Conformations of calix[5]arenes—a molecular mechanics study

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The conformational possibilities of *p*-methylcalix[5]arene 1 and its pentamethyl ether 2 have been assessed by means of molecular mechanics calculations using the TRIPOS and MM3 force fields. Starting from a comprehensive search of the energy hypersurface numerous low energy structures have been identified and analysed. The customary way of describing calixarene conformers by the 'up' and 'down' arrangement of the aromatic moieties relative to the reference plane through the methylene carbon atoms proved to be inappropriate to assign all computationally generated conformers. Instead, a simple algorithm for the classification of calix[5]arene conformers has been developed. The results of the molecular mechanics calculations are in reasonable agreement with the available experimental data in the case of MM3 but the TRIPOS force field fails to reproduce the stability of the cone conformation of 1. Molecular dynamics simulations indicate that the dynamic behaviour of 1 is characterised by the pseudorotation of the pentagon formed by the methylene carbon atoms on the one hand and by the well-known ring inversion process of calixarenes on the other.

Introduction

Calixarenes, a class of synthetic macrocycles derived from metacyclophanes, have elicited wide interest due to their use as building blocks for the construction of highly selective host molecules.[1] Computational methods, particularly molecular mechanics, have been used to study the conformational preferences of calix[4]arenes depending on the substitution pattern.[2] In contrast, little is known about the conformational possibilities of their five-membered homologues despite the fact that they are of interest as hosts for larger guest molecules.[3]

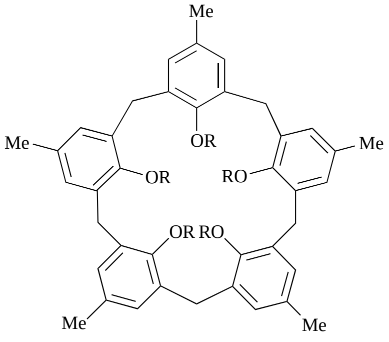
It is commonly assumed that calix[5]arenes exist in analogy to the calix[4]arenes in four basic conformations, namely the cone, partial cone (paco), 1,2-alternate (1,2-alt) and 1,3-alternate (1,3-alt).[4] However, very recently Harada and Shinkai[5] represented ten main conformations resulting from a systematic conformational search but they did not describe their energetical and geometrical characteristics in detail. In a comprehensive study on calix[5]arenes Gutsche and co-workers[6] pointed out the existence of other types of conformations resulting from the increased mobility of this calixarene system that show energetical stabilities comparable to those of the four basic structures. For the description of these conformers the authors introduced a notation which takes into account not only the up and down orientations of the phenolic units but also the canting of the aryl groups relative to the average plane defined by the methylene carbons or the Ar(1) aryl carbons.

In the present paper we report on a comprehensive investigation of the conformational preferences of *p*-methylcalix[5]arene **1** and its pentamethyl ether **2** by means of molecular mechanics calculations. We will demonstrate that due to the high flexibility of the compounds a multitude of low energy conformers exist and that these structures can be grouped into altogether 32 subclasses of the four basic conformations. In order to simplify the description of the conformations of calix[5]arenes we have developed a notation that allows the easy determination and assignment of conformers.

Results and discussion

Computational methods

A crucial point in the conformational analysis of highly flexible cyclic compounds is the choice of an appropriate method for the evaluation of the energy hypersurface. Since we recently showed for some calix[4]arene derivatives[2f,h] that by means of the RANDOMSEARCH procedure included in the SYBYL program it was possible to reproduce the experimental results both with respect to the energetical stabilities of the four main conformers and their geometrical shape, we applied this method also to the *p*-methylcalix[5]arene **1** despite the fact that it requires a long CPU time.† A total number of 175 low-energy conformers was obtained which were subsequently subjected to further energy minimisation using both the TRIPOS and the MM3(92) force field. The latter force field was additionally chosen since we could show[7] that it is most reliable in the reproduction of geometric properties of calix[*n*]arenes.



1 R = H
2 R = Me

In the case of the pentamethyl ether **2** a random conformational search proved to be unsuitable because of the additional degrees of conformational freedom introduced by the methoxy groups. Thus, we decided to use the minimised conformers of **1** as starting structures for the conformational search of **2**. For this purpose the 175 conformers obtained from the MM3 optimisation were assigned to 23 subclasses by structural similarity (superposition, comparison of O···O distances and dihedral angles). Their lowest energy conformers were converted into the pentamethoxy derivatives and partially optimised with respect to the arrangement of the ether groups using MM3. In order to determine possible orientations of the methoxy residues a

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† The random conformational search of **1** required a time of 3 months on a IBM/RISC 6000 workstation.

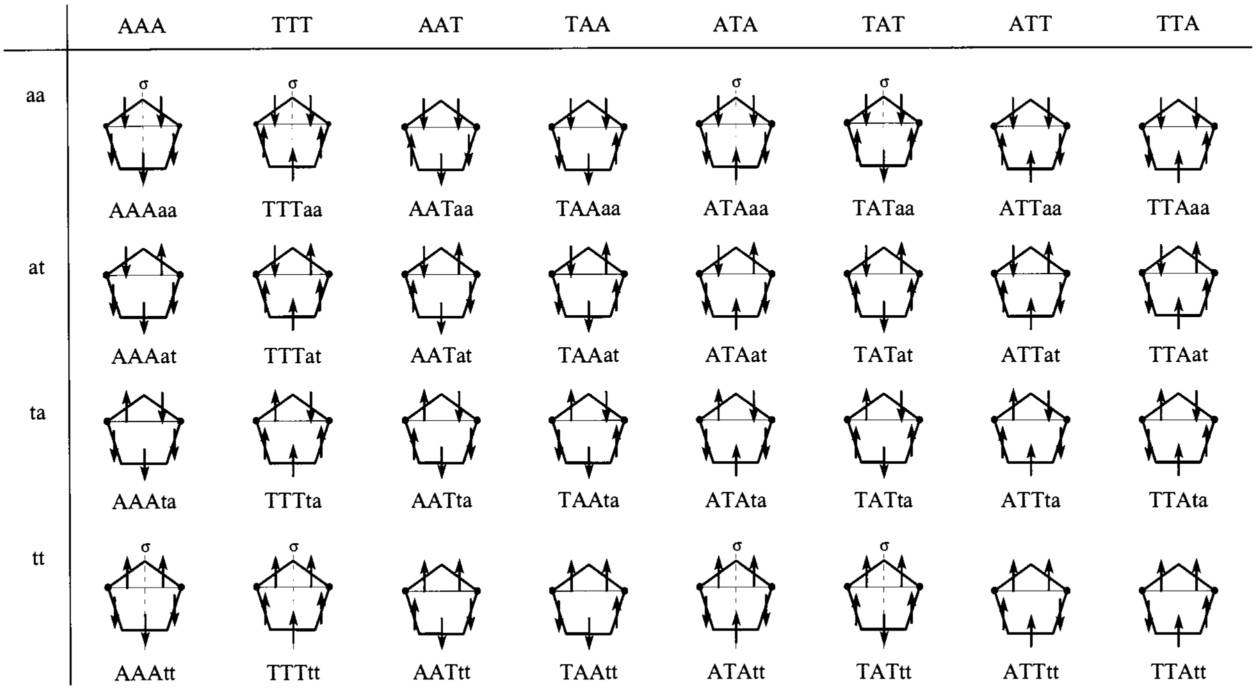

Fig. 1 Schematic representation of the possible conformations of calix[5]arenes. The major and minor planes are represented by a trapezium and a triangle, respectively. The letters 'T/t' and 'A/a' denote the position of the lower rim substituent, which is indicated by the arrowhead, relative to the concave region spanned by the two planes. The letter codes are given clockwise starting from the right-most vertex.

systematic search was performed by varying the dihedral angles of the C(Ar)–O ether bonds in increments of 30°. The thus obtained 26 070 crude structures were again partially optimised holding the calixarene scaffold fixed. For each of the 23 subclasses possible combinations of the dihedral angles of the five methoxy groups were determined by a statistical analysis of their distribution using a threshold of 30° for structural equivalence. The lowest energy structures of each of these combinations were finally optimised using both the TRIPOS and MM3 force field. From this approach 280 (MM3) and 333 (TRIPOS) unique conformers were obtained and analysed.

Classification of calix[5]arenes

The conformational searches of both the *p*-methylcalix[5]arene **1** and its methyl ether **2** afforded a multitude of low-energy conformers. This fact may be ascribed to the increased flexibility of the calix[5]arene scaffold compared to the calix[4]arenes. From a molecular dynamics simulation (*vide infra*) it can be concluded that the mutual coupling of the movements of aryl rings is less pronounced and, as a result, a single aryl unit can adopt different orientations by small variations of the dihedral angles to the adjoining methylene bridges without substantially affecting the arrangement of the other four aryl moieties. Moreover, manifold combinations of inward and outward orientations of the methoxy groups exist for compound **2**.

The analysis and classification of the conformers were additionally complicated by the fact that the five methylene carbons showed markedly large deviations from a mean plane (see also Tables 2–5). In the case of the parent calix[4]arenes this reference plane is commonly used for the description of conformers which differ in the orientation and inclination angles of the aryl moieties. A classification of conformers by a simple up/down arrangement of the aryl rings with respect to an average plane seemed inappropriate or even impossible for **1** and **2**.

It was found, however, that four of the five methylene carbons are reasonably close to a common plane in all minimum energy conformations. In order to analyse and to classify the conformers, we used therefore two planes for the structural description, as proposed earlier by Shinkai and co-workers for calix[6]arenes[5] and for the semi-1,2-alt conformation[2d] of calix[4]arenes. Among the five possible planes through four methylene carbon atoms that with the lowest root mean square (rms) deviation was chosen as the major plane and the remaining methylene carbon together with its two adjoining methylene carbons were used to define the minor plane. The interplanar angle may be considered as either <180° (concave region) or >180° (convex region). The calix[5]arene conformations can be determined *e.g.* by means of the orientation of the lower rim substituents to the concave region. If a substituent points to the concave region the arrangement of the aryl moiety is denoted with the uppercase or lowercase 'T/t' depending whether it belongs to the major or minor plane, respectively. Otherwise, the arrangement is correspondingly denoted with the uppercase or lowercase 'A/a' to indicate that the substituent is pointing away from this region. Altogether 32 conformations result from this notation which are illustrated in Fig. 1. Several conclusions can be deduced from this representation. (i) For five equally substituted aromatic moieties in a calix[5]arene the following letter codes characterise pairs of enantiomers (regardless of the value of the interplanar angle and of the tilt of the aromatic moieties): AATaa–TAAaa, ATTaa–TTAaa, AAAat–AAAta, TTTat–TTTta, AATat–TAAta, TAAat–AATta, ATAat–ATAta, TATat–TATta, ATTat–TTAta, TTAat–ATTta, AATtt–TAAtt, ATTtt–TTAtt. (ii) Conformations in which uppercase and lowercase are exchanged by their counterparts (*e.g.* AATaa–TTAtt) differ only in the sign of the interplanar angle of the two reference planes. (iii) From the pseudo planar representation in Fig. 1 the assignment of the 32 individual conformations to four basic calixarene conformations is easy to accomplish:

cone: AAAaa, TTTtt
paco: AATaa, TAAaa, ATAaa, AAAat, TTTat, AAAta, TTTta, TATtt, ATTtt, TTAtt
1,2-alt: TTTaa, ATTaa, TTAaa, TAAat, TTAat, AATta, ATTta, AAAtt, AATtt, TAAtt
1,3-alt: TATaa, AATat, ATAat, TATat, ATTat, TAAta, ATAta, TATta, TTAta, ATAtt

In order to prove the applicability of the method we have considered the calix[5]arenes available in the Cambridge Structural Database.[8] However, among the currently twenty calix-

[5]arenes only three adopt other conformations than the cone in the crystal (Table 1). The conformations of YOFLAG and YOFLEK have been described[6] as 1,2-alt which is consistent with the classification developed in this paper, while Fukazawa and co-workers[9] assigned WEJYOZ to a paco conformation which is in contradiction to the 1,2-alt TTAat arrangement obtained from the description by two planes. In fact, due to the folded arrangement of the five methylene carbons the 1,2-alt conformation becomes obvious only when this plane is bisected as described above.

Table 1 Conformations of selected calix[5]arenes from the Cambridge Structural Database

Refcode[a]	rms deviation/Å[b]	Conformation
BIMXIE	0.12	cone AAAaa
KUPTUK	0.20	cone TTTtt
PEMRAA	0.31	cone TTTtt
SOVJES	0.14	cone TTTtt
WEJYOZ	0.93	1,2-alt AAAtt
YOFLAG	0.30	1,2-alt TTTaa
YOFLEK	0.23	1,2-alt AATta
YOFLIO	0.43	cone TTTtt

[a] Compounds are coded according to names in the files of the CSD: BIMXIE 25,26,27,28,29-pentahydroxycalix[5]arene bis(acetone) clathrate[10]; KUPTUK 5,11,17,23,29-penta-*tert*-butyl-31,32,33,34,35-pentahydroxycalix[5]arene tetralin ethanol solvate[11]; PEMRAA penta-*tert*-butylpentakis(ethoxycarbonylmethoxy)calix[5]arene[12]; SOVJES 5,11,17,23,29-pentakis(1,1,3,3-tetramethyl-*n*-butyl)-31,32,33,34,35-pentahydroxycalix[5]arene toluene clathrate[13]; WEJYOZ 5,11,17,23,29-pentamethyl-35-deoxy-31,32,33,34-tetrahydroxycalix[5]arene; YOFLAG 5,11,17,23,29-penta-*tert*-butyl-31,32,33,34,35-penta-2-propoxycalix[5]arene; YOFLEK 5,11,17,23,29-penta-*tert*-butyl-31.32.33.34.35-penta-allyloxycalix[5]arene; YOFLIO 5,11,17,23,29-penta-*tert*-butyl-31-*n*-propoxy-32,33,34,35-tetrahydroxycalix[5]arene hexane solvate.[6]
[b] Root mean square deviation of the five methylene carbon atoms from planarity.

Stabilities and geometries of the conformations of 1 and 2

Tables 2 and 3 summarise the results of the molecular mechanics calculations on the *p*-methylcalix[5]arene **1**.

For the four basic conformations the calculations with MM3 predict the order of relative stabilities cone >1,2-alt > paco > 1,3-alt. This sequence roughly parallels the number of possible hydrogen bonds: 5 for the cone, 3 for the 1,2-alt and the paco conformations as well as 1 for the 1,3-alt conformation. The lowest energy 1,2-alt structure (AATtt) is stabilised over the paco conformation by the formation of an additional hydrogen bond between adjacent phenolic rings pointing into opposite directions but assume a flattened arrangement ‡ relative to their reference planes which results in a helical orientation of the hydrogen bonding system. Furthermore, with the exception of this conformer the energy differences among the four basic conformations are only somewhat lower than those of the corresponding calix[4]arene derivatives (*e.g. p-tert*-butylcalix[4]-

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‡ The term 'flattened' is used in this paper for the arrangement of an aromatic moiety if the absolute value of the inclination angle between the plane of the aromatic ring and its reference plane is larger than 130°.

Table 2 Relative energies (kcal mol^{-1}) and geometric parameters of the lowest energy conformers of **1** obtained with the MM3 force field

Conformation	Code[a]	ΔE	rms1/Å[b]	rms2/Å[c]	τ/°[d]	Plane angle/°[e]			Plane angle/°[f]	
cone	AAAaa	0.0	0.00	0.00	0.0	124.5	124.3	124.5	124.4	124.4
1,2-alt	AATtt	2.9	0.83	0.26	53.5	133.3	99.8	−72.2	−95.8	−148.5
	AAAtt	5.0	1.02	0.05	68.1	141.1	106.0	137.2	−153.3	−102.8
	TTTaa	9.2	0.42	0.10	−26.5	67.6	144.7	81.4	−127.0	−117.1
	TTAat	18.9	0.62	0.23	−37.0	71.0	132.1	−142.6	−90.2	104.3
	TTAaa	21.1	0.68	0.27	−40.4	65.7	128.5	−144.7	−101.9	−129.0
paco	TATtt	5.2	0.35	0.12	−22.4	89.9	−91.0	95.1	126.4	117.2
	AATaa	5.3	0.37	0.06	24.5	146.8	100.9	−82.9	109.5	138.5
	TTAtt	9.4	0.84	0.09	−55.0	64.4	148.6	−114.5	149.9	97.2
	ATAaa	14.9	0.32	0.01	19.9	169.6	−95.0	84.3	157.9	94.2
1,3-alt	TATat	10.9	0.44	0.14	−28.2	74.5	−90.1	106.2	89.0	−103.2
	TATaa	11.1	0.42	0.10	−27.4	72.1	−74.2	77.8	−124.7	−121.8
	AATat	14.6	1.24	0.36	80.5	142.3	80.6	−50.6	151.9	−112.1
	TTAta	15.3	1.09	0.29	−68.4	156.7	102.3	−114.0	110.1	−167.1
	ATAtt	16.8	0.57	0.19	35.0	101.3	−96.1	110.3	−164.2	−96.3

[a] From the pairs of enantiomers (see text) only one code is given here. [b] Root mean square deviation of the five methylene carbon atoms from a mean plane. [c] Root mean square deviation of the four methylene carbon atoms from the major plane. [d] Interplanar angle between the two reference planes. [e] Interplanar angles between the planes of the aromatic rings and the major plane. [f] Interplanar angles between the planes of the aromatic rings and the minor plane.

Table 3 Relative energies (kcal mol^{-1}) and geometric parameters of the lowest energy conformers of **1** obtained with the TRIPOS force field[a]

Conformation	Code	ΔE	rms1/Å	rms2/Å	τ/°	Plane angle/°			Plane angle/°	
1,2-alt	AATtt	0.0	1.10	0.31	71.7	145.6	83.4	−62.4	−101.5	−140.8
	AAAtt	0.9	1.19	0.10	81.6	147.1	66.3	146.6	−126.3	−124.3
	TTTaa	2.0	0.58	0.13	−37.1	59.2	149.4	75.8	−115.3	−129.4
	TTAaa	8.0	0.70	0.29	−41.4	55.2	125.4	−141.7	−109.7	−128.8
	TTAat	8.8	0.78	0.34	−45.8	57.5	126.6	−137.2	−90.1	104.6
cone	AAAaa	0.7	0.00	0.00	0.0	123.5	123.3	123.5	123.4	123.4
paco	AATaa	2.1	0.57	0.16	34.9	154.2	92.8	−67.9	112.1	133.4
	TATtt	2.8	1.08	0.07	−81.2	67.4	−69.0	68.8	161.8	68.4
	TTTat	4.7	0.43	0.05	−26.6	52.5	148.7	80.9	94.9	−97.9
	TTAtt	4.9	0.90	0.09	−58.8	65.0	124.9	−104.6	144.5	91.5
1,3-alt	TATaa	2.6	0.62	0.06	−40.2	65.0	−81.1	71.5	−123.0	−121.2
	ATAtt	6.5	0.42	0.09	27.4	93.9	−77.5	78.5	−165.8	−63.8
	AATat	7.4	1.32	0.38	85.7	149.2	71.8	−50.4	156.8	−112.8
	TTAta	8.3	0.99	0.09	−57.0	156.8	84.4	−99.6	136.7	117.7
	ATAat	17.1	0.59	0.05	31.8	81.8	−84.9	70.8	142.4	−145.5

[a] For footnotes see Table 2.

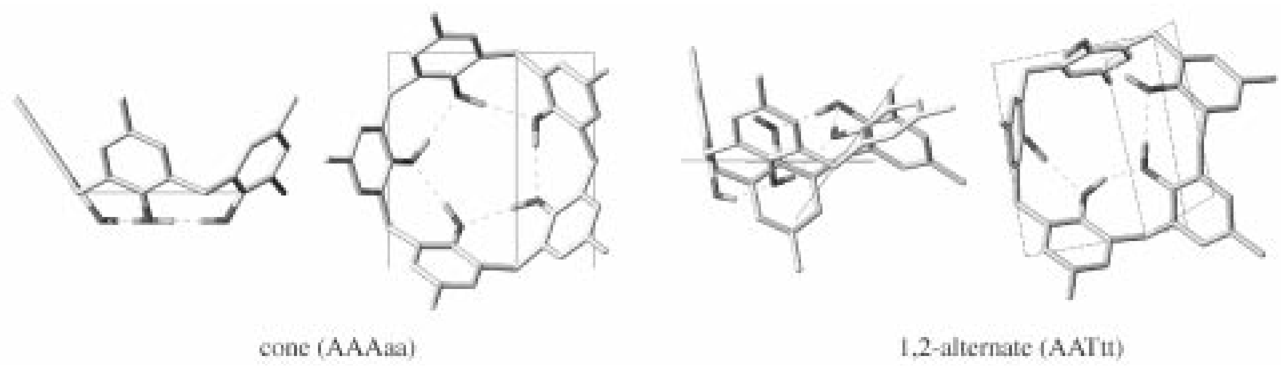

Fig. 2 Top and side views of the geometries of the lowest energy cone and 1,2-alt (AATtt) conformers of **1** calculated with the MM3 force field. The structures are oriented such that the major and minor plane (represented by thin lines) are on the left and right-hand side, respectively. Hydrogen atoms bonded to carbon have been omitted for clarity.

arene[14] cone 0.0, paco 6.0, 1,2-alt 7.7, 1,3-alt 11.3 kcal mol^{-1}§).

The calculations with the TRIPOS force field show some differences compared to the MM3 results.¶ The energetical order of the basic conformations cone and 1,2-alt is reversed, the 1,2-alt (AATtt) arrangement with four hydrogen bonds as described above represents the global energy minimum. In contrast to the MM3 calculations the energy differences between the basic conformations are rather small which would suggest the coexistence of conformers under experimental conditions. Both are in obvious contradiction to the experimental observations that pentahydroxycalix[5]arenes exist both in solution[1] and in the crystalline state (*e.g.* refs. 10, 11, 13) exclusively in the cone conformation.

The results of the molecular mechanics calculations of the pentamethyl ether **2** are listed in Tables 4 and 5. Again, the order of the relative stabilities of the four basic conformations is different among the two force fields: while MM3 predicts the order 1,3-alt > paco > 1,2-alt > cone, from the TRIPOS calculations the order 1,2-alt > paco > 1,3-alt > cone was obtained. However, in both cases the energy differences are relatively small and should suggest the presence of various conformers under experimental conditions. Indeed, Gutsche and coworkers[6] have stated the existence of a mixture of conformers for the pentamethoxy derivative of *p-tert*-butylcalix[5]arene from NMR investigations at low temperature.

The structures of the lowest energy conformers obtained by MM3 represented in Fig. 3 indicate that within the paco and the two alternate conformations very distinct structures exist dependent on the position of the anisole rings relative to the two reference planes and their inclination angle τ. In contrast to the pentahydroxy derivative **1** where the calixarene skeleton of the most stable cone conformer adopts a nearly regular C_5-symmetrical shape the cone conformation of **2** assumes two unsymmetrical structures in which the five lower rim substituents are pointing either towards or away from the concave region spanned by the reference planes. A nearly C_5-symmetrical structure has a steric energy of 12.9 kcal mol^{-1} above the global minimum, which means that the stabilisation of this regular cone conformation in **1** is entirely due to the cyclic array of hydrogen bonds. This fact is underlined by the structures of the lower rim substituted calix[5]arenes PEMRAA and YOFLIO (Table 1) which show among the cone conformers the largest deviations from a regular shape.

The comparison of the low energy structures obtained with both force fields revealed that the geometries of the calixarene scaffold are very similar in most cases but that the orientations of the methoxy groups differ peculiarly. The conformers calculated with the TRIPOS force field are in general characterised by strong interactions between the methoxy groups and the aromatic rings. Obviously, attractive van der Waals interactions of these groups are overestimated in this force field. This fact might also be responsible for the different order of stabilities among the four basic conformations with the two force fields. The low energy structures calculated with MM3 frequently reveal the self-inclusion of one or more methoxy groups within the cavity but in comparison with calix[4]arenes this should be attributed to the larger cavity size of the calix[5]arenes compared to their four-membered homologues.‖**

Molecular dynamics simulations

In order to gain an insight into the dynamic behaviour of the pentahydroxycalix[5]arene **1** we performed a molecular dynamics simulation of 2.5 ns of one isolated molecule at 300 K *in vacuo*. These simulation conditions were chosen to allow the observation of conformational interconversions since in the gas phase the rate of such processes is drastically increased compared to the experimental timescale.

Visual inspection of the MD movie showed that two different processes are characteristic for the dynamic behaviour of **1**. The first consists of the pseudorotation of the 'imaginary' pentagon formed by the five methylene carbons which corresponds to that known from cyclopentane.[16] Since this process exchanges the reference planes which bisect the pentagon it interconverts the different subclasses of a given basic conformation (*e.g.* paco AATaa $\rightleftharpoons$ AAAta). The pseudorotation proceeds very fast and no single conformer could be observed over a longer time period thus pointing to low energy barriers.

The second process comprises the rotation of phenolic rings and interconverts the four basic conformations. Fig. 4 shows that during the first 0.2 ns the molecule interconverts several times between the cone and paco conformations but a stable paco conformation (characterised by a plateau) is only reached at the end of this period. After 0.2 ns the molecule starts interconverting between the paco and the 1,3-alt conformation, the latter is maintained only over a short period around 0.37 ns. These two interconversions dominate in the dynamic behaviour of **1** over a period of 2 ns. Although several stable cone, paco and 1,3-alt conformations exist over a certain space of time no

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§ 1 cal = 4.184 J.

¶ Depending on the force field used, not all possible conformers have been obtained from the conformational searches. Their manual generation followed by force field optimisation resulted in conformations different from the starting structure which would suggest that these conformers do not represent local minima on the energy hypersurface in the context of the given force field.

‖ MM3 calculations of the tetramethylether of *p-tert*-butylcalix[4]arene[15] have shown that for this compound 'all-out' orientations of the methoxy groups are energetically favourable.

** Supplementary data (SUPPL NO. 57282, 9 pp.) are available from the British Library. For details of the Supplementary Publications Scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 2*, 1997, Issue 1.

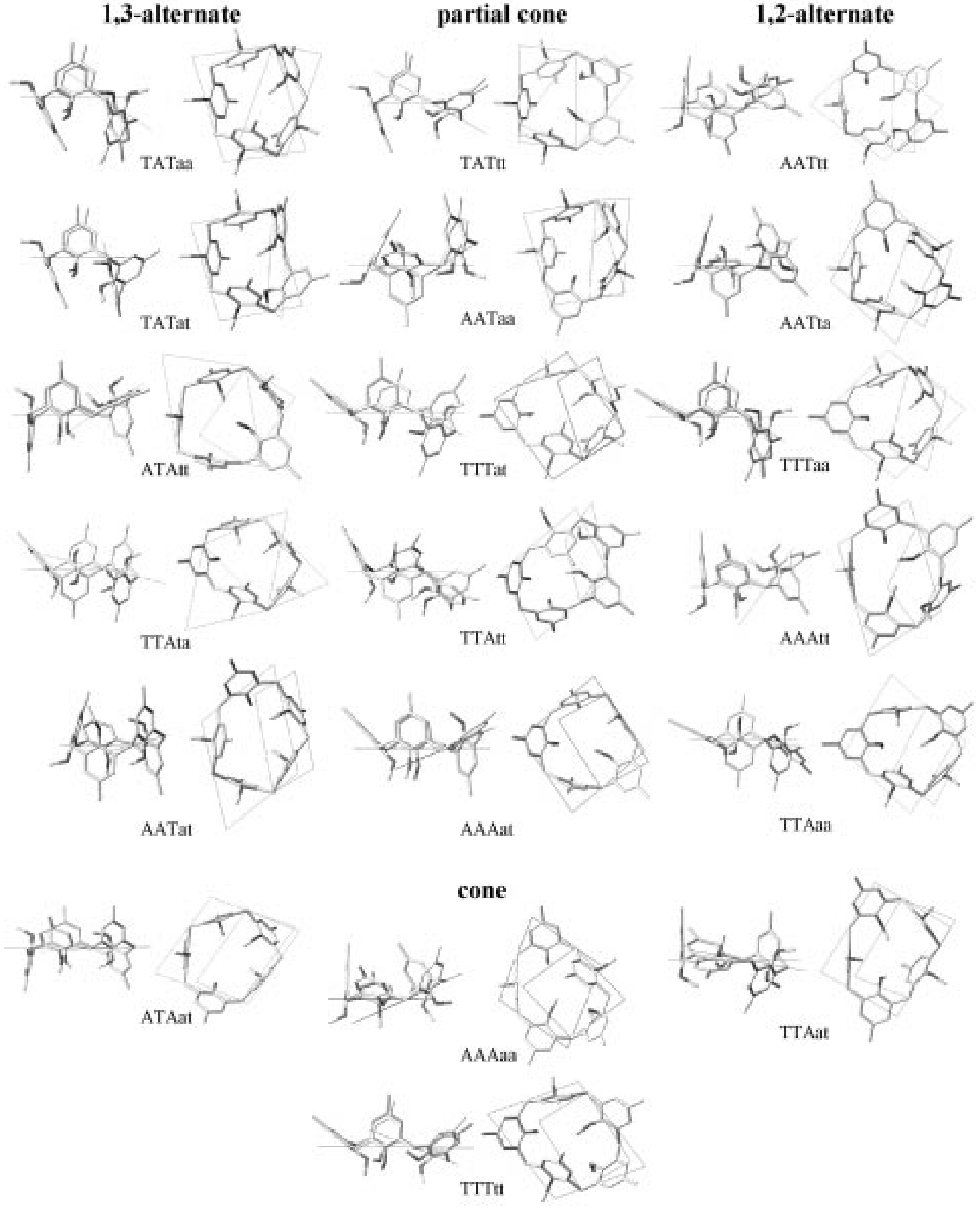

Fig. 3 Top and side views of the geometries of the low energy conformers of **2** calculated with the MM3 force field. The structures are oriented analogously to Fig. 2.

complete inversion transforming the cone conformation into its mirror image could be observed. Between 2.0 and 2.2 ns the molecule oscillates between the paco and the 1,2-alt conformations and neither of the two conformations is stabilised. The reason for this behaviour can be sought in the geometry of the two states. Both are characterised by a strongly flattened orientation of a phenolic ring so that a slight movement of this ring causes the switch between the two conformational extremes. After this period the 1,2-alt conformation seems to be stable until the end of the dynamics simulation. However, the visual inspection of the MD movie showed that this apparent stability results from a dynamic process in which in a continuing process the rotation of a phenolic ring produces another 1,2-alt topomer.

Table 4 Relative energies (kcal mol^{-1}) and geometric parameters of the lowest energy conformers of **2** obtained with the MM3 force field[a]

Conformation	Code	ΔE	rms1/Å	rms2/Å	τ/°	Plane angle/°			Plane angle/°	
1,3-alt	TATaa	0.0	0.50	0.13	−34.7	59.1	−62.0	72.9	−139.6	−104.0
	TATat	2.4	1.03	0.10	−74.0	72.6	−67.0	61.6	69.0	−177.0
	ATAtt	5.5	0.54	0.13	33.0	101.6	−91.7	103.7	−69.4	−168.4
	TTAta	6.2	0.21	0.05	−13.3	66.7	127.7	−101.5	89.5	−93.6
	AATat	6.2	0.21	0.06	15.4	132.1	72.4	−84.4	107.5	−90.0
	ATAat	14.6	0.06	0.02	4.0	95.7	−95.8	127.9	97.6	−105.4
paco	TATtt	1.6	0.41	0.01	−29.1	72.4	−68.3	64.3	112.1	128.4
	AATaa	3.0	0.46	0.12	32.2	152.5	61.9	−74.6	135.6	107.7
	TTTat	3.2	0.44	0.14	−26.7	50.0	139.1	88.9	102.3	−94.5
	TTAtt	5.2	0.87	0.05	−54.6	43.0	117.3	−116.5	146.7	95.3
	AAAat	10.0	0.36	0.11	22.5	106.8	133.0	97.8	167.3	−71.2
1,2-alt	AATtt	1.8	0.91	0.30	56.9	133.6	83.7	−59.1	−91.9	−148.3
	AATta	2.1	0.57	0.13	35.8	166.2	72.4	−75.1	−99.7	101.5
	TTTaa	2.4	0.52	0.18	−34.4	60.4	148.0	77.1	−136.3	−103.1
	AAAtt	3.8	0.81	0.00	55.1	130.4	93.0	135.8	−149.5	−61.5
	TTAaa	6.2	0.20	0.05	−12.4	65.1	153.1	−95.4	−153.6	−90.4
	TTAat	6.3	0.18	0.07	−12.0	144.4	88.7	−157.1	−74.4	77.7
cone	AAAaa	3.2	0.38	0.08	24.2	148.6	87.3	147.8	138.5	78.8
	TTTtt	3.6	0.33	0.11	−21.1	81.9	141.1	59.9	115.1	130.5

[a] For footnotes see Table 2.

Table 5 Relative energies (kcal mol^{-1}) and geometric parameters of the lowest energy conformers of **2** obtained with the TRIPOS force field[a]

Conformation	Code	ΔE	rms1/Å	rms2/Å	τ/°	Plane angle/°			Plane angle/°	
1,2-alt	AATta	0.0	0.62	0.03	39.6	173.9	67.6	−69.9	−91.8	103.8
	AATtt	1.5	0.27	0.08	21.1	125.3	75.3	−84.8	−129.5	−74.2
	AAAtt	1.6	0.85	0.22	59.0	134.2	81.3	143.2	−156.5	−52.6
	TTAaa	1.6	0.25	0.07	−15.0	59.2	168.7	−85.9	−147.7	−89.2
	TTTaa	2.0	0.38	0.12	−25.1	73.1	140.5	61.1	−109.0	−125.2
	TTAat	8.1	0.45	0.10	−26.5	50.1	126.3	−134.2	−91.0	113.0
paco	TTAtt	1.8	0.77	0.13	−48.0	58.7	167.9	−90.5	152.2	79.6
	AAAat	2.0	0.38	0.04	27.4	125.0	68.2	163.3	96.5	−76.3
	TATtt	2.4	0.65	0.04	−47.4	71.3	−75.6	68.7	137.8	83.9
	AATaa	2.6	0.54	0.07	38.0	171.9	65.1	−74.0	127.7	103.9
	TTTat	2.6	0.43	0.07	−26.1	75.6	160.3	63.2	100.3	−98.3
1,3-alt	TATat	2.4	0.59	0.04	−38.3	173.9	−71.9	82.3	88.6	−97.8
	ATAtt	2.5	0.45	0.13	30.6	89.2	−79.7	103.6	−70.0	−149.7
	TATaa	2.7	0.24	0.03	−16.8	78.5	−96.9	76.2	−108.1	−121.8
	AATat	3.9	0.23	0.02	17.0	125.8	80.5	−91.9	98.7	−79.5
	TTAta	4.7	1.05	0.14	−60.1	152.6	84.9	−110.1	128.4	−125.0
cone	TTTtt	2.5	0.31	0.03	−20.2	66.5	143.5	66.9	124.3	108.8
	AAAaa	2.6	0.32	0.04	21.6	163.7	76.8	138.7	128.0	82.5

[a] For footnotes see Table 2.

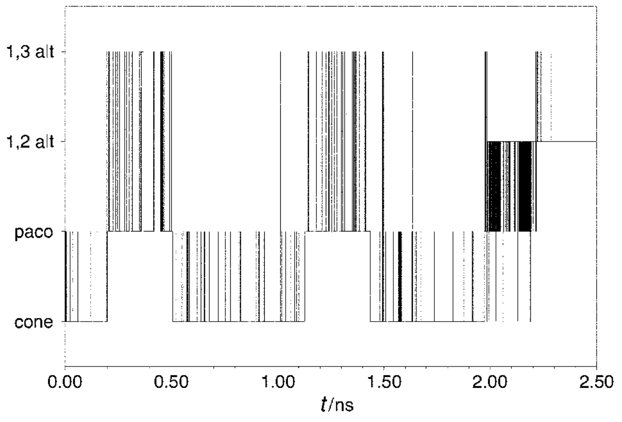

Fig. 4 Schematic representation of the evolution of conformations in the time course of the molecular dynamics simulation of **1**

Interestingly, some direct interconversions from the cone to one of the alternate conformations are detectable in Fig. 4. They are again caused by extremely flattened arrangements of two phenolic rings in both conformations so that slight movements of these rings result in another conformation.

Conclusions

The conformational possibilities of calix[5]arenes have been investigated for two model compounds by means of molecular mechanics calculations. Due to the enhanced flexibility compared to their four-membered homologues calix[5]arenes can adopt a multitude of conformations. This may also be considered in terms of the lower mutual coupling of the orientations of the aromatic moieties compared to the parent calix[4]arenes. The conformational description of calix[5]arenes is easy to accomplish by means of two reference planes.

The dynamic behaviour of *p*-methylcalix[5]arene is characterised by the pseudorotation of the folded pentagon formed by the methylene carbon atoms and the ring inversions of the phenolic units. Both processes are fast on the MD timescale but with increasing size of the substituents not only should the ring inversion process be hindered but also the pseudorotation leading to several discrete structures for a given basic conformation.

Computational details

All calculations were performed on either SGI Crimson or IBM RISC/6000 workstations. For the search procedures as well as for the visualisation and analysis of the results the corresponding modules of the SYBYL program[17] were used. The molecular mechanics calculations were carried out with the TRIPOS (version 5.2)[18] and the MM3(92)[19,20] force fields. Within the TRIPOS force field we used some modified parameters[2f] and a partial charge distribution calculated according to the Gasteiger–Hückel method.[21] The optimisations were performed using the Powell-minimiser included in the MAXIMIN2 routine until the cut-off value for the rms energy gradient of 10^{-3} kcal mol^{-1} Å^{-1} was reached. The optimisations with the MM3 force field were carried out using the block diagonal Newton–Raphson scheme for energy minimisation to the default termination values followed by one step of full-matrix Newton–Raphson minimisation to check the eigenvalues of the Hessian matrix.

For the random conformational search procedure a maximum number of 25 000 cycles with an energy cut-off of 25 kcal mol^{-1}, a rms gradient of 0.01 kcal mol^{-1} Å^{-1} as well as a maximum number of 1000 iterations per optimisation were chosen. The systematic search of the methoxy group orientations in **2** was performed using an increment of 30° with a scaling factor of 0.6 for the van-der-Waals radii. Neither charges nor energies were taken into consideration in this step.

The molecular dynamics simulations were carried out using the MD module of SYBYL which is based on the TRIPOS force field. The interval length was 2.5 ns at a temperature of 300 K using a time step of 1 fs. The co-ordinates were saved every 25 fs. The SHAKE algorithm was applied to constrain all bonds involving hydrogen to their equilibrium length.

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