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Computational Studies of Calix[4]arene Homologs: Influence of 5,11,17,23- and 25,26,27,28-Substituents on the Relative Stability of Four Conformers

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Abstract: The effects of 5,11,17,23- and 25,26,27,28-substitutents on the relative stability of four conformers of calix[4]arene are discussed on the basis of a computational method using molecular mechanics (MM3) calculations. It is shown that a substituent in the lower rim site has a decisive role in the determination of the stability order among four conformers of calix[4]arene, while a substituent in the upper rim site only slightly affects the energy differences. It is also shown that in [1_4]metacyclophanes with no substituent in the lower rim the structure of 1,2-alternate conformers is very different from the typical 1,2-alternate structure common to calix[4]arenes.

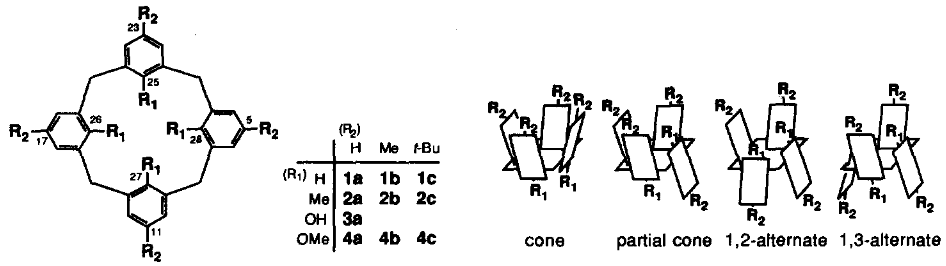
Introduction

Computational studies of conformational isomerism in calix[n]arenes and their analogs have been of much recent concern.[1-6] Among them, a calix[4]arene family draws particular interest because calix[4]arenes consist of a 16-membered ring but involve only four significant conformers, cone, partial cone, 1,2-alternate and 1,3-alternate.[7,8] The limitation in the conformational freedom has been attributed to the rigid metacyclophane framework.[7-9] In 1990, Grootenhuis *et al.*[3] reported extensive computational studies on calix[4]arenes using several force fields. They succeeded in the computational elucidation of several characteristics of calix[4]arenes. A few but essential observations, however, remained unexplainable. In the case of calix[4]arene-25,26,27,28-tetrol, for example, calculations by AMBER 3.0 predict that the energy difference between cone and other three conformers is greater than 7 kcal mol^{-1} whereas the results of MM2 predict that the difference is only

0.96 - 3.18 kcal mol^{-1}.[3] While, the ^{1}H NMR studies show that in most solvents only cone exists.[7] The discrepancy means that the exceptional stability of the cone form, which arises from intramolecular hydrogen-bonding interactions, is not adequately reproduced by MM2. Also misinterpreted is the relative stability of 25,26,27,28-tetramethoxycalix[4]arene and its *p-tert*-butyl derivative. Both AMBER 3.0 and MM2 predict that the relative stability of four conformers appears in the order of 1,3-alternate (most stable) > partial cone > cone > 1,2-alternate (least stable).[3] In contrast, the experimental findings reveal that cone and partial cone are more stable than 1,2-alternate and 1,3-alternate.[2,10,11]

A lot of discussions have been given about calix[4]arenes, both from experimental[3,10-16] and computational[1-6] perspectives. However, relatively few reports considered partially or completely OH-depleted species, namely [1_4]metacyclophanes.[17,18] The use of a molecule without hydroxyl groups as a model for calix[4]arene may be questionable.[19] However, [1_4]metacyclophanes represent an interesting class of compounds closely related to calix[4]arenes and the computational modelling of their structures and conformational equilibria should bring important insights into the role of the [1_4]metacyclophane framework and 5,11,17,23- and 25,26,27,28-substituents in calix[4]arenes themselves.[20] Potential energy surfaces of calix[4]arenes are very complex and except one attempt[4] there is no solid computational report describing the full picture (all stationary points with their optimized energies) for their significant interconversion pathways. As mentioned above, [1_4]metacyclophanes are the right model compounds for such studies. Moreover, the weakness of computational methods applied to the studies of the relative stability among calix[4]arene conformers has been pointed out repeatedly.[1-6,19] We considered, therefore, that it must be essential to test these techniques on model compounds where the complex factors like hydroxyl groups are absent.

The purpose of this work is to study the influence of 5,11,17,23- and 25,26,27,28-substituents on the relative stability of the four calix[4]arene conformers based on molecular mechanics calculations. We discuss the relative stability of calix[4]arene conformers in terms of calculated potential energies. We also point out the significant differences in the results produced by molecular mechanics (MM3) and semi-empirical molecular orbital methods (AM1 and PM3). We chose structures **1** through **4** as models for our computational study (scheme 1). All the structures have [1_4]metacyclophane framework (**1a**) in common. We placed substituents symmetrically on the metacyclophane frame in positions 5,11,17,23 and 25,26,27,28. Four (**1c**, **3a**, **4a** and **4c**) of them are known and the results obtained in our previous molecular mechanics study for **4a** and **4c** agree reasonably well with experimental findings.[21]



(R1) \ (R2)	H	Me	t-Bu
H	**1a**	**1b**	**1c**
Me	**2a**	**2b**	**2c**
OH	**3a**		
OMe	**4a**	**4b**	**4c**

Scheme 1

Computational Technique

Two computational approaches were used in this work: a molecular mechanics technique (MM3)[22] and semi-empirical molecular orbital methods (AM1 and PM3)[23] implemented in the MOPAC ver.6 program.[24] ANCHOR II[25] was used to model the structures as well as to analyze the results of the calculations. The structures were first pre-optimized with MM2(77)[26] force field in its BIGSTRN3[27] implementation. MOLGRAPH[28] was also used to analyze the calculated structures. In MM3 calculations a block-diagonal Newton-Raphson method was used followed by full-matrix Newton-Raphson optimization wherever possible.

All possible conformations were generated with BIGSTRN3 program followed by MM3 optimizations. The four families of conformations, cone, partial cone, 1,2-alternate and 1,3-alternate, are represented here by the lowest energy conformer. In MOPAC calculations the MM3-optimized structures were used as starting points in geometry optimizations. Since the conformational search for all possible rotamers within each family was not conducted with AM1 and PM3 methods, it was assumed that the MM3 calculated structures represent the global energy minima within each family. In this respect the results of AM1 and PM3 calculations are MM3-dependent.

Results and Discussion

The MM3-calculated relative potential energies and 'effective symmetries' of the four main conformational isomers of [1_4]metacyclophane derivatives are given in Table 1. The term 'effective symmetry' here means the symmetry of the [1_4]metacyclophane framework regardless of substituents. There are several ways in which the conformation of a calix[4]arene molecule can be described. In Tables 2-1(a-c) through 2-4(a-c) we summarize the conformational features of **1-4** obtained with MM3, including the inclination of the phenyl rings with respect to the best plane of the methylene groups chosen as a reference plane, bond angles between neighboring phenyl rings centered on the methylene carbon atoms, and the distances between the distal methylene carbon atoms. Tables containing contributions to MM3 energy terms of the calculated structures as well as the results of AM1 and PM3 methods, are given in the supplementary material. Drawings of the MM3 optimized structures of some compounds are also shown in Figure 1.

Table 1. MM3-calculated relative energies(E)[a] and 'effective symmetries'(PG)[b] of the four main conformers of [1$_4$]metacyclophane derivatives.

	R$_1$	R$_2$	Cone		Partial Cone		1,2-Alternate		1,3-Alternate	
			E	PG	E	PG	E	PG	E	PG
1a	H	H	0.00	C$_{4v}$	1.16	C$_s$	1.77	C$_1$	1.67	D$_{2d}$
1b	H	Me	0.00	C$_{4v}$	1.10	C$_s$	1.76	C$_1$	1.27	D$_{2d}$
1c	H	*t*-Bu	0.00	C$_{4v}$	1.04	C$_s$	4.66	C$_1$	2.70	D$_{2d}$
2a	Me	H	8.48	C$_{2v}$	4.52	C$_s$	5.46	C$_{2h}$	0.00	D$_{2d}$
2b	Me	Me	7.97	C$_{2v}$	4.44	C$_s$	5.54	C$_{2h}$	0.00	D$_{2d}$
2c	Me	*t*-Bu	5.94	C$_{2v}$	2.09	C$_s$	3.80	C$_{2h}$	0.00	D$_{2d}$
3a	OH	H	0.00	C$_{4v}$	9.85	C$_s$	11.65	C$_i$	18.65	D$_{2d}$
4a	OMe	H	0.27	C$_{2v}$	0.00	C$_s$	4.10	C$_{2h}$	1.50	D$_{2d}$
4b	OMe	Me	0.69	C$_{2v}$	0.00	C$_s$	4.52	C$_{2h}$	1.64	D$_{2d}$
4c	OMe	*t*-Bu	1.50	C$_{2v}$	0.00	C$_s$	6.08	C$_{2h}$	1.46	D$_{2d}$

[a] Energies in kcal mol^{-1}. [b] Symmetry point group of the metacyclophane framework regardless the orientation of the substituent.

Table 2-1a: Geometries of MM3 optimized structures for **1a** : R$_1$=H, R$_2$=H

	Cone	P.C.	1,2-Alt.	1,2-Alt.[e]	1,3-Alt.
Plane Angle[c] /deg					
Ph_1	53.7	-88.3	-72.9	-60.4	-87.8
Ph_2	53.7	77.5	-61.7	-48.8	87.8
Ph_3	53.7	33.5	-17.3	-1.1	-87.8
Ph_4	53.7	77.5	81.8	93.7	87.8
Angle /deg					
Ph_1-CH_2-Ph_2	113.2	113.6	112.7		112.6
Ph_2-CH_2-Ph_3	113.2	112.8	113.8		112.6
Ph_3-CH_2-Ph_4	113.2	112.8	114.6		112.6
Ph_4-CH_2-Ph_1	113.2	113.6	114.4		112.6
Distance[d] /Å					
C(1,2)-C(3,4)	7.15	7.14	6.91		7.12
C(2,3)-C(4,1)	7.15	7.14	7.05		7.12

Table 2-1b: Geometries of MM3 optimized structures for **1b** : R$_1$=H, R$_2$=Me

	Cone	P.C.	1,2-Alt.	1,2-Alt.[e]	1,3-Alt.
Plane Angle[c] /deg					
Ph_1	54.0	-88.4	-73.2	-60.8	-90.9
Ph_2	54.0	79.3	-61.8	-49.0	90.9
Ph_3	54.0	32.9	-17.8	-1.9	-90.9
Ph_4	54.0	79.2	82.5	101.6	90.9
Angle /deg					
Ph_1-CH_2-Ph_2	113.1	113.4	112.6		112.0
Ph_2-CH_2-Ph_3	113.1	112.7	113.7		112.0
Ph_3-CH_2-Ph_4	113.1	112.7	114.6		112.0
Ph_4-CH_2-Ph_1	113.1	113.4	114.2		112.0
Distance[d] /Å					
C(1,2)-C(3,4)	7.14	7.13	6.91		7.10
C(2,3)-C(4,1)	7.14	7.13	7.05		7.10

Table 2-1c: Geometries of MM3 optimized structures for **1c** : R_1=H, R_2=*tert*-Bu

	Cone	P.C.	1,2-Alt.	1,2-Alt.^{e}	1,3-Alt.
Plane Angle^c /deg					
Ph_1	58.4	-87.9	-74.5	-59.3	-82.6
Ph_2	58.4	89.9	-64.8	-49.2	82.6
Ph_3	58.4	34.6	-14.9	9.7	-82.6
Ph_4	58.4	81.8	68.3	82.1	82.6
Angle /deg					
Ph_1-CH_2-Ph_2	112.1	112.2	112.9		113.7
Ph_2-CH_2-Ph_3	112.1	112.2	113.9		113.7
Ph_3-CH_2-Ph_4	112.1	111.4	114.5		113.7
Ph_4-CH_2-Ph_1	112.1	113.3	115.7		113.7
Distance^d /Å					
C(1,2)-C(3,4)	7.14	7.08	6.83		7.03
C(2,3)-C(4,1)	7.14	7.14	6.96		7.03

Table 2-2a: Geometries of MM3 optimized structures for **2a** : R_1=Me, R_2=H

	Cone	P.C.	1,2-Alt.	1,3-Alt.
Plane Angle^c /deg				
Ph_1	104.3	-82.8	-66.4	-75.7
Ph_2	43.5	86.7	-66.4	75.7
Ph_3	104.3	43.4	66.4	-75.7
Ph_4	33.5	86.7	66.4	75.7
Angle /deg				
Ph_1-CH_2-Ph_2	111.7	115.0	113.8	116.8
Ph_2-CH_2-Ph_3	111.7	112.7	113.6	116.8
Ph_3-CH_2-Ph_4	112.4	112.7	113.8	116.8
Ph_4-CH_2-Ph_1	112.4	115.0	113.6	116.8
Distance^d /Å				
C(1,2)-C(3,4)	7.22	7.26	6.79	7.26
C(2,3)-C(4,1)	7.22	7.26	7.77	7.26

Table 2-2b: Geometries of MM3 optimized structures for **2b** : R_1=Me, R_2=Me

	Cone	P.C.	1,2-Alt.	1,3-Alt.
Plane Angle^c /deg				
Ph_1	102.0	-84.2	-67.0	-76.1
Ph_2	44.7	88.1	-66.9	76.1
Ph_3	102.0	42.9	66.8	-76.1
Ph_4	34.8	88.1	67.1	76.1
Angle /deg				
Ph_1-CH_2-Ph_2	111.7	114.7	113.2	116.7
Ph_2-CH_2-Ph_3	111.7	112.7	118.1	116.7
Ph_3-CH_2-Ph_4	112.5	112.7	113.2	116.7
Ph_4-CH_2-Ph_1	112.5	114.7	118.1	116.7
Distance^d /Å				
C(1,2)-C(3,4)	7.23	7.25	6.87	7.26
C(2,3)-C(4,1)	7.23	7.25	7.69	7.26

Table 2-2c: Geometries of MM3 optimized structures for **2c** : R_1=Me, R_2=*tert*-Bu

	Cone	P.C.	1,2-Alt.	1,3-Alt.
Plane Angle^c /deg				
Ph_1	91.0	-82.5	-66.6	-75.6
Ph_2	50.9	84.2	-66.6	75.7
Ph_3	92.2	47.5	66.5	-75.7
Ph_4	52.7	84.1	66.4	75.6
Angle /deg				
Ph_1-CH_2-Ph_2	112.4	115.1	113.8	117.0
Ph_2-CH_2-Ph_3	112.1	112.5	117.5	117.0
Ph_3-CH_2-Ph_4	112.6	112.5	113.8	116.9
Ph_4-CH_2-Ph_1	111.8	115.3	117.5	117.0
Distance^d /Å				
$C_{(1,2)}$-$C_{(3,4)}$	7.22	7.26	6.78	7.26
$C_{(2,3)}$-$C_{(4,1)}$	7.27	7.24	7.75	7.26

Table 2-3a: Geometries of MM3 optimized structures for **3a** : R_1=OH, R_2=H

	Cone	P.C.	1,2-Alt.	1,3-Alt.
Plane Angle^c /deg				
Ph_1	55.9	-75.1	-60.8	-76.9
Ph_2	55.9	69.1	-53.7	76.9
Ph_3	55.9	43.0	60.8	-76.9
Ph_4	55.9	70.3	53.7	76.9
Angle /deg				
Ph_1-CH_2-Ph_2	113.0	117.4	111.9	115.9
Ph_2-CH_2-Ph_3	113.0	112.6	120.8	115.9
Ph_3-CH_2-Ph_4	113.0	112.2	111.9	115.9
Ph_4-CH_2-Ph_1	113.0	117.0	120.8	115.9
Distance^d /Å				
$C_{(1,2)}$-$C_{(3,4)}$	7.25	7.22	6.96	7.22
$C_{(2,3)}$-$C_{(4,1)}$	7.25	7.24	7.53	7.22

Table 2-4a: Geometries of MM3 optimized structures for **4a** : R_1=OMe, R_2=H

	Cone	P.C.	1,2-Alt.	1,3-Alt.
Plane Angle^c /deg				
Ph_1	83.3	-94.0	-63.8	-88.2
Ph_2	44.5	94.5	-63.8	88.1
Ph_3	83.3	32.3	63.8	-88.2
Ph_4	44.5	94.5	63.8	88.3
Angle /deg				
Ph_1-CH_2-Ph_2	113.4	113.6	114.2	115.1
Ph_2-CH_2-Ph_3	113.4	113.6	119.4	115.1
Ph_3-CH_2-Ph_4	113.4	113.6	114.2	115.1
Ph_4-CH_2-Ph_1	113.4	113.6	119.4	115.1
Distance^d /Å				
$C_{(1,2)}$-$C_{(3,4)}$	7.19	7.16	6.71	7.18
$C_{(2,3)}$-$C_{(4,1)}$	7.19	7.16	7.70	7.18

Table 2-4b: Geometries of MM3 optimized structures for **4b** : R_1=OMe, R_2=Me

	Cone	P.C.	1,2-Alt.	1,3-Alt.
Plane Angle[c] /deg				
Ph_1	83.2	-93.9	-63.7	-88.4
Ph_2	44.5	94.3	-63.7	88.2
Ph_3	83.2	32.2	63.7	-88.3
Ph_4	44.6	94.4	63.7	88.4
Angle /deg				
Ph_1-CH_2-Ph_2	113.6	113.8	114.4	115.2
Ph_2-CH_2-Ph_3	113.5	113.8	119.6	115.1
Ph_3-CH_2-Ph_4	113.6	113.8	114.4	115.1
Ph_4-CH_2-Ph_1	113.6	113.8	119.6	115.1
Distance[d] /Å				
C(1,2)-C(3,4)	7.18	7.16	6.71	7.17
C(2,3)-C(4,1)	7.19	7.16	7.70	7.18

Table 2-4c: Geometries of MM3 optimized structures for **4c** : R_1=OMe, R_2=*tert*-Bu

	Cone	P.C.	1,2-Alt.	1,3-Alt.
Plane Angle[c] /deg				
Ph_1	83.1	-91.9	-63.7	-88.0
Ph_2	44.5	88.7	-63.7	87.8
Ph_3	83.1	34.1	63.7	-87.9
Ph_4	44.5	89.2	63.7	88.0
Angle /deg				
Ph_1-CH_2-Ph_2	113.5	114.9	114.5	115.0
Ph_2-CH_2-Ph_3	113.5	114.1	119.4	115.1
Ph_3-CH_2-Ph_4	113.5	114.4	114.5	115.1
Ph_4-CH_2-Ph_1	113.5	114.4	119.4	115.2
Distance[d] /Å				
C(1,2)-C(3,4)	7.18	7.19	6.69	7.18
C(2,3)-C(4,1)	7.17	7.14	7.70	7.17

[c] Dihedral angle between the phenyl plane and the mean plane of four methylene carbons.

[d] Distance between two distal methylene carbons: C(*x*,*y*) indicates the methylene carbon connecting Ph*x* and Ph*y*. [e] Dihedral angle between the phenyl plane and the 'new reference plane' (see scheme 2).

Results of MM3 Calculations. All studied compounds are divided into four classes reflecting four different orders of stability among cone, partial cone, 1,2-alternate and 1,3-alternate conformers on potential energy surface. In the MM3 calculations they appear as follows:

1) R_1=H; R_2=H, Me, *tert*-Bu :**1a,1b,1c**

cone (most stable) > partial cone > 1,3-alternate > 1,2-alternate (least stable)

2) R_1=Me; R_2=H, Me, *tert*-Bu :**2a,2b,2c**

1,3-alternate (most stable) >> partial cone > 1,2-alternate >> cone (least stable)

3) R_1=OH; R_2=H :**3a**

cone (most stable) >> partial cone > 1,2-alternate >> 1,3-alternate (least stable)

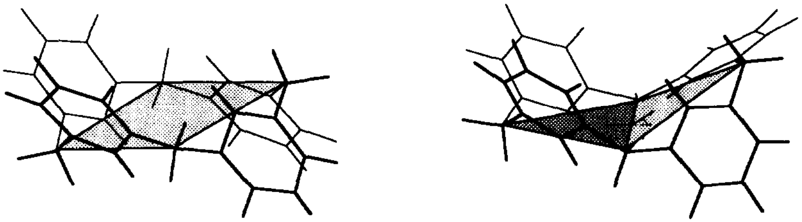
4) R_1=OMe; R_2=H, Me, *tert*-Bu :**4a**,**4b**,**4c**
partial cone (most stable) > cone > 1,3-alternate >> 1,2-alternate (least stable)

The stability order depends on the R_1-substituent in the lower rim site, but is much less affected by the R_2-substituent in the upper rim site. This fact indicates that the R_1-substituent has a decisive role in determining the relative order of stability among the four conformers. Cone is the most stable on the MM3 conformational potential energy surface among compounds with no substituent in the lower rim (**1**). Introduction of methyl groups into the lower rim (**2**) results in relative destabilization of cone and stabilization of 1,3-alternate. It is well known that in calix[4]arene-25,26,27,28-tetrol (**3**), OH groups play a special role: strong intramolecular hydrogen-bonds are formed among four OH groups.[3] Cone is largely stabilized by this four cyclic hydrogen-bonds. Furthermore, the order of stability among four conformers correlates well with the number of expected hydrogen-bonds: cone=4, partial cone=2, 1,2-alternate=2 and 1,3-alternate=0. When hydroxy protons are replaced with methyl groups (**4**), the strong stabilization factor (hydrogen-bonds) disappears. For this series, partial cone is the most stable conformer.

The R_2-substituent in the upper rim seems to have a minor effect on the order of stability, but affects the energy differences between conformers: the degree of this effect depends on the type and size of the substituent. The presence of four methyl substituents in the upper rim (**1b**) has very little effect on the relative stability of the conformers when compared with [1_4]metacyclophane (**1a**). The *tert*-butyl substitution in the upper rim (**1c**) destabilizes 1,2- and 1,3-alternate conformers to some extent. Geometries of the metacyclophane framework are slightly affected (compare the inclinations of the phenyl rings with respect to the reference plane in Table 2), but the effective symmetries are preserved among the four conformers, namely C_{4v}, C_s, C_1 and D_{2d} for cone, partial cone, 1,2-alternate and 1,3-alternate, respectively.

The '1,2-alternate' conformer in the series **1a** through **1c** deserves special attention here due to its unique geometry (C_1 symmetry point group). Strictly speaking, it does not resemble a typical 1,2-alternate conformation common to calix[4]arene, wherein the inclination of all the phenyl rings with respect to the methylene reference plane varies between 50°-70°, all having more or less similar values (Tables 2-2abc, 2-3a, 2-4abc). In the MM3 calculated 1,2-alternate structures of **1** one of the phenyl rings is inclined more towards the methylene reference plane than three other: its angle varys between 15°-17°.

The inclination of the phenyl ring with respect to the reference plane, defined as a mean plane of the four methylene carbon atoms, is commonly used in the literature as a conformational descriptor in calix[4]arene derivatives. In most cases all four methylene carbon atoms are in one plane, *i.e.* the angle between planes defined by any two opposite methylene carbon atoms and one each of the remaining, is nearly zero. In the present semi-1,2-alternate conformations (**1**) this is no longer true. The two planes are inclined about 30° (in **1a**-1,2-alternate is 34°) (scheme 2) and that is why in these cases the inclination of the phenyl ring with respect to the reference plane (mean plane of the four methylene carbons) cannot be directly compared with the corresponding angles in non-1,2-alternate structures. To do so, however, we can use a different conformational descriptor for this semi-1,2-alternate structures. We divide the molecule into two parts along the line connecting two opposite methylene carbons so that two of the four phenyl rings can be on the same side of the reference plane (scheme 2). In each substructure the angle between phenyl ring and the plane defined by the three methylene carbon atoms can be directly compared to the angle between the phenyl ring and the reference plane in other structures. In Table 2-1a,b,c it can be seen that in these semi-1,2-alternate structures one of the phenyl ring is nearly parallel to the plane defined by three methylene carbons.



Conventional mean plane for typical-1,2-alternates 'New reference plane' for **1a**, **1b** and **1c**

Scheme 2

It is interesting to note that **1c** exists in the crystal in a 1,2-alternate conformation possessing C_i molecular symmetry, where one pair of opposite phenyl rings is inclined more than the other (29° and 84°).[18] It is not surprising, however, that in the crystal **1c** appears in a different conformation other than it would appear in gas phase or in solution. In molecules with such a plenty of conformational freedom the crystal conformation is very often determined by the crystal packing force. Additional fact is also interesting: before starting MM3 optimizations, we attempted to describe the MM2 potential energy surface of **1a**, that is to locate not only the energy minima but also the transition state structures. On the MM2 potential energy surface the 1,2-alternate conformer of **1a** possesses also C_1 symmetry (having the same geometry as the MM3 calculated metacyclophane framework in **1a**, **1b** and **1c**), but the 1,2-alternate conformation possessing C_i symmetry appeared as a transition state structure connecting the two C_1 minima. Interestingly, the C_i transition state structure on MM2 potential energy surface of **1a** resembles the conformation of **1c** found in the crystal. We also attempted to establish the relative stability among conformers of **1c** by 300MHz ^{1}H NMR spectroscopy, however, with no success: we measured the spectra in CD_2Cl_2 at various temperatures (-90°C to 25°C) but all signals appeared in singlets. This shows that the barrier to conformational interconversion is apparently very low and the process is faster than the NMR time scale, even at -90°C.

The presence of methyl substituents in the lower rim strongly destabilizes only the cone conformer, it is manifested by the symmetry change from C_{4v} in **1** to C_{2v} in **2**. Moreover, the 1,2-alternate conformer of **2** appears now in typical 1,2-alternate geometry common to calix[4]arenes (C_{2h}).

In the series of structures with methoxy groups in the lower rim (**4**) neither methyl nor *tert*-butyl substitution in the upper rim changes the effective symmetries of the conformers in **4a** through **4c**, which are C_{2v}, C_s, C_{2h} and D_{2d} for cone, partial cone, 1,2-alternate and 1,3-alternate, respectively. The methyl and *tert*-butyl groups in the upper rim destabilize cone and 1,2-alternate structures, with larger substituent bringing bigger effect. We have already reported the results of

MM3 calculations on **4a** and **4c**, and compared them to the data from ^{1}H NMR spectroscopy.[21] Both, from experiment and calculations, partial cone appears to be the most stable conformer. Moreover the MM3-calculated energy differences between partial cone and cone of **4a** and **4c** agree well with experimental findings.[21]

What are the driving forces of these changes? Detailed examination of the structural data and energy terms (Supplementary material) reveals that in the series of compounds with no substituent in the lower rim (**1**) the greater stability of cone conformers is attributed to lower values in the torsional energy term, lower by 2 - 3 kcal mol^{-1} when compared to the same term in other conformers. Introduction of methyl groups into the lower rim (**2**) reverses the stability order, so that 1,3-alternate becomes the most stable and cone the least stable, mainly owing to increase in torsional contributions in cone species amounting to 7 - 9 kcal mol^{-1}. This happens because the presence of the four methyl substituents in cone brings large non-bonded repulsion in the lower rim region, and the conformation changes from C_{4v} symmetry in **1** to C_{2v} in **2**. This, in turn, affects the torsional energy term.

The MM3 calculated structure and energetics of calix[4]arene-25,26,27,28-tetrol (**3a**) is also of great interest: how well can the method (MM3) reproduce the contribution of intramolecular hydrogen-bonding interactions? The correlation between the stability order and the number of formed hydrogen-bonds has already been mentioned. The distances between hydrogen and oxygen atoms of neighboring hydroxyl groups are 1.75 Å, 1.77 Å and 1.79 Å in cone, partial cone and 1,2-alternate conformers of **3a**, respectively (the corresponding distances between two oxygen atoms are 2.61 Å, 2.64 Å and 2.73 Å). These values lie between the limits of normal hydrogen-bonding distances determined experimentally.

Note on the results of AM1 and PM3 Calculations. The MM3-optimized structures were recalculated with AM1 and PM3 semi-empirical molecular orbital schemes. It appeared that the results of these calculations (Suplementary material) are quite different from those of MM3. Despite all the differences the results produced by AM1 are similar to those of MM3 while the results of PM3 are quite different from the two other methods. Intrigued by this very different behavior of PM3 (where for instance **2a** through **2c** appear in cone as the most stable among conformers), we checked the geometries of **1** - **4** produced by all three methods. We found that PM3 produces the structures with very short H/H nonbonded distances in compounds with methyl or *tert*-butyl substituents, some of them being as short as 1.7 Å.

To see what are the reasons for these short H/H distances, we performed a test to see how the potential changes when two methane molecules are brought together from a distance in a fixed D_{3h} symmetry. The PM3 gave a minimum at 1.73 Å while AM1 in 2.24 Å. This large difference in behavior of these two semi-empirical schemes is apparently responsible for the difference in the order of stability among the four conformations of **1** - **4** studied here. The exaggerated attractive interaction between protons in PM3 is responsible for these surprising discrepancies: the cone conformation appears as the most stable species in the methyl-substituted [1_4]metacyclophane in the lower rim (**2a** through **2c**), just opposite to the results of both MM3 and AM1 calculations. This is an apparent drawback of the PM3.

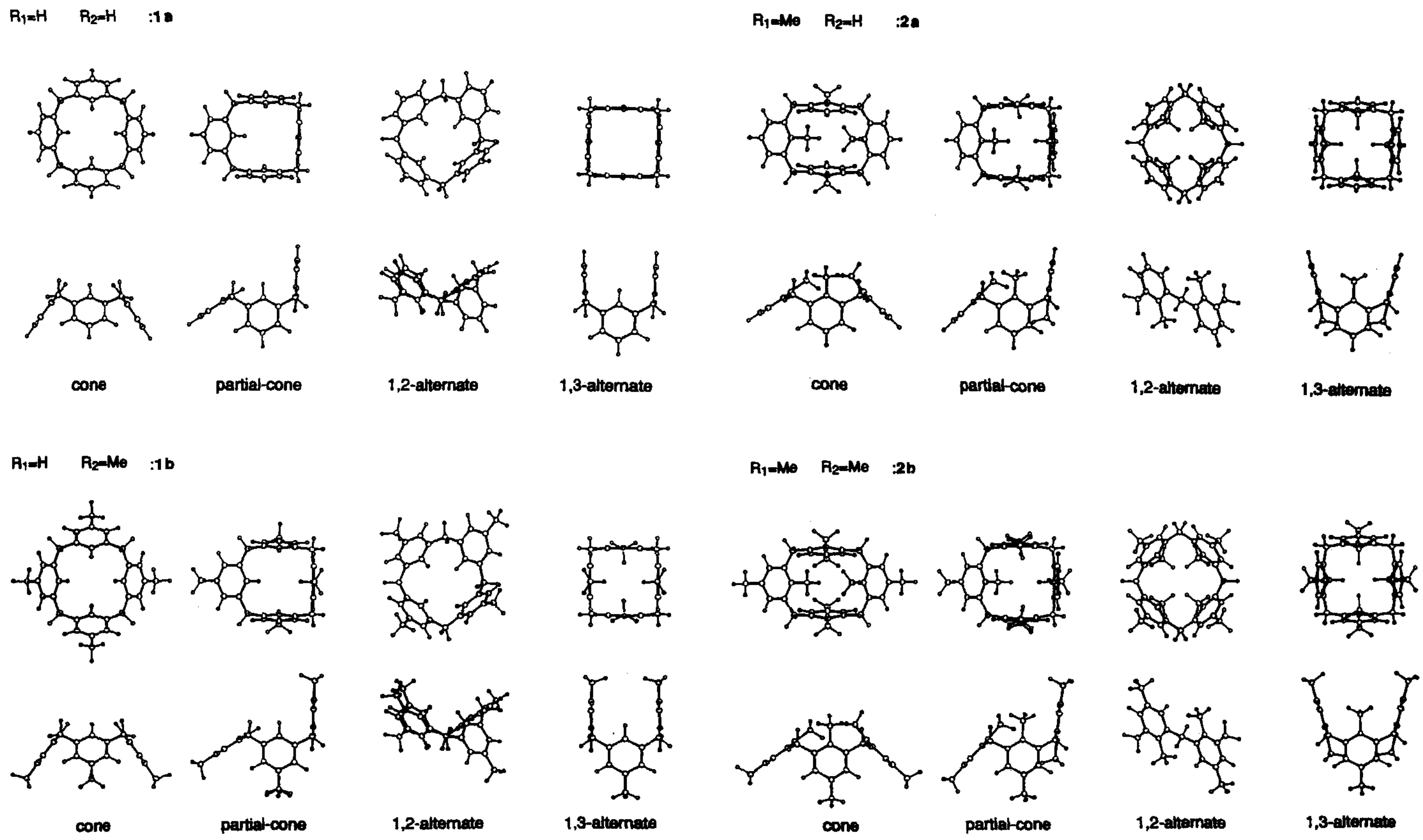


Fig. 1-1 ORTEP views[29] of the MM3 optimized structures (top views and side views)

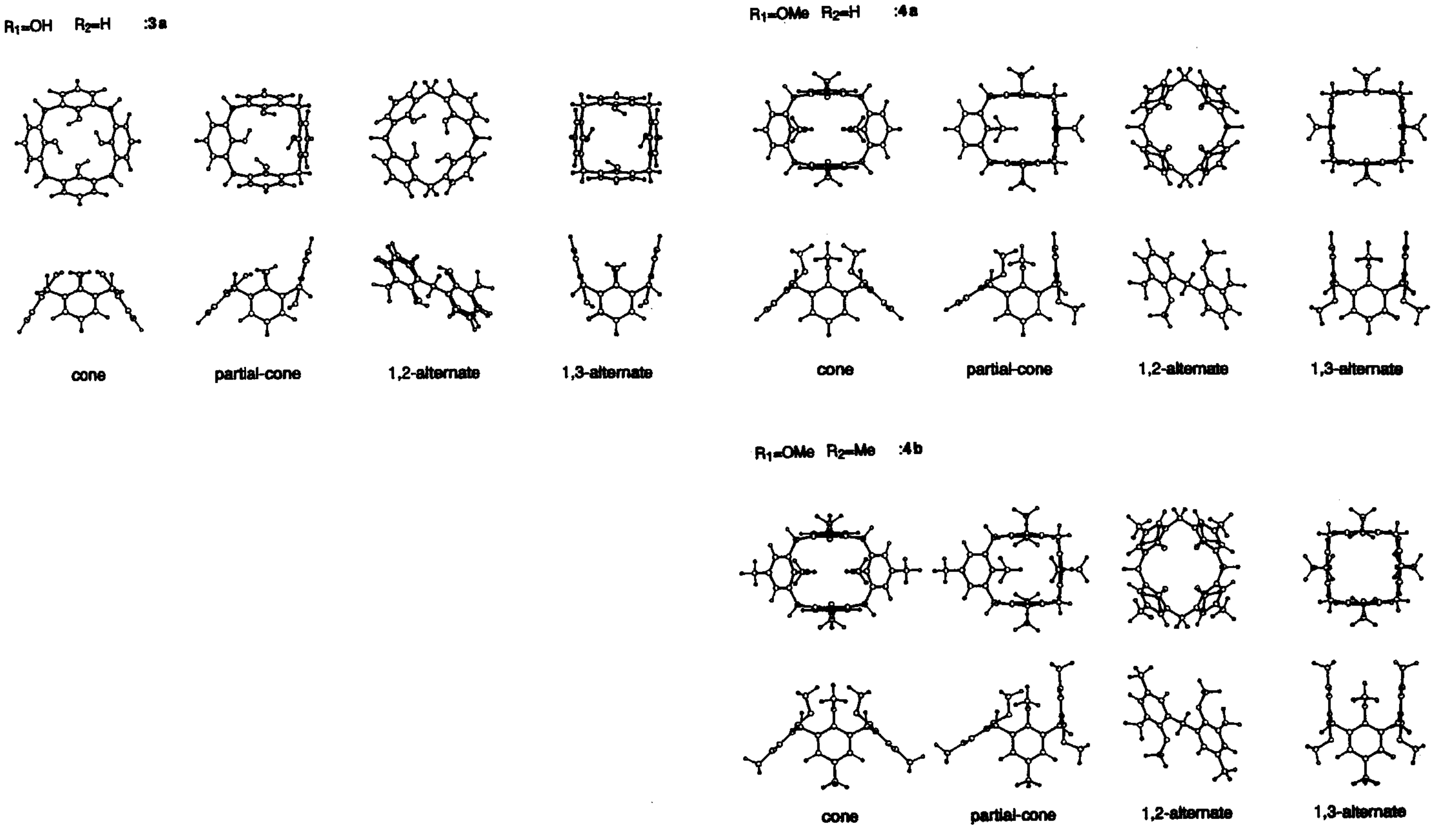


Fig. 1-2 ORTEP views[29] of the MM3 optimized structures (top views and side views)

Conclusions. (i) In the series of studied compounds the stability order and the symmetry of the metacyclophane framework depend on the substituents in the lower rim site, but are not affected by the substituents in the upper rim site, (ii) the substituents in the upper rim site affects the energy difference among the four conformers, (iii) in compounds with no substituent in the lower rim site the semi-1,2-alternate conformation does not resemble a typical 1,2-alternate structure common to calix[4]arenes: one of the aromatic rings is very much inclined toward the center of the cavity, (iv) the structures and energy differences among conformers produced by MM3 and AM1 are similar but those of PM3 are very different. PM3 underestimates nonbonded H/H repulsions, thus producing structures with unusually short H/H contacts. We believe that these conclusions are useful to understand and to predict the conformational isomers of calix[4]arene homologs.

Supplementary Material Available. Tables of MM3 calculated energies and results of AM1 and PM3 for all compounds shown in scheme 1.

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