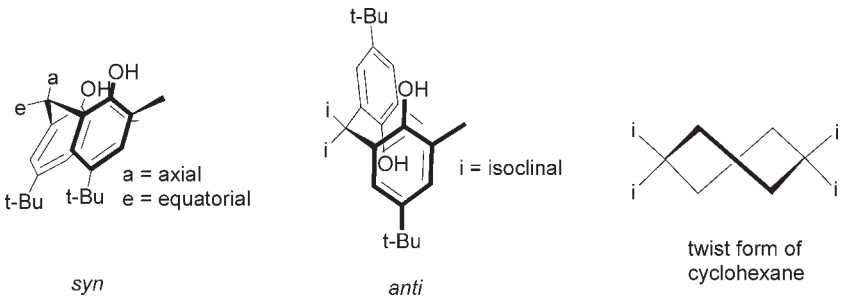
groups are present. On the other hand, in the *cone* and the *1,3-alternate* forms, the four methylene groups are symmetry related. Pairs of methylene groups connected to a given ring are homotopic in the *cone* form but enantiotopic in the *1,3-alternate* conformation (Scheme 2). The different stereotopic relationship between the bridges could be used to distinguish between the two forms[6] in a ketocalixarene lacking methylene protons, taking advantage that enantiotopic groups are rendered anisochronous in NMR spectra in a chiral non-racemic medium.[7]

In the *cone* conformation, the four methylene groups are equivalent but the two protons belonging to a given methylene are diastereotopic. By analogy with cyclohexane derivatives adopting the *chair* conformation, these protons are usually designated 'equatorial' and 'axial' (Scheme 2).[8] More generally, the terms can be used also for the methylene protons of other conformations of the macrocycle provided that the two rings connected to a given methylene are oriented *syn* since the steric surroundings near those protons are similar to (albeit not identical with) those of the axial and equatorial protons of the *cone* conformation. If the two rings are oriented *anti*, the two methylene protons can be designated isoclinal,[9] borrowing the term used for the pair of geminal protons that are mutually exchanged by a $C_2$ axis in the twist form of cyclohexane (Scheme 3).[10] For **1**, pairs of geminal protons located at isoclinal positions are homotopic in the *1,2-alternate* form and diastereotopic in the *partial cone* conformation.

Several conformations are possible for a calix[4]arene derivative possessing a single monosubstituted bridge, or two opposite bridges each monosubstituted. These conformations arise from the possible up–down orientations of the aryl groups and the axial/equatorial/isoclinal disposition of the substituent(s). The ideal conformers for each substitution pattern are collected in Table 1.

## CALIXARENE WITH A SINGLE MONOSUBSTITUTED BRIDGE

The conformational preferences of tetrahydroxycalix[4]arene derivatives substituted at a methylene bridge by an alkyl or an aryl group have been examined in detail.[11] All derivatives were prepared by the fragment condensation method (for other applications of the fragment condensation method, see Ref. 12a–c; for a review on the synthesis of calixarenes via the stepwise and fragment

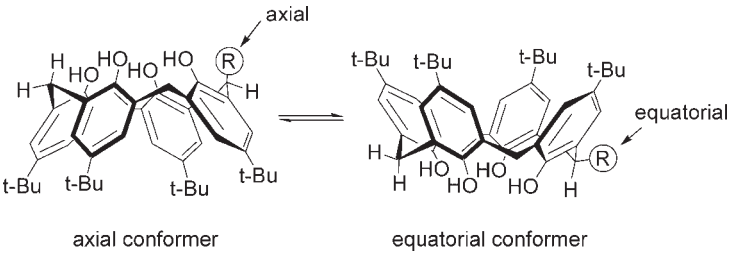



**Scheme 3**

**Table 1.** Possible arrangements of the substituents in calix[4]arene derivatives possessing one or two monosubstituted bridges

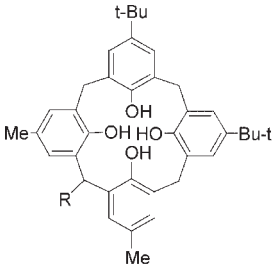
| Substitution pattern | Conformation | | | |
|---|---|---|---|---|
| | *Cone* | *Partial cone*[a] | *1,3-Alternate* | *1,2-Alternate* |
| One monosubstituted methylene bridge | Axial<br>Equatorial | Axial<br>Equatorial<br>Isoclinal (I)<br>Isoclinal (II) | Isoclinal | Axial<br>Equatorial<br>Isoclinal |
| Two opposite monosubstituted methylene bridges (*cis*) | Diaxial<br>Diequatorial | Axial isoclinal (I)<br>Equatorial isoclinal (II) | Diisoclinal | Axial–equatorial<br>Diisoclinal |
| Two opposite monosubstituted methylene bridges (*trans*) | Equatorial-axial | Axial isoclinal (II)<br>Equatorial isoclinal (I) | Diisoclinal | Diaxial<br>Diequatorial<br>Diisoclinal |

[a] The terms 'isoclinal (I)' and 'isoclinal (II)' denote the isoclinal positions pointing away or towards the unique ring oriented *anti* to the rest, respectively.[9]

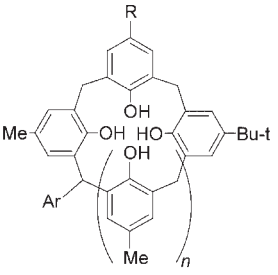



**Scheme 4**

condensation methods, see Ref. 12d). In this method, two suitable fragments possessing the proper functionalities at the bridges [e.g. an alkanediyl diphenol and a bis(bromomethylated) diphenol] are synthesized and then cyclocondensed. As indicated by the NMR data, all compounds were found to adopt a *cone* conformation.[11] For simplicity, the *cone* forms of a calix[4]arene possessing an axial or equatorial disposition of the substituent at the bridge will be designated the axial and equatorial conformers, respectively (Scheme 4). Both forms mutually interconvert by a *cone*-to-*cone* inversion process.



**2a** R = Me
**2b** R = Et
**2c** R = *i*-Pr
**2d** R = *t*-Bu



**3a** Ar = *p*-Tol, R= *t*-Bu, *n* = 1
**3b** Ar = *p*-$O_2NC_6H_4$,R= *t*-Bu, *n* =1
**3c** Ar = *p*-Tol, R= Me, *n* = 2
**3d** Ar = *p*-$O_2NC_6H_4$, R= Me, *n* =2

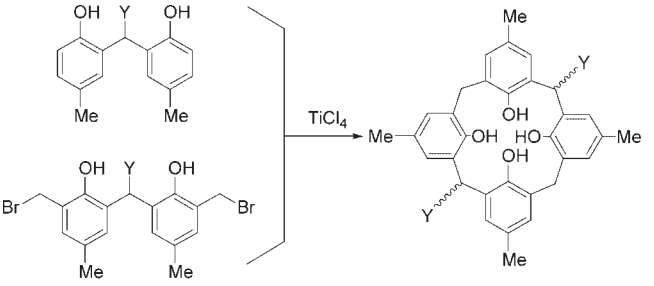
## Monoalkyl derivatives

The conformation of calix[4]arenes substituted at one bridge by a methyl, ethyl, isopropyl or *tert*-butyl group (**2a**–**d**) was examined.[11] In general, it was found that the bulkier the alkyl group, the greater is the preference for the equatorial conformer.[11] Because in all cases the conformational equilibrium was strongly biased towards the equatorial form, when moving from the slow-exchange to the fast-exchange regime in the $^1$H NMR spectrum (on raising the temperature), lineshape changes characteristic of the 'exchange with a hidden partner' were observed.[13] The interconversion barrier between the axial and equatorial forms (a process requiring rotation through the annulus of the aryl rings) increased in the order methyl (**2a**, $\Delta G^{\ddagger} = 15.0$ kcal mol$^{-1}$) < ethyl (**2b**, $\Delta G^{\ddagger} = 15.8$ kcal mol$^{-1}$) < *tert*-butyl (**2d**,$\Delta G^{\ddagger} = 16.2$ kcal mol$^{-1}$) < isopropyl(**2c**, $\Delta G^{\ddagger} =$ 17.2 kcal mol$^{-1}$). The relatively low inversion barrier of **2d** was interpreted as indicating a preferential ground-state steric destabilization of the *tert*-butyl-substituted derivative.[13]

## Monoaryl derivatives

In contrast to the alkyl-substituted derivatives, solution NMR data of the monoaryl calix[4]arene derivatives **3a**,**b**

indicated that the equatorial and axial conformers are nearly equally populated.[11] The conformational behavior of these calix[4]arenes thus departs significantly from that of cyclohexyl derivatives where an equatorial disposition of a phenyl substituent is about 2.8 kcal mol$^{-1}$ lower in energy than the axial one.[14] In contrast, for pentahydroxycalix[5]arenes substituted at one bridge by a *p*-tolyl or *p*-nitrophenyl group (**3c**,**d**) a 'normal' conformational behavior was observed, the equatorial form being more stable than the axial form (for both compounds $K_{eq/ax} = 11.2 \pm 0.6$ at 210 K in $CDCl_3$). Force field calculations of the axial–equatorial energy gap of calix[4]arene and calix[5]arene derivatives substituted at one bridge by an aryl group suggested that in the case of the calix[4]arene series, the equatorial conformer is destabilized by steric interactions between its *ortho* positions and the adjacent phenolic moieties.[15] In the calix[5]arene derivatives these steric interactions are reduced in the equatorial conformation due to the widening of the Ar—C—Ar angle and the slightly larger tilt angle of the phenolic rings with respect to the mean macrocyclic plane.[15]



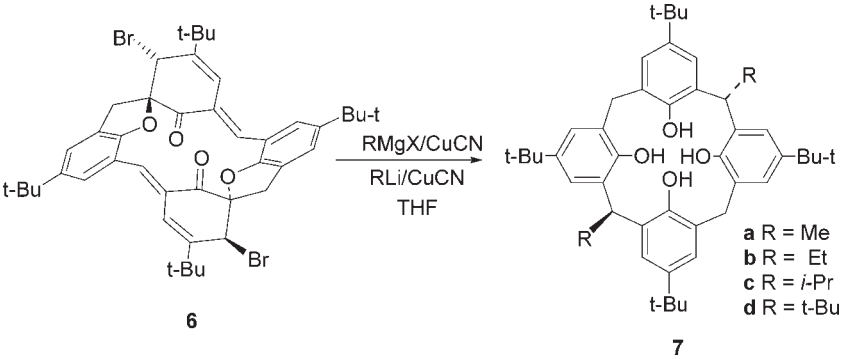

**Scheme 5**

## CALIXARENES SUBSTITUTED ON OPPOSITE BRIDGES: *CIS* AND *TRANS* DIASTEREOMERS

*Cis* and *trans* 1,3-disubstituted calix[4]arenes have been studied in detail. The *cis* derivatives are readily available via the fragment condensation method. When the substituents at the bridges were alkyl groups, the method afforded exclusively the more thermodynamically stable *cis* isomers **4a**–**d**.[11] Only in the case of the methyl substituent could traces of the *trans* isomer **5a** be isolated (Scheme 5). In the case of aryl substituents on the bridges, the method afforded mixtures of the *cis* and *trans* isomers.[11]

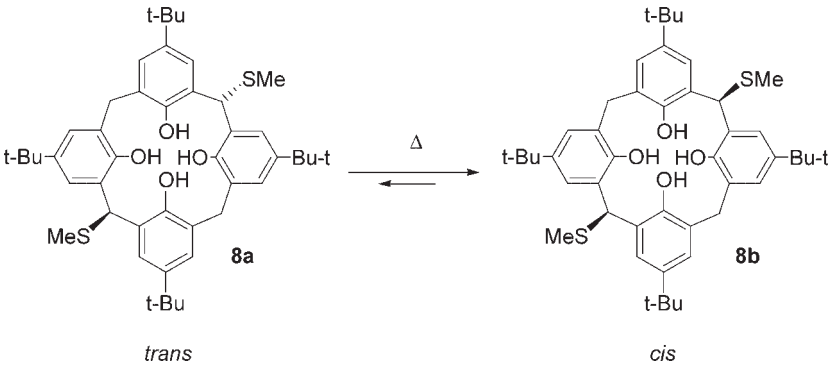
Calixarene derivatives possessing a pair of distal bridges substituted in a *trans* fashion (**7a**–**d**) were prepared by addition of the proper alkyl organocopper reagent to the spirodiene derivative **6** of $C_i$ symmetry (Scheme 6)[5c,16] (for a review on spirodienone calixarene derivatives, see Ref. 17). The stereochemical outcome of the reaction is the result of the molecular symmetry of the starting material. The two double bonds of **6** are related by an inversion center and are oriented in an antiparallel fashion and therefore addition to their *exo* faces results in a *trans* disposition of the substituents on the methylene bridges.

Interconversion between the *cis* and *trans* isomers of calixarenes substituted at two distal bridges requires bond fission (e.g. cleavage of the $Ar_2CH$—R bond). *Cis–trans* interconversion was not observed for calixarenes possessing bridges substituted by alkyl or aryl substituents, but such isomerization was observed when the substituents were connected to the bridges via a heteroatom (e.g. thiomethoxy, anilino). For example, heating solutions of either the *trans* (**8a**) or *cis* (**8b**) isomers of a bis(thiomethoxy) calix[4]arene derivative in 1,1,2,2-tetrachloroethane-$d_2$ at 400 K for 3 h, gave identical mixtures ($K_{cis/trans}$ was 3.3 at 400 K, $-\Delta G^\circ = 0.96$ kcal mol$^{-1}$) (Scheme 7).[5b] From this study, it could be demonstrated experimentally that the *cis* stereoisomer **8b** is the thermodynamically most stable isomer. A combination of selective crystallization and mutual isomerization in solution allowed the isolation of a pure sample of the *cis* isomer **8b** by slow evaporation of a chloroform solution of the *trans* isomer **8a** to dryness.[5b]




6 7

**Scheme 6**




**Scheme 7**

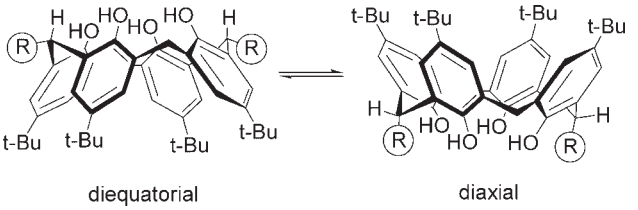
## CALIX[4]ARENES POSSESSING *CIS* ALKYL SUBSTITUENTS ON OPPOSITE BRIDGES

A *cone*-to-*cone* inversion process in calix[4]arenes substituted in a *cis* fashion at a pair of opposite bridges interconverts the diaxial and diequatorial forms (Scheme 8). As indicated by NMR data, when the substituents are alkyl groups the energy gap between the diequatorial and diaxial conformers is larger than for the monosubstituted case. Force field calculations indicated that for the small alkyl substituents the $\Delta E_{eq-ax}$ energy gap in the *cis* derivatives is almost twice as large as for the compounds with only one bridge substituted.[11] Similar additivity is seen in *trans*-1,4-substituted cyclohexane derivatives.[18]

## AXIAL SUBSTITUENTS IN THE *CONE* FORM OF THE *TRANS* DERIVATIVES

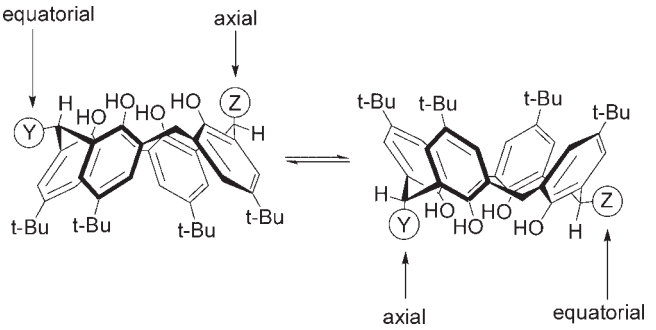
Tetrahydroxycalixarenes possessing a pair of *trans* monosubstituted bridges are of stereochemical interest since in the *cone* conformation one substituent must be located in the more hindered axial position. In these *trans* derivatives, the axial disposition of a substituent cannot be relieved by a *cone*-to-*cone* inversion. As exemplified in Scheme 9, although an axial group Z will become equatorial after the inversion process, a group Y originally positioned in the equatorial position will be relocated into an axial one. If the two groups Y and Z are identical, the *cone*-to-*cone* inversion process results in homomerization, in contrast to the corresponding *cis* derivatives where such process exchanges the diequatorial and diaxial conformers (Scheme 8).

In cyclohexane derivatives, the presence of bulky axial substituents may destabilize the chair conformation and render the twist form the preferred conformation.[10] A systematic MM3 study revealed that the minimal steric requirements for the relative stabilization of the twist conformation of cyclohexane are two methyls and two isopropyl groups arranged in either a *cis–trans–trans*-1,2,3,4- or all-*cis*-1,2,4,5-substitution pattern.[19] In

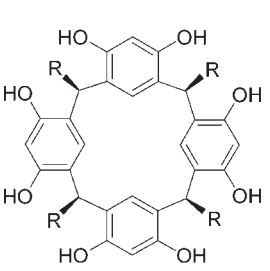



**Scheme 8**

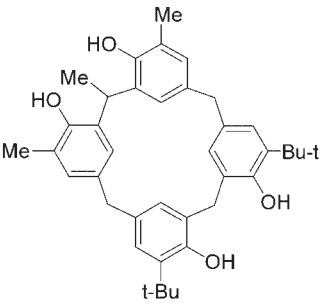
principle, if the steric destabilization ensuing from the presence of a bulky axial substituent in a tetrahydroxycalix[4]arene is sufficiently large, it could be expected that the intrinsic conformation preferences of the calix skeleton for the *cone* conformation may be altered. However, analysis of the NMR spectra of the *trans* alkyl-substituted derivatives **7a–d** indicated that, in all cases, the preferred conformation is still the *cone*.[5c,16] MM3 calculations suggest that, although the energy gap between the *cone* and the different up–down forms is reduced with the increase in bulk of the substituent, in all cases the *cone* conformation remains the lowest energy form.[16] As observed along the series **2a–d**, the barrier for the *cone*-to-*cone* interconversion process of **7a–d** increased with the bulk of the substituent ($\Delta G_c^{\ddagger} =$ 13.9, 14.9 and 17.6 kcal mol$^{-1}$ for **7a**, **7b** and **7c**, respectively) reaching its maximum value for the isopropyl substituent, and then decreasing for the *tert*-butyl group ($\Delta G_c^{\ddagger} =$ 15.7 kcal mol$^{-1}$),[16] probably as the result

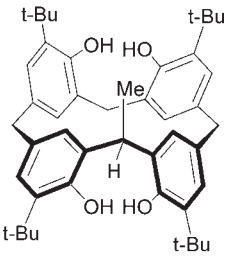



**Scheme 9**




**9** R= Alkyl




**10**

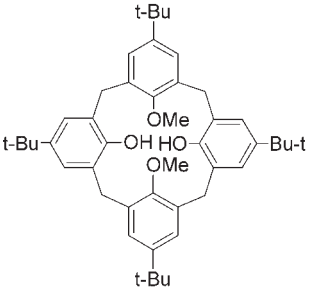
of the selective destabilization of the ground state conformation.

## ALKYL/OH INTERACTIONS IN THE AXIAL CONFORMATION

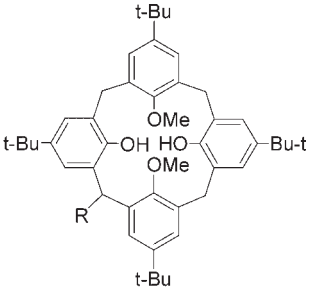
The conformational preferences of tetrahydroxycalixarene derivatives bearing a pair of *cis* monosubstituted bridges is in marked contrast to that found in the all-*cis* (*rccc*) resorcinarene family (e.g., **9**) [see, for example, Refs 20a and b; for a review on resorcinarenes, see Ref. 20c; for a computational study of the conformational preferences of the (unsubstituted) methylene-bridged resorcinarenes, see Ref. 21]. In these octahydroxy derivatives the alkyl groups attached to the bridges prefer the axial positions of the macrocycle, which also adopts a *cone*-like conformation (in resorcinarene chemistry this conformation is usually referred as 'crown'). The different conformational preferences observed in the calixarene and resorcinarene families suggest that alkyl substituents will favor those positions that will minimize the steric interactions with the oxygen substituents. In the calixarene family the OH groups are located at the *endo* positions, and since the steric interactions are larger when the substituents are located in axial positions, the equatorial conformation is favored. In contrast, in the all-*cis*-resorcinarene family, alkyl groups in the equatorial positions are in close contact with the OH groups located in the *exo* positions of the macrocycle, and therefore the preferred conformation is the all-axial. Solution NMR data in $CDCl_3$ of calixarene **10** (with four *exo* OH groups) indicates that the preferred conformation is the *1,2-alternate* with the methyl group located at an axial position of the macrocycle. As observed for the all-*cis* resorcinarenes, the alkyl favors an axial position to minimize the repulsive steric interactions with the *exo* OH groups.

## CONE–1,2-ALTERNATE EQUILIBRIUM IN CALIXARENE 1,3-DIMETHYL ETHER DERIVATIVES

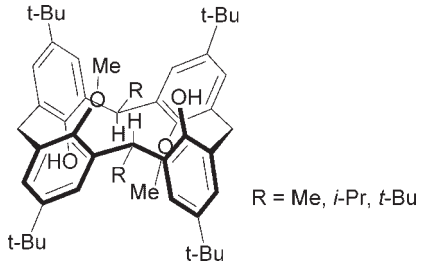
The 1,3-dimethyl ether derivative of *p-tert*-butylcalix[4]-arene (**11**) adopts in solution a 'pinched' *cone* conformation significantly more rigid than the *cone* conformation of the parent calixarene **1**.[22] Molecular mechanics calculations suggest that the relative stability of the *cone* form relative to the other conformations is smaller for **11** than for **1**. For example, whereas the energy gap between the *cone* and the *1,2-alternate* conformer was calculated for **1** by the AMBER and MM3 force fields as 11.8–7.5 kcal $mol^{-1}$,[23,24] calculations conducted on the *p*-Me analogue of **11** predict an energy gap of 1.9 (TRIPOS) and 3.5 kcal $mol^{-1}$ (MM2) between the two forms.[25] This is reasonable, since although the *cone* and *1,2-alternate* forms of **1** differ in the number of intramolecular hydrogen bonds between the OH groups (four and two, respectively), in **11** both conformations possess two hydrogen bonds. It could be expected that the presence of a bulky axial substituent in the *cone* form of the dimethyl ether derivatives **12a–c** (possessing a pair of *trans* substituted bridges) should destabilize the conformation. As shown in Table 1, if the macrocycle adopts, for example, the *1,2-alternate* instead of the *cone* conformation, both substituents at the bridges can be located at the less hindered equatorial positions. It may seem counterintuitive at first that although one substituent necessarily must be located in an axial position in the *cone* form of the *trans* derivatives, both substituents can be located at diequatorial positions in the *1,2-alternate* form. However, whereas the diequatorial positions are in a *cis* relationship in the *cone* form, they are mutually *trans* in the *1,2-alternate*, and therefore the diequatorial arrangement of the substituents at the bridges is possible.




**11**




**12a** R = Me
**12b** R = *i*-Pr
**12c** R = *t*-Bu




**Scheme 10**

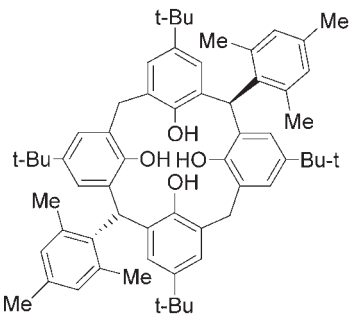
The *cone* and *1,2-alternate* forms of **12a** are nearly equally populated in $CDCl_3$, but if the bulk of the substituent is increased (i.e. **12b** and **c**) the *1,2-alternate* form becomes the major conformer.[16] According to the NMR data, the alkyl substituents are located at equatorial positions of the macrocycle (Scheme 10). In the case of **12a** and **b**, increasing the polarity of the solvent increased the relative stability of the more polar *cone* conformation, which in DMF-$d_7$ was the major conformer in solution (the *cone*:*1,2-alternate* ratio was 9.4 and 3.3 for **12a** and **b**, respectively). The repulsive steric interactions resulting from the presence of an axial *tert*-butyl substituent in **12c** are so large that the *1,2-alternate* was in all cases the preferred conformation irrespective of the polarity of the solvent examined.[16]

## NON-*CONE* CONFORMATIONS OF A TETRAHYDROXYCALIXARENE

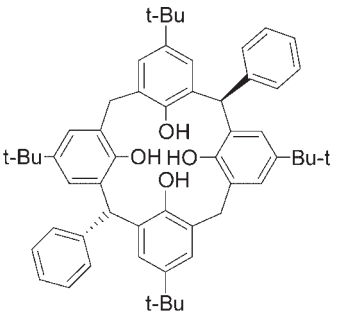
The repulsive steric interactions ensuing from the presence of an axial substituent in tetrahydroxycalixarenes **7a**–**d** are insufficient to overcome the stabilization of the circular array of hydrogen bonds and, as in the parent **1a**, the preferred conformation is the *cone*. However, in the mesityl derivative **13** [prepared by addition of MesMgBr–CuCN to the spirodiene derivative **6** followed by $LiAlH_4$ reduction of the resulting substituted bis(spirodienone)-derivative], NMR data indicate that the molecule adopts a *1,2-alternate* conformation. The conformational behavior of **13** is markedly different from that of **14**, which adopts the usual *cone* conformation, suggesting that the larger bulk of the substituents at the bridges is responsible for the conformational change in the calix macrocycle. X-ray crystallography of **13** indicated that in the solid state the molecule also adopts a *1,2-alternate* conformation of crystallographic $C_i$ symmetry. Calixarene **13** is the first example of a 'classical' [the term 'classical' is sometimes used to designate calixarenes possessing pairs of phenol units connected by a single $sp^3$ carbon as opposed to, for example, 'thiacalixarenes' (sulfur bridges)] tetrahydroxycalixarene, which does not favor a *cone* conformation.[26] The solution and the x-ray data indicate that the mesityl substituents are located at the isoclinal positions of the *1,2-alternate* form. Assuming that the steric environments of the equatorial positions in the *cone* and *1,2-alternate* forms are similar, then the *cone* conformation is destabilized not only by the presence of the axial substituent, but also by the equatorial substituent. From the equality in rotational barriers measured for the rings inversion process of the *1,2-alternate* form and the rotation around the C—Mes bond (15.2 and 15.1 kcal $mol^{-1}$, respectively), it was concluded that the minimum energy pathway for rotation of the mesityl rings requires a conformational change of the calix macrocycle.

## CONCLUSIONS

Tetrahydroxycalixarenes may avoid the *cone* conformation to minimize the repulsive steric interactions between the substituents at the bridges and the aryl rings. Similar effects should operate in an octol resorcinarene when the relative configuration of the four substituted bridges is different from all-*cis* since at least one substituent must be located in a sterically hindered equatorial position in the crown form and destabilize the conformation.




**13**




**14**

## Acknowledgments

We thank Dr Volker Böhmer (Mainz) and Dr Iris Thondorf (Halle) for their longstanding collaboration on the subject of this review and for their comments on the manuscript, and to Dr Flavio Grynszpan, Dr Ishay Columbus and Dr Kasim Agbaria for their scientific contributions.

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