Molecular Modelling Study of a Dissymmetric Calix[4]arene and its Methyl Ethers

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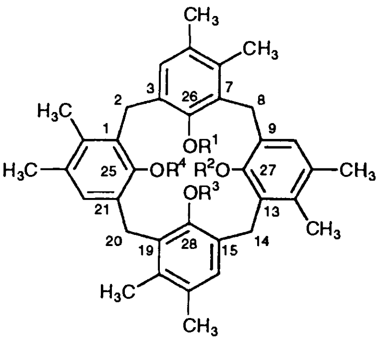
A dissymmetric calix[4]arene consisting of four 3,4-dimethylphenol units **1** and its methyl ethers **2–6** have been investigated by applying various force fields as well as by the PM3 semiempirical molecular orbital method. The exploration of the conformational space by random conformational searching has led to numerous local energy minima which differ in the torsion angles around the aryl–methylene bonds. By adjustment of some parameters of the TRIPOS force field a good correspondence could be obtained with experimental data whereas the MM2P force field was not reliable in this respect. Furthermore, a method is proposed for the characterization of calix[4]arenes by a single parameter derived from the torsion angles of the aryl–methylene bonds.

Computational investigations of calix[4]arenes and related systems[1–14] have elicited wide interest due to the importance of these compounds either as host molecules or as building blocks for the construction of more sophisticated host molecules.[15]

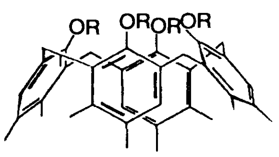
Various force fields, *e.g.* AMBER,[3] MM2P,[2,4] CHARMM,[5,13] MM3,[6,12] MM2,[10] CVFF,[11] have been employed for the study of the molecular properties of calix[4]arenes. However, regarding the calculation of the relative stabilities of the four main conformations of calix[4]arenes the different force fields gave quite different results. A reliable prediction of the energy order and of the exact geometry of these main conformations would be helpful for the design of calix[4]arenes with a desired function based on a certain geometric shape, *e.g.* for the development of 'enzyme mimics'.



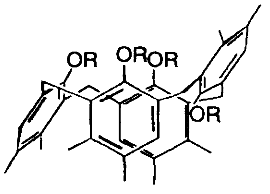
1 R^1, R^2, R^3, R^4 = H
2 R^1 = CH$_3$, R^2, R^3, R^4 = H
3 R^1, R^2 = CH$_3$, R^3, R^4 = H
4 R^1, R^3 = CH$_3$, R^2, R^4 = H
5 R^1, R^2, R^3 = CH$_3$, R^4 = H
6 R^1, R^2, R^3, R^4 = CH$_3$

ϕ	χ
25–1–2–3	1–2–3–26
26–7–8–9	7–8–9–27
27–13–14–15	13–14–15–28
28–19–20–21	19–20–21–25

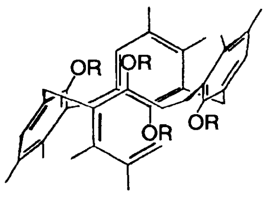
We report here the investigation of an 'inherently' chiral calix[4]arene **1** consisting of four 3,4-dimethylphenol units and its methyl ethers **2–6** by means of computational methods. We have chosen these molecules, since the steric strain exerted by the four *meta*-methyl groups competes with the stabilisation of the cone conformation by the cyclic array of intramolecular hydrogen bonds between the phenolic hydroxy groups. From this competition between deformation and stabilisation of a fourfold geometry more detailed information should be available with respect to the correct description of these factors. We have investigated the relative stability of the four calix[4]arene conformations depending on the oxygen substituents by molecular mechanics calculations [TRIPOS, AMBER, MM2P(85) force fields] and by the PM3 semiempirical molecular orbital method. We have tested and adjusted TRIPOS force field parameters by comparison with conformational properties of calix[4]arenes included in the Cambridge Crystallographic Database. Furthermore, we describe a simple method for the characterization of the calix[4]arene conformation based on the torsion angles of the aryl–methylene bonds which is especially helpful for the analysis of data obtained by computational methods, *e.g.* conformational searching and molecular dynamics simulations.



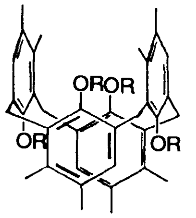
cone



partial cone



1,2-alternate



1,3-alternate

Results and Discussion

Molecular Mechanics Calculations.—In order to find the lowest energy conformers of the cone, partial cone, 1,2-alternate and 1,3-alternate conformations for each of the calix[4]arenes **1–6** we performed a conformational search using the RANDOMSEARCH routine of the SYBYL program package.

Table 1 Relative energies of the lowest energy conformers obtained by using the TRIPOS force field[a]

Conformation	1	2	3	4	5	6
Cone	6.28	4.91	4.73	7.44	7.47	12.39
Partial cone	7.09	7.97	8.74	7.59	8.62	10.65
1,2-Alternate	11.61	9.41	8.76	8.39	16.05	17.82
1,3-Alternate	10.39	11.05	13.11	9.93	14.28	15.26

[a] All energies in kcal mol^{-1} (1 kcal = 4.184 kJ).

This routine uses a Monte Carlo procedure to cover the conformational space.[16] A further energy minimisation of the conformers obtained in this way using the TRIPOS force field with decreased termination criteria was performed in order to prove that the conformers were unique energy minima. By using a rms fitting routine[17] as well as by comparison of the torsion angles around the methylene groups (see below) and visual inspection the conformers were divided into families according to the four main conformations. The results of the molecular mechanics calculations using the TRIPOS force field with respect to the lowest energy conformer of each family for the parent calix[4]arene **1** and its methyl ethers **2**–**6** are summarised in Table 1.

The ^1H NMR spectroscopic data and the X-ray analysis[18] (**1**) show for the calix[4]arene **1**, the monomethyl ether **2** and the 1,3-dimethyl ether **4** that they exist predominantly in the cone conformation. This is in agreement with the calculations which also predict a cone conformation to be the most stable conformation. The calix[4]arene tetramethyl ether **6** was found by ^1H NMR spectroscopic investigations to consist of a mixture of the cone and partial cone conformation whereas the calculations predict the partial cone conformation to be the most stable one. The 1,2-dimethyl ether **3** and the trimethyl ether **5** have not yet been synthesized, however, the corresponding methyl ethers of *p-tert*-butylcalix[4]arene exist in a cone conformation[19] which is in agreement with our calculations.

We performed a careful visual examination of the geometrical shape of the local energy minima obtained by random conformational searching and further optimisation. It turned out that the phenyl rings of the calix[4]arene framework were not planar in the calculated conformations. Therefore, we assumed that the standard parameters for the torsional strain between aromatic carbons (2.35 kcal mol^{-1} $degree^{-2}$)* as well as the out-of-plane bending term for the aromatic carbons (630 kcal mol^{-1} $Å^{-2}$) of the TRIPOS force field are unsuited for calculations on the sterically strained calix[4]arenes. (Because of the non-planarity of phenyl rings obtained by calculations with this force field these parameters have already been increased from the SYBYL versions 5.2 to 5.3.) By testing several variations for these parameters we found values of 5.3 kcal mol^{-1} $degree^{-2}$ for the torsional strain between aromatic carbons and 930 kcal mol^{-1} $Å^{-2}$ for the out-of-plane bending term of aromatic carbons well suited for further calculations.

The 'high flexibility' of the phenyl rings due to the standard TRIPOS-parameters is also responsible for the occurrence of the numerous local energy minima (100–300) which were obtained by random conformational searching. Repeating the calculations with modified parameters (see below) we found that several local minima collapsed by a unique local energy minimum.

The most stable cone conformer of the calix[4]arene **1** shows a C_2-symmetry. By fitting this conformer with the structure obtained by X-ray analysis we got a rms value of 0.6 Å. Two phenol rings are bent further out of the cavity in the calculated structure and only three hydrogen bonds were found. In general, none of the calculated cone conformers of compound **1** shows more than three hydrogen bonds. A circular hydrogen bonding pattern of four hydrogen bonds is, however, commonly accepted to be responsible for the stability of the cone conformation of calix[4]arenes at low temperature.

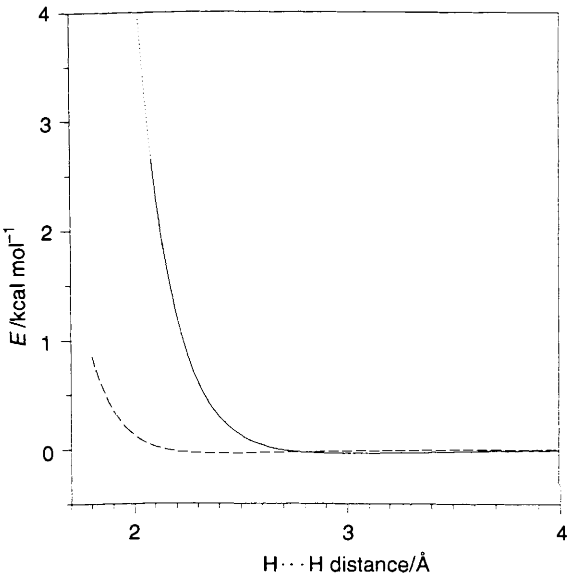


Fig. 1 Potential energy function depending on the H··· H distance (dashed line: van der Waals radius of hydrogen 1.2 Å, solid line 1.5 Å.

Looking for the reason of the non-existence of such a hydrogen bonding scheme in the calculated structures we have examined the non-bonded interactions of the hydroxy groups of the cone conformers. The TRIPOS force field includes no explicit hydrogen bonding terms. Hydrogen bonds are controlled by the electrostatic potential such that hydrogens attached to atom types designated as hydrogen bond donors are given zero van der Waals radii in the 6–12 Lennard–Jones potential for their interactions with hydrogen bond acceptors. The standard van der Waals radii for hydrogen and sp^3-hybridised oxygen provided by the TRIPOS force field are 1.5 and 1.52 Å, respectively. In contrast to other force fields, *e.g.* AMBER,[20] CVFF[21] and MM3[22] these parameters are very similar and the van der Waals radius of hydrogen is rather large. The potential energy curve of the 6–12 Lennard–Jones potential depending on the H··· H distances is shown in Fig. 1. An examination of the calix[4]arenes included in the Cambridge Crystallographic Database[23] provided H··· H distances of the hydroxy hydrogens of 2.03 to 2.67 Å. From Fig. 1 it is clear that short H··· H distances of 2.0 to 2.3 Å will produce repulsive van der Waals energy contributions. As a result, the attractive electrostatic forces which would lead to the formation of four hydrogen bonds are overcompensated by repulsive interactions between the four hydrogens of the hydroxy groups. Using the standard TRIPOS parameters the calculations show that the hydroxy groups avoid the repulsive interactions by turning out at least one hydrogen from the approximate plane of the oxygen atoms. This fact is also indicated by the small difference in energy between the cone and partial cone conformation of compound **1** resulting from similar contributions of the electrostatic energy.

To overcome these problems we have tested various sets of van der Waals radii for hydrogen and sp^3-oxygen using calix[4]arenes in the following way. The coordinates of various calix[4]arenes were retrieved from the Cambridge Crystallographic Database and the energy of these structures was minimised with the TRIPOS force field. Subsequently, the

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* 1 kcal = 4.184 kJ.

calculated conformations were compared with the original structures by rms fitting of the calix[4]arene framework, that is, of the aromatic and methylene carbons as well as the phenolic oxygen atoms, and by geometric parameters such as the inclination angle δ between the least-squares plane through the four methylene carbons and the phenolic rings as well as the O··· O-distances. Although packing effects were not considered with this method we think that this approach may be used to test the reliability of the force field. It turned out that van der Waals radii of 1.2 Å for hydrogen and 1.6–1.65 Å for sp^3-oxygen sufficiently reproduced the crystallographic data with respect to the calix[4]arene framework. The results of these calculations are summarised in Table 2. This method is similar to the approach of Bayard *et al.*[2,4] who have scaled down van der Waals parameters of the MM2P force field for calculations of calix[4]arenes in order to reflect the experimental data.

We now repeated the calculations on the calix[4]arenes **1**–**6** by using the TRIPOS force field with modified parameters. The results of the molecular mechanics calculations and the torsion angles of the aryl–methylene bonds of the lowest energy conformers are summarised in Tables 3 and 4.

For compound **1** the calculations predict a cone conformation with C_2-symmetry and four hydrogen bonds. This is in full agreement with the experimental data. Moreover, the fitting of the most stable calculated conformer and the structure obtained by X-ray analysis yields a rms value of 0.18 Å. The angles between the aromatic rings and the mean plane through the four methylene carbons are 108.7° (105.0°), 138.8° (145.9°), 108.7° (117.2°) and 138.8° (149.3°), those for the X-ray structure are in parentheses. A good agreement was also observed for the O··· O distances: 2.72 (2.74), 2.62 (2.68), 2.72 (2.69) and 2.62 (2.70) Å. Fig. 2 shows the structure of the calix[4]arene **1** obtained by X-ray analysis compared with the lowest energy conformer calculated by the TRIPOS and MM2P force fields as well as with the PM3 method.

Table 2 Comparison of selected calix[4]arenes obtained from the Cambridge Crystallographic Database and calculated with the TRIPOS force field using modified parameters

Code[a]	Conformation	rms value[b]
DACLUO	Cone	0.09
DOGGAH	Cone	0.18
FACBEQ10	1,3-Alternate	0.16
JABVUD	Cone	0.07
JIJHEP	Partial cone	0.14
KOPPUA	Cone	0.11
SIGCIU	Cone	0.16
SIGCOA	Partial cone	0.20
VIBPIF	Cone	0.18

[a] Compounds are coded according to names in the files of the Cambridge Crystallographic Database: DACLUO calix[4]arene acetone clathrate;[24] DOGGAH 5,11,17,23-tetra-*p*-*tert*-butyl-25,26,-27,28-tetrakis(*tert*-butoxycarbonyl)methoxycalix[4]arene;[25] FACBEQ10 5-allyl-25-methoxy-26,27,28-tribenzoylcalix[4]arene;[26] JABVUD 11,23-dimethyl-5,17-hexano-25,26,27,28-tetrahydroxycalix-[4]arene;[27] JIJHEP ethylthiocalix[4]arene methyl ether;[28] KOPPUA 5,11,17,23-tetraethyl-25,26,27,28-tetrahydroxycalix[4]arene;[29] SIGCIU 1,3-dimethoxy-*p*-*tert*-butylcalix[4]arene;[30] SIGCOA 1,3-bis(benzyloxy)-*p*-*tert*-butylcalix[4]arene;[30] VIBPIF *p*-(methyl,*tert*-butyl,nitro,*tert*-butyl)calix[4]arene toluene clathrate.[31] (Note that the various names used in the above cited references are not entirely consistent.) [b] Obtained by fitting the heavy atoms of the calix[4]arene framework (carbon atoms of the phenyl rings and of the methylene groups as well as the phenolic oxygen atoms).

The difference in the electrostatic contribution of four hydrogen bonds in the cone conformation *vs.* those of two hydrogen bonds in the partial cone conformation is readily distinguishable in contrast to the calculated energies with standard TRIPOS parameters. A cone conformer with a fourfold axis of symmetry is 0.15 kcal mol^{-1} less stable than the cone conformer with a twofold symmetry axis.

For the monomethyl ether **2** the flattened cone conformation is the geometric isomer with the lowest energy. This is in accordance with the experimental data. The larger stability of the cone conformer results from the electrostatic term due to the presence of three hydrogen bonds in this isomer compared with two hydrogen bonds in the partial cone conformer whereas the bonding and van der Waals energy contributions of the cone and partial cone conformers are comparable.

For the 1,2-dimethyl ether **3**, the 1,3-dimethyl ether **4** and the trimethyl ether **5** the cone conformation with a C_2 symmetry with respect to the calix[4]arene framework remains the lowest energy structure. However, the energy differences between the cone and partial cone conformations are smaller compared with compounds **1** and **2**. This results from small differences in the electrostatic contributions due to possible hydrogen bonding on the one hand and from favourable van der Waals contributions of the partial cone conformation owing to the reduction of repulsive O··· O contacts on the other.*

For the tetramethyl ether **6** the calculations predict the order of stability partial cone > cone ~ 1,3-alternate > 1,2-alternate. This is not entirely in accordance with the ^{1}H NMR spectroscopic results which show in $CDCl_3$ at −50 °C partial cone and cone conformation in a ratio 2 : 1, while no indication of other conformations is found. However, tetramethyl ethers of calix[4]arenes often adopt a partial cone conformation.[32]

It is worth mentioning that we found several conformers of the methyl ethers **2**–**6** with one or two methoxy groups pointing in towards the cavity. These conformers have a similar or even lower relative energy than the corresponding conformers with methoxy groups pointing out from the cavity. Furthermore, we also found local energy minima which represent 'borderline

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* It is worth mentioning that structural isomers exist for several conformations of the monomethyl ether **2** (cone and partial cone), the 1,2-dimethyl ether **3** (partial cone and 1,2-alternate), the 1,3-dimethyl ether **4** (cone and partial cone) and the trimethyl ether **5** (cone and partial cone). In Tables 3–6 only the energy and geometric parameters of the lowest energy isomers are documented (see also footnote of Table 3).

Table 3 Relative energies of the lowest energy conformers of the calix[4]arenes **1**–**6** obtained by using the TRIPOS force field with modified parameters[a]

Conformation	1	2	3	4	5	6
Cone	−20.24	−17.25[b]	−14.57	−14.02[b]	−11.21[f]	−6.78
Partial cone	−16.44	−15.67[c]	−14.03[d]	−12.78[e]	−10.63[e]	−8.43
1,2-Alternate	−13.82	−12.87	−11.45[d]	−12.16	−5.60	−5.16
1,3-Alternate	−12.15	−11.17	−10.03	−9.72	−8.37	−6.41

[a] All energies in kcal mol^{-1}. [b] Conformers where the phenol units are flattened. [c] One phenol unit is rotated through the plane of the four methylene carbons. [d] The anisole moieties are pointing into opposite directions. [e] One anisole unit is rotated through the plane of the four methylene carbons. [f] Two anisole moieties are nearly parallel.

Table 4 Torsion angles φ and χ of the aryl–methylene bonds of the lowest energy conformers of the calix[4]arenes **1–6**

	Cone										Partial cone									
	φ	χ	φ	χ	φ	χ	φ	χ	$(\lvert\Sigma\varphi_i\rvert + \lvert\Sigma\chi_i\rvert) - \Sigma\lvert\varphi_i + \chi_i\rvert$[a]		φ	χ	φ	χ	φ	χ	φ	χ	$(\lvert\Sigma\varphi_i\rvert + \lvert\Sigma\chi_i\rvert) - \Sigma\lvert\varphi_i + \chi_i\rvert$[a]
1	−101.8	77.3	−74.8	101.8	−101.8	77.3	−74.8	101.8	608.4		70.6	−107.5	58.5	58.9	−66.2	−46.8	104.3	−73.9	38.5
2	−103.7	75.1	−72.0	106.3	−107.5	74.7	−73.2	102.6	590.0		72.4	−105.8	52.9	64.0	−66.4	−49.0	104.2	−73.1	30.1
3	−108.5	71.4	−70.7	108.0	−108.4	68.4	−68.0	110.3	557.1		72.5	−106.4	50.2	64.6	−60.2	−56.6	106.2	−70.0	35.4
4	−105.3	69.9	−75.2	114.6	−105.3	69.9	−75.2	114.6	580.4		76.4	−106.4	51.7	62.8	−64.1	−49.1	103.7	−77.2	53.3
5	−118.7	50.9	−54.6	123.4	−119.5	59.2	−62.6	126.9	454.4		51.8	−115.5	62.9	62.9	−59.6	−69.4	115.2	−49.2	−40.1
6	−116.7	55.2	−64.0	131.2	−116.8	54.3	−63.0	130.8	472.9		52.1	−116.8	62.5	67.7	−61.9	−72.1	115.6	−48.0	−59.2
	1,2-Alternate										1,3-Alternate									
1	112.1	−62.5	−15.9	84.5	−95.0	90.3	−48.0	−51.4	−114.5		64.1	54.7	−61.4	−57.1	64.4	53.5	−61.5	−56.4	−462.2
2	102.9	−81.7	20.9	59.7	−103.1	82.1	−18.9	−63.2	−199.9		66.1	55.5	−61.6	−59.0	67.6	54.7	−61.9	−57.7	−467.4
3	105.9	−77.1	2.8	72.7	−98.6	87.7	−39.1	−48.6	−139.2		65.3	56.8	−65.6	−57.4	63.1	58.5	−64.3	−56.7	−485.0
4	102.7	−82.8	20.1	60.2	−102.6	82.9	−20.3	−60.0	−199.8		66.9	56.1	−63.4	−57.3	66.9	56.1	−63.4	−57.3	−478.0
5	102.0	−94.7	67.0	10.3	−84.7	100.8	−29.6	−62.7	−92.0		66.1	57.0	−66.8	−57.1	64.7	58.4	−65.1	−56.6	−488.8
6	118.1	−41.6	−46.8	103.3	−91.6	98.7	−65.7	−55.9	−70.8		67.3	57.5	−57.5	−67.3	67.3	57.5	−67.3	−57.5	−498.9

[a] For the explanation see the text.

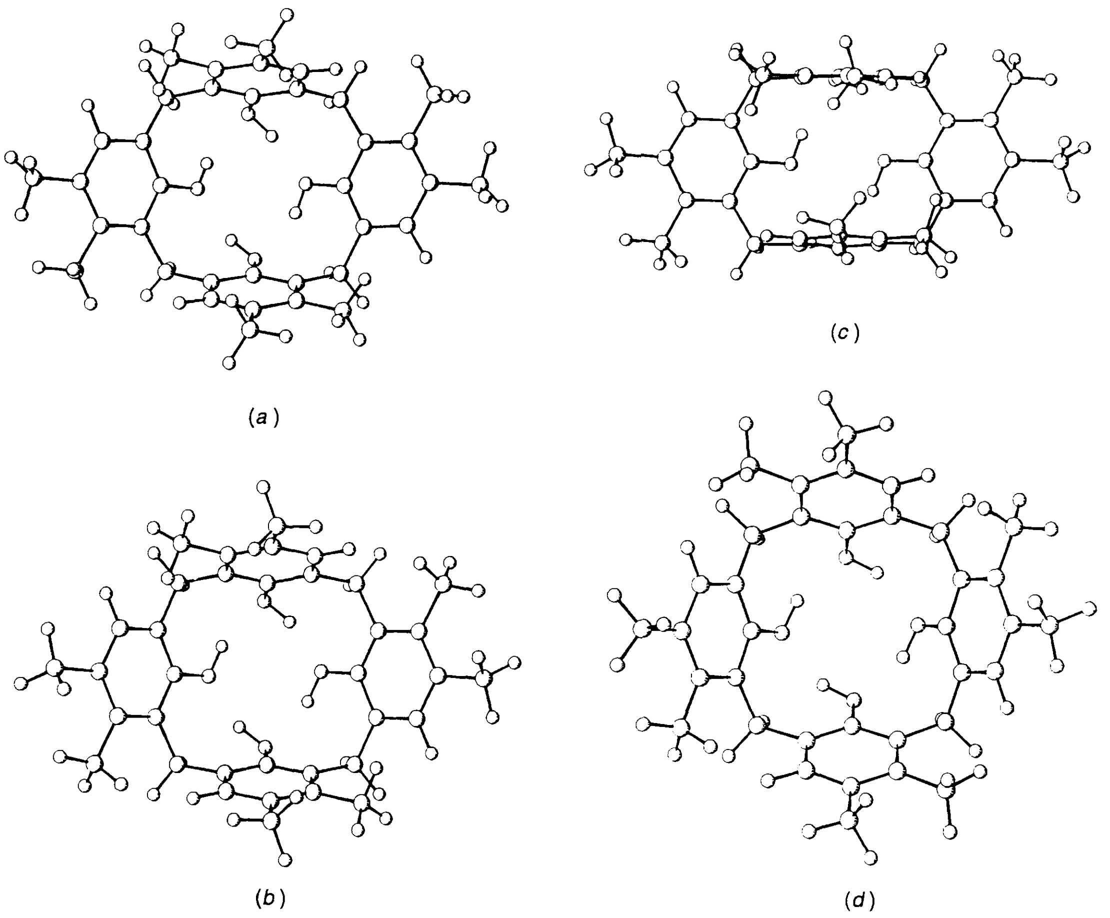

Fig. 2 Comparison of the conformers of the calix[4]arene **1** obtained by X-ray structure analysis (*a*) and by geometry optimisation with the TRIPOS (*b*) and MM2P (*c*) force fields as well as with the PM3 method (*d*)

cases' between the cone and partial cone, between the partial cone and 1,2-alternate as well as between the partial cone and 1,3-alternate conformations. A characteristic of all these 'borderline cases' is that at least one methoxy group points into the cavity. Similar structures are known from experimental data for the sodium and rubidium picrate complexes of calixcrowns and calixspherands[33] where the *p*-*tert*-butylcalix[4]arene moieties assume a conformation in between a cone and a partial cone conformation, often named 'flattened partial cone'. Its formation results probably from the coordination of the metal cation. Although the existence of such 'borderline cases' cannot be excluded in the case of the compounds **1**–**6**, their relative stability in comparison to the four main conformations seems to be overestimated by the force fields. Owing to close contacts between the positively charged hydrogen atoms of the methoxy groups and the negatively charged carbon atoms of the phenyl rings (the charges have been calculated topologically and do not depend on the geometry) the attractive electrostatic contribution of this interaction is overestimated. However, these kinds of conformers were also obtained from optimisations with the MM2P and AMBER force fields. In order to prove further the relative stability of these conformers with respect to the four main conformations we have recalculated these structures using the PM3 semiempirical molecular orbital method (see below).

For means of comparison we performed molecular mechanics calculations for the compounds **1**–**6** using the MM2P and for the 1,3-dimethyl ether **4** also using the AMBER force fields starting from the conformers obtained by the random conformational searching. The results of these calculations and geometric parameters of the lowest energy conformers are summarised in Tables 5 and 6.

The energy minimisations using the MM2P force field yielded the cone conformation as the most stable isomer for compounds **1**, **3** and **4** which is in accordance with the available experimental findings for compounds **1** and **4**. In contradiction to the experimental data an order of stability 1,3-alternate ~ partial cone > cone ~ 1,2-alternate is predicted for the monomethyl ether **2** and the order partial cone > 1,3-alternate > 1,2-alternate > cone for the tetramethoxy derivative **6**. For the trimethyl ether **5** the calculations yielded similar energies for the partial cone as well as the two alternate conformations and a higher energy for the cone conformer. Although this compound has not yet been synthesized it can be concluded from analogous derivatives that this predicted order of stability will not be confirmed by the experiment.

Calculations of the 1,3-dimethyl ether **4** with the AMBER force field yielded a cone conformer as the lowest energy structure. This is in accord with the experimental findings. However, starting from the geometries obtained by random conformational searching we found also numerous local energy minima for each conformational family differing not only in the position of the substituents but also in the torsion angles of the aryl–methylene bonds. The same was observed for calculations with the MM2P force field. The results of the AMBER calculations and geometric parameters of the lowest energy conformers are shown in Tables 5 and 6.

The examination of the geometric features of the conformers obtained with the MM2P force field revealed that the number of hydrogen bonds actually found is lower than the expected

Table 5 Relative energies of the lowest energy conformers obtained by using the MM2P(85) (**1**–**6**) and AMBER 3.0 A (**4**) force fields[a]

	MM2P						AMBER 3.0 A
Conformation	**1**	**2**	**3**	**4**	**5**	**6**	**4**
Cone	−8.97	−0.38	3.89	4.60	11.66	20.94	18.23
Partial cone	−7.33	−2.19	3.90	6.59	10.31	18.45	20.63
1,2-Alternate	−4.31	−0.31	5.76	8.14	10.18	18.80	21.50
1,3-Alternate	−6.72	−2.21	4.18	6.87	10.22	18.56	22.78

[a] All energies in kcal mol^{-1}.

number, especially for the calix[4]arene **1** and the monomethyl ether **2**. The lowest energy conformers exhibit only three and two hydrogen bonds, respectively. This results probably from the repulsion of the oxygen atoms as reported by Bayard *et al.*[2] As a consequence the cone conformers are extremely distorted in such a way that two phenolic rings are bent towards the cavity by an inclination angle δ of less than 90°. The comparison of the lowest energy conformer of the calix[4]arene **1** with the structure of the X-ray analysis for this compound showed a poor accordance: the inclination angles are 84.7° (105.0°), 154.6° (145.9°), 84.7° (117.2°) and 154.6° (149.3°) and the O • • • O distances are 3.07 (2.74), 3.08 (2.68), 3.03 (2.69) and 3.12 (2.70) Å (the values of the X-ray structure are in parentheses) (see Fig. 2).

Semiempirical Calculations.—Starting from conformers obtained by molecular mechanics we performed calculations with the semiempirical PM3 method. This was done in order to compare the energy sequence of the main conformations of each of the compounds **1**–**6** with those of the molecular mechanics calculations. Furthermore, we used at least two different geometries of each family of the main conformations as starting structures in order to investigate whether they will fall into the same local energy minimum on the one hand and if not, whether the energetically most stable conformer of each family corresponds to the energetically most stable conformer obtained by molecular mechanics calculations. Finally, we used 'borderline' conformers (see above) as starting geometries in order to compare their energies with those of the main conformational isomers.

The results of the PM3 calculations with respect to the lowest energy conformers are shown in Table 7. The analysis of the results yielded first that there exist several local energy minima for each of the four main conformations as with the molecular mechanics calculations. These minima differ geometrically mainly in the torsion angles of the aryl–methylene bonds and, unexpectedly, energetically by some kcal mol^{-1}. Second, in most cases the lowest energy structure obtained by molecular mechanics calculations is not the most stable conformer found using the PM3 method. A consequence of these two facts is that by using merely the lowest energy conformers of molecular mechanics calculations for the input of PM3 calculations this will frequently result in a wrong energy order of the main conformations.

For all of the calix[4]arenes the cone conformation is the lowest energy structure predicted by the PM3 method which corresponds to the experimental findings. The comparison of the X-ray structure of compound **1** with the calculated structure showed a poor accordance with respect to the geometric parameters: the rms value is 0.48 Å (see Fig. 2). This poor accordance results from the C_4-symmetry of the calculated lowest energy structure in contrast to the C_2-symmetry of the X-ray structure.

The examination of the results of the calculated borderline cases showed that the overall conformation was preserved, that is, the geometry has not changed to one of the main conformations. However, the energy differences to the main structures became quite large, thus underlining our assumption that these geometries are energetically overestimated by the force fields.

A Simple Approach to Describe the Conformation of Calix[4]*arenes.*—The conformations of calix[4]arenes are often described by a set of structural parameters, for instance by the inclination angles δ between the four phenolic units and the least-squares plane through the four methylene carbons. These angles differ markedly among the four conformations of the calix[4]arene derivatives.[34]

Ugozzoli and Andreetti[35] have proposed a new approach of assigning molecular conformations by use of pairs of torsion angles φ and χ around the $ArCH_2Ar$ bonds. Those torsion angles are—especially in the case of higher homologues of the calixarene family—the most unambiguous parameter to characterise a conformation.

However, for computational investigations it is often desirable to have a single value for the characterisation of the molecular conformation since *e.g.* as a result of random conformational searching as well as of a molecular dynamics simulation more than the lowest energy conformers of each of the four main conformations will be obtained. The distinction and subdivision into the main conformational families by means of comparison of the above mentioned inclination angles δ or the pairs of torsion angles φ and χ is rather time-consuming and impracticable for these purposes.

For the analysis of molecular dynamics simulations Grootenhuis *et al.*[3] have measured the distance between averaged positions of the oxygen atoms on the one hand and the methylene carbon atoms on the other hand as a function of time. The monitored distances are characteristic for the cone, partial cone and the alternate conformations (the latter are in the same range).

We used another approach to get a single value for the analysis of the conformers obtained by random conformational searching. Starting from the pairs of torsion angles φ and χ characterising the flexible calix[4]arene framework we have summed up the values of the φ and χ angles in different ways which eventually led to a single unique value for each conformation. (For the definition of the torsion angles φ and χ see earlier.) This can be illustrated in the following way. Taking into account the different combination of signs depending on the conformation according to the convention of Ugozzoli and Andreetti positive signs are replaced by +1 and negative signs by −1, respectively (Table 8).

If the absolute values of the sums of the φ_i and χ_i torsion angles are added ($|\Sigma\varphi_i| + |\Sigma\chi_i|$), different values for the cone, partial cone and the alternate conformations are obtained. However, the two alternate conformations cannot be distinguished. For this purpose, the φ_i and χ_i pairs are summed up and the sum of the absolute values is formed ($\Sigma|\varphi_i + \chi_i|$). Herewith, equal values are obtained for the partial cone and the

Table 6 Torsion angles φ and χ of the aryl–methylene bonds of the lowest energy conformers of the calix[4]arenes **1–6** calculated with the MM2P(85) and AMBER 3.0 A force fields

	Cone									Partial cone								
	φ	χ	φ	χ	φ	χ	φ	χ	$(\lvert\Sigma\varphi_i\rvert + \lvert\Sigma\chi_i\rvert) - \Sigma\lvert\varphi_i + \chi_i\rvert$	φ	χ	φ	χ	φ	χ	φ	χ	$(\lvert\Sigma\varphi_i\rvert + \lvert\Sigma\chi_i\rvert) - \Sigma\lvert\varphi_i + \chi_i\rvert$
1	−116.1	58.0	−58.4	118.4	−115.3	58.3	−58.0	119.3	465.5	61.8	−113.6	59.9	57.5	−55.6	−61.0	112.0	−62.3	22.1
2	−125.3	58.4	−56.1	115.5	−120.9	59.1	−57.0	118.4	461.2	61.9	−112.2	57.3	66.0	−59.4	−67.2	112.6	−59.5	−7.8
3	−121.3	52.9	−54.0	119.3	−115.8	60.8	−59.6	124.9	454.7	63.9	−110.6	63.6	57.2	−63.9	−63.4	121.1	−64.5	14.7
4	−116.9	55.5	−60.3	127.7	−117.5	53.8	−58.2	127.9	455.5	58.6	−115.1	69.1	56.6	−60.2	−62.2	121.2	−62.0	7.5
5	−117.4	59.2	−62.2	126.0	−119.0	52.5	−55.5	126.6	458.8	70.7	−111.4	43.3	69.0	−57.6	−58.0	110.9	−68.0	24.4
6	−119.2	64.8	−66.6	125.7	−119.5	62.2	−63.9	125.4	514.9	57.2	−117.4	75.4	62.8	−71.5	−65.2	123.1	−61.5	−31.2
4[a]	−106.1	57.1	−65.5	121.2	−106.1	57.1	−65.5	121.1	490.4	64.8	−106.6	48.7	64.5	−56.4	−63.9	113.2	−62.1	12.0
	1,2-Alternate									1,3-Alternate								
1	118.7	−64.2	−6.2	91.1	−116.6	69.2	−9.1	−80.3	−247.3	58.2	56.8	−58.3	−56.6	56.5	55.9	−58.3	−56.3	−458.7
2	112.5	−66.5	−11.4	96.1	−113.6	72.3	−25.3	−62.6	−183.1	66.5	53.1	−57.5	−55.8	59.9	56.3	−64.0	−58.3	−462.0
3	120.2	−64.7	−8.8	89.9	−111.3	82.4	−26.3	−73.3	−204.7	64.9	54.3	−57.3	−57.9	64.0	60.2	−70.3	−58.4	−484.2
4	120.9	−57.4	−17.1	98.6	−103.0	80.3	−41.4	−63.9	−174.6	66.2	55.6	−61.7	−59.7	65.6	55.3	−62.4	−59.0	−470.0
5	121.2	−61.9	−13.9	91.9	−92.5	100.6	−55.6	−64.4	−157.1	56.1	68.4	−57.9	−63.3	52.8	63.9	−56.0	−69.8	−482.2
6	115.3	−62.6	−11.8	96.5	−107.1	76.9	−86.1	−75.4	−204.1	47.9	63.7	−37.8	−70.1	44.5	62.1	−51.6	−56.6	−430.5
4[a]	106.0	−68.9	−6.6	76.6	−99.7	81.4	−19.6	−61.5	−159.0	50.0	65.8	−55.0	−60.1	50.0	65.8	−55.0	−60.1	−440.4

[a] Calculated with the AMBER force field.

Table 7 Heats of formation for the lowest energy conformers of compounds **1**–**6** calculated with the PM3 semiempirical molecular orbital method[a,b]

	1	2	3	4	5	6
Cone	−166.2	−149.7	−137.9	−138.4	−123.7	−108.6
Partial cone	−157.0	−145.4	−134.7	−133.7	−120.7	−107.7
1,2-Alternate	−151.8	−140.4	−130.7	−131.1	−119.8	−106.7
1,3-Alternate	−152.2	−141.3	−130.7	−130.4	−119.3	−107.8

[a] All heats of formation are in kcal mol^{-1}. [b] Since the PM3 calculations started with TRIPOS-calculated conformers they depend on them, however, at least two low-energy conformers of each family were used as starting structures.

Table 8

	φ	χ	φ	χ	φ	χ	φ	χ	$\lvert\Sigma\varphi_i\rvert + \lvert\Sigma\chi_i\rvert$	$\Sigma\lvert\varphi_i + \chi_i\rvert$	$(\lvert\Sigma\varphi_i\rvert + \lvert\Sigma\chi_i\rvert) - \Sigma\lvert\varphi_i + \chi_i\rvert$
Cone	+1	−1	+1	−1	+1	−1	+1	−1	8	0	8
Partial cone	+1	−1	+1	−1	+1	+1	−1	−1	4	4	0
1,2-Alternate	+1	−1	+1	+1	−1	+1	−1	−1	0	4	−4
1,3-Alternate	+1	+1	−1	−1	+1	+1	−1	−1	0	8	−8

Table 9 Determination of the conformation of calix[4]arenes by an unique value

Code[a]	Conformation	φ	χ	φ	χ	φ	χ	φ	χ	$(\lvert\Sigma\varphi_i\rvert + \lvert\Sigma\chi_i\rvert) - \Sigma\lvert\varphi_i + \chi_i\rvert$
DOGGAH	Cone	−73.8	114.1	−113.1	76.5	−73.8	114.7	−111.9	76.1	600.4
KOPPUA	Cone	89.5	−88.2	89.3	−92.0	91.7	−86.3	86.3	−89.3	700.2
SIGCIU	Cone	114.6	−74.7	68.9	−113.9	115.0	−81.8	75.5	−114.3	601.8
JIJHEP	Partial cone	119.1	−68.4	67.8	−112.6	62.2	64.0	−66.5	−59.9	11.4
KEVXUE	Partial cone	61.2	66.1	−62.9	−58.7	111.9	−68.2	69.0	−112.1	16.4
SIGCOA	Partial cone	−109.3	89.9	−45.3	−53.8	84.7	8.7	−75.8	112.1	54.4
FUTJUZ	1,2-Alternate	117.6	−92.6	38.8	67.8	−117.6	92.6	−38.8	−67.8	−263.2
VIVDUZ	1,2-Alternate	80.9	−116.3	57.4	58.2	−112.7	80.8	−40.5	−32.7	−231.2
FACBEQ10	1,3-Alternate	60.0	56.4	−57.7	−53.1	60.2	49.3	−53.3	−58.4	−433.4
FUTKEK	1,3-Alternate	65.4	45.6	−53.1	−53.1	45.6	65.4	−58.4	−58.4	−444.0
KOMTEL	1,3-Alternate	62.0	58.1	−60.5	−62.2	62.0	58.1	−60.5	−62.2	−474.4

[a] DOGGAH 5,11,17,23-tetra-*p*-*tert*-butyl-25,26,27,28-tetrakis(*tert*-butoxycarbonyl)methoxycalix[4]arene;[25] KOPPUA 5,11,17,23-tetraethyl-25,26,27,28-tetrahydroxycalix[4]arene;[29] SIGCIU 1,3-dimethoxy-*p*-*tert*-butylcalix[4]arene;[30] KEVXUE tetramethyl-*p*-*tert*-butylcalix[4]arene;[3] JIJHEP *p*-ethylthiocalix[4]arene methyl ether;[28] SIGCOA 1,3-bis(benzyloxy)-*p*-*tert*-butylcalix[4]arene;[30] FUTJUZ [*p*-*tert*-butylcalix[4]arene methyl ether][$MeAlMe_2]_2$;[36] VIVDUZ *p*-*tert*-butylethylcalix[4]arene dichloromethane solvate;[5] FACBEQ10 5-allyl-25-methoxy-26,27,28-tribenzoylcalix[4]arene;[26] FUTKEK (*tert*-butylcalix[4]arene methyl ether)-bis[dichloro(ethyl)aluminium];[36] KOMTEL 5,17-di-*tert*-butyl-25,27-bis(3,5-dinitrobenzoyloxy)-26,28-dihydroxycalix[4]arene.[37]

1,2-alternate conformations. By subtraction of the two sums $[(|\Sigma\varphi_i| + |\Sigma\chi_i|) - \Sigma|\varphi_i + \chi_i|]$, however, an unique value is obtained for each conformation.

We have examined 29 calix[4]arenes from the Cambridge Crystallographic Database in this respect. The ranges of the values obtained with the formula described above are 532–700° for the cone conformation (15 structures), −1–88° for the partial cone conformation (six structures), −263 and −231° for the 1,2-alternate conformation (two structures) and −316 to −573° for the 1,3-alternate conformation (six structures).

In Table 9 the efficiency of this method is illustrated by some example structures retrieved from the Cambridge Crystallographic Database.

The analysis of the torsion angles φ and χ and the calculation of the corresponding sums is easy to accomplish and hence very helpful for the processing of numerous data resulting *e.g.* from random conformational searching or MD simulations. Furthermore, we assume that this approach also may be used for the conformational characterisation of larger calix[*n*]arenes and their derivatives.

Conclusions

For the investigated calix[4]arenes **1**–**6** numerous local energy minima were found for the main conformations both with molecular mechanics and semiempirical calculations. These conformers differ mainly in the torsion angles around the methylene groups connecting the phenolic rings and hence in the energy. None of the four main conformations (cone, partial cone, 1,2- and 1,3-alternate) is characterised by a determined energy range of its local minima. In order to obtain the order of the relative stability of these conformations and to find the global energy minimum it is therefore necessary to carry out an extensive conformational search, *e.g.* by random conformational searching. The MM2P and TRIPOS force fields applied in our study were not reliable with respect to the reflection of the experimental data both regarding to the prediction of the most stable conformation and of the geometrical characteristics. By the adjustment of some TRIPOS parameters we could obtain a good correspondence between theoretical predictions and experimental findings. However, these parameters were changed especially in order to reflect the hydrogen bonding situation of the calix[4]arenes and are perhaps not optimal for tetra-*O*-substituted derivatives.

Several low-energy borderline structures lying geometrically in between the four main conformations were obtained by molecular mechanics calculations with the MM2P, TRIPOS and AMBER force fields for the methyl ethers **2**–**5**. Obviously, the force fields tend to overestimate the electrostatic interactions between the aromatic rings and the methoxy groups. The recalculation of these geometries by means of the semiempirical PM3 method yielded a substantially higher energy than those of the main conformations.

Experimental

The computational studies were done with the SYBYL[38] software (TRIPOS[39] and AMBER 3.0 A force fields) as well as with the MM2P(85)[40] force field. The programs were run on either an Evans and Sutherland 10 workstation, a Silicon Graphics Crimson VGXT or an IBM RISC/6000.

Each compound was subjected to a random conformational search of maximum 6000 cycles with an energy cut-off of 10 kcal mol^{-1} by using the RANDOMSEARCH routine of SYBYL. The default termination criteria of the TRIPOS force field were used for this search. The conformers obtained in this way served as starting structures for further energy minimisations using different force fields.

The optimisations using the TRIPOS and AMBER force field were performed with a distance-dependant dielectric with $\varepsilon = 1$ until the rms energy gradient was less than 0.001 kcal mol^{-1} Å^{-1} using the Powell minimiser included in the SYBYL/MAXIMIN2 routine. The Gasteiger–Hückel method[41] was used for the calculation of the partial charge distribution of the molecules. As recommended in the SYBYL manual for the AMBER minimisations the one-four-scaling factor applied to the 1–4 energy term was set to 0.5. Missing parameters were taken from ref. 3

For calculations with the MM2P(85) force field its default parameters and termination criteria were used. For the semiempirical calculations the PM3 Hamiltonian[42] in the MOPAC 5.0[43] package was used. The geometries were fully optimised using increased precision (keyword PRECISE) without applying any constants. Tables of calculated inclination angles and O···O distances have been deposited as supplementary data.*

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* For details of the Supplementary Publication Scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, 1994, issue 1. [Suppl. Publ. No. 57025 (7 pp.)].

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