Relative Stabilities of Tetramethoxycalix[4]arenes: Combined NMR Spectroscopy and Molecular Mechanics Studies

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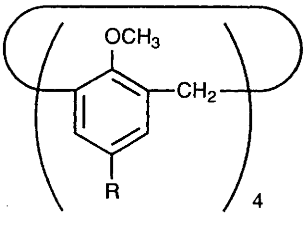
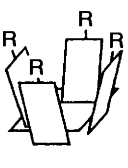
Relative stabilities of four conformers and thermodynamic parameters for interconversion among four conformers of 25,26,27,28-tetramethoxycalix[4]arene (**1a**) and 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetramethoxycalix[4]arene (**1b**) have been determined by ^{1}H NMR spectroscopy. The relative stability of **1a** is in the order partial cone (most stable) > cone > 1,2-alternate and 1,3-alternate (undetected) and that for **1b** is in the order partial cone (most stable) > cone > 1,2-alternate > 1,3-alternate (least stable). These orders are reproduced well by MM3, in contrast with MM2. In particular, the energy differences between partial cones and cones computed by MM3 (0.27 kcal mol^{-1} for **1a** and 1.50 kcal mol^{-1} for **1b**)† show good agreement with those determined by ^{1}H NMR spectroscopy (0.32 ± 0.13 kcal mol^{-1} for **1a** and 1.2 ± 0.3 kcal mol^{-1} for **1b**). Both the computational and the spectroscopic results suggest that the basic skeletons for cones, 1,2-alternates and 1,3-alternates are relatively rigid (sharp potential energy surfaces) whereas that for partial cones is more or less flexible (flattened potential energy surface). Thus, introduction of the *tert*-butyl groups into the *para*-positions destabilizes cones and 1,2-alternates because it is difficult to reduce the increased steric crowding by the conformational change. In 1,3-alternates four phenol units are parallel, so that introduced *tert*-butyl groups would increase the steric crowding to a lesser extent. The basic skeleton for partial cones changes significantly upon introduction of *tert*-butyl groups, indicating that the increased steric crowding is relaxed by the conformational change. The finding clearly explains why partial cones frequently appear as the most stable conformer.

Computational studies of conformational isomerism in calix[*n*]arenes and their analogues have been of much concern recently.[1–6] Among them, calix[4]arene derivatives are of special interest.[1–6] Calix[4]arene derivatives actually consist of a 16-membered ring but involve only four stable and significant conformers: cone, partial cone, 1,2-alternate and 1,3-alternate because of the rigid metacyclophane framework.[7–9] This particular characteristic makes the computational approach to the conformational studies extremely simple and reliable. In 1990, Grootenhuis *et al.*[3] reported the extensive computational studies on calix[4]arene derivatives using several force fields such as AMBER 3.0, MM2/MACROMODEL, MM2P(85) and CHARMm/QUANTA.[10–13] They succeeded in the reproduction of several characteristic properties of calix[4]arene derivatives, *e.g.*, (*i*) in unmodified calix[4]arene-25,26,27,28-tetraols forming intramolecular hydrogen bonds among OH groups, the cone conformer is the most stable, (*ii*) the pK_a value for the first OH dissociation is lowered by 9–11 pK_a units and (*iii*) in tetramethoxycalix[4]arenes the cone conformer is no longer the most stable because of the absence of the intramolecular hydrogen bonds.[3] However, several questions remained unsolved. For example, molecular mechanics calculations predicted that the order of the relative stability for 5,11,17,23,tetra-*tert*-butyl-25,26,27,28-tetramethoxycalix[4]arene (**1b**) is 1,3-alternate (most stable) > partial cone > cone > 1,2-alternate (least stable)[3] whereas the experimental data inform us that the cone and partial cone conformers are more stable than the 1,2-alternate and 1,3-alternate conformers.[2,14,15]

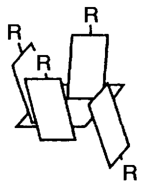
Recently, a new force field, MM3[16] which includes the well-refined algorithm for aromatic ring systems, has become available. Several papers[17–19] have already demonstrated that MM3 provides more reliable data than MM2. In this study we applied MM3 to calix[4]arene derivatives **1a** and **1b** for the first time and discuss the relative stabilities in comparison with the experimental data obtained from ^{1}H NMR measurements. We have found that the order of the relative stabilities and the structures of four conformers are reproducible to a satisfactory level by the MM3 computational approach.



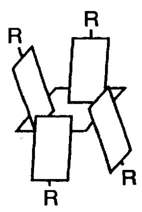
1a; R = H
1b; R = Bu^t



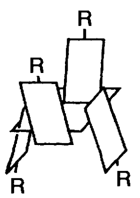
cone



partial cone



1, 2-alternate



1, 3-alternate

Results and Discussion

^{1}H *NMR Studies*.—The ^{1}H NMR spectra of **1a** and **1b** measured in CDCl$_3$ are shown in Figs. 1 and 2. These spectra

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† 1 cal = 4.184 J.

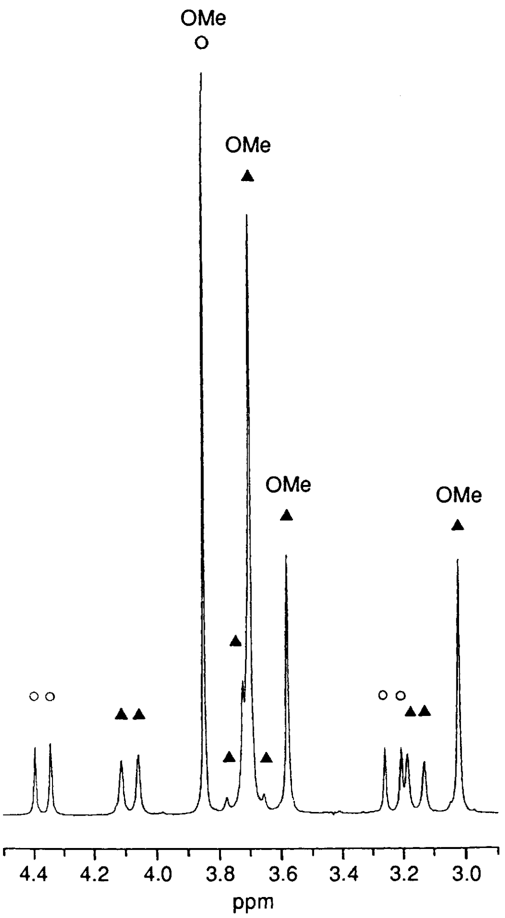


Fig. 1 Partial ^{1}H NMR spectrum of **1a** (250 MHz, $CDCl_3$, 243 K): ○, cone; ▲, partial cone. The signals assignable to the OMe protons are marked in the figure. The residual signals are assigned to the $ArCH_2Ar$ methylene protons.

are basically similar to those reported previously.[2,14,15] Assignment of the $ArCH_2Ar$ methylene protons characteristic of each conformer indicates that in **1b** all of four conformers are observable whereas in **1a** only cone and partial cone conformers appear. The results indicate that the relative stability is strongly influenced by the *p-tert*-butyl substituent. From the integral intensities for each conformer we estimated the conformer distribution at 243 K as follows: in **1a**, 27.0% cone and 73.0% partial cone; in **1b**, 5.5% cone, 85.6% partial cone, 6.1% 1,2-alternate and 2.8% 1,3-alternate.

Fig. 3 shows the temperature dependence of the ^{1}H NMR spectra. The conformer distribution changes (although not sharply) with an increase in the measurement temperature and the spectra become significantly broad at around 298 K. Figs. 4 and 5 show plots of the conformer distribution against the measurement temperature. It is seen from Fig. 4 that with an increase in the temperature partial cone **1a** decreases while cone **1a** increases. Similarly, Fig. 5 shows that in **1b** the decrease in partial cone **1b** is compensated by the increase in cone **1b** and 1,2-alternate **1b**. We estimated thermodynamic parameters from van't Hoff plots of these temperature dependences. A plot for **1a** is demonstrated in Fig. 6 (plots for **1b** are omitted). Here, the partial cone is considered to be a universal intermediate for interconversion of four conformers (Scheme 1), so that we calculated all thermodynamic parameters against the partial cone. The results are summarized in Table 1.

A number of important points arise from Table 1. Firstly, the relative stability of **1b** conformers appears in the order partial cone (most stable) > cone > 1,2-alternate > 1,3-alternate

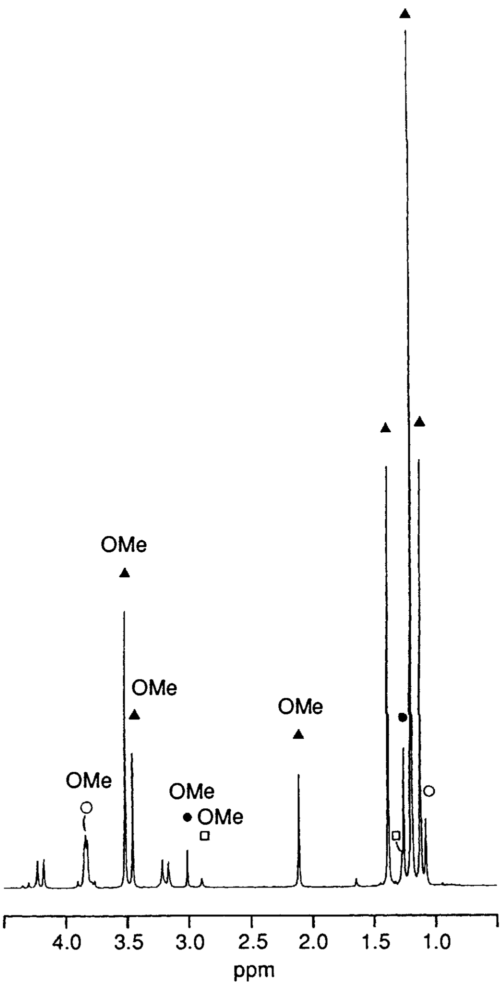
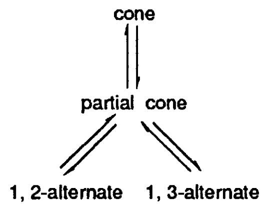


Fig. 2 Partial ^{1}H NMR spectrum of **1b** (250 MHz, $CDCl_3$, 243 K): ○, cone; ▲, partial cone; ●, 1,2-alternate; □, 1,3-alternate. The signals assignable to the OMe protons are marked in the figure. The residual signals are assigned to the $ArCH_2Ar$ methylene protons (3.0–4.5 ppm) and the *tert*-butyl protons (1.0–1.5 ppm).



Scheme 1

(least stable) at 298 K. The result indicates that the relative stability is poorly reproduced by the previous MM2 calculation.[1–4] Secondly, the isomerization from partial cone to cone, the most significant process as shown by the experiment, accompanies the unfavourable ΔH increase and the favourable ΔS increase.* In Fig. 7, chemical shifts of the proton signals in **1b** are plotted against temperature. Clearly, the OMe protons and *tert*-butyl protons in partial cone **1b** shift either to higher or to lower magnetic field whereas the corresponding protons in other three conformers are hardly affected. The result supports

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* The experimental results imply that isomerization from partial cone to cone accompanies the favourable entropy change whereas that to 1,2-alternate and 1,3-alternate accompanies the unfavourable entropy change. However, the correspondence between the entropy change and the structural change is not well understood.

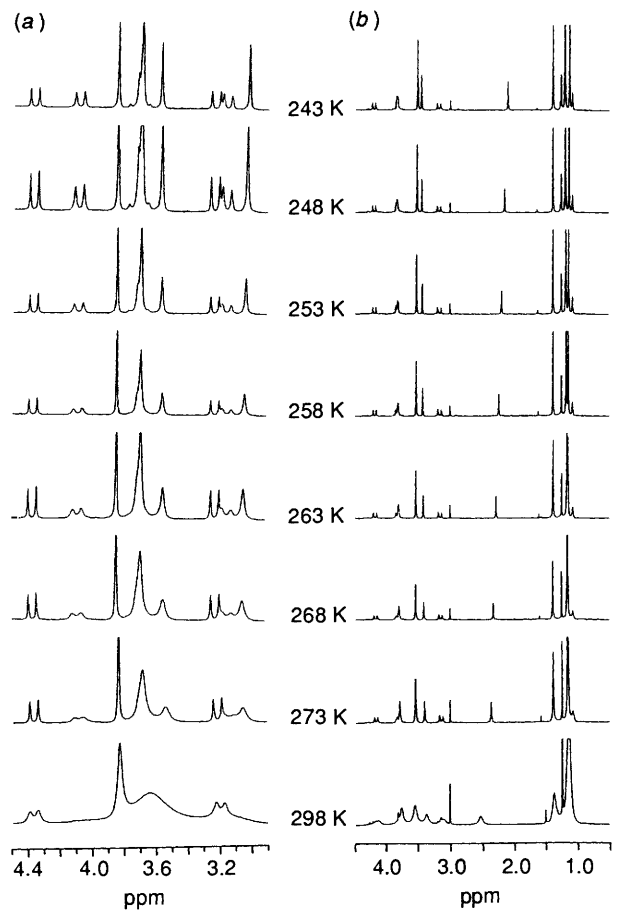

Fig. 3 Temperature dependence of the ^{1}H NMR spectra for (*a*) **1a** and (*b*) **1b** (250 MHz, $CDCl_3$)

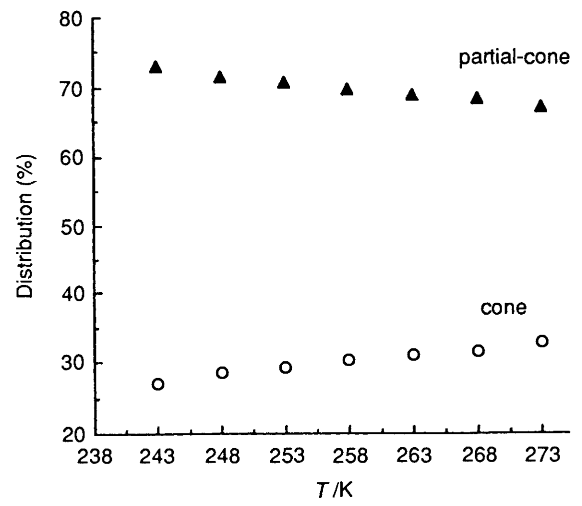

Fig. 4 Temperature dependence of the conformer distribution in **1a**

the view that the partial cone conformation is sensitively affected by the temperature change.

Thirdly, it is seen from Table 1 that the isomerization from partial cone to 1,2-alternate accompanies the positive ΔH and the negative ΔS and that from partial cone to 1,3-alternate accompanies the negative ΔH and the large negative ΔS.* This means that the rotation of a phenyl unit proximal to an inversed phenyl unit (to give 1,2-alternate) is thermodynamically different from the rotation of a phenyl unit distal to an inversed phenyl unit (to give 1,3-alternate). The large ΔS decrease observed for the isomerization to 1,3-alternate is particularly interesting. The X-ray crystallographic studies clarified that in 1,3-alternate calix[4]arenes the four phenyl units are more or less parallel to each other.[20–22] This structure is least affected among the four conformers by the steric effect of the introduced substituents. Therefore, the large ΔS decrease should be ascribed to the nature of the basic calix[4]arene skeleton with the 1,3-alternate conformation.

The last interest is related to the influence of the *tert*-butyl

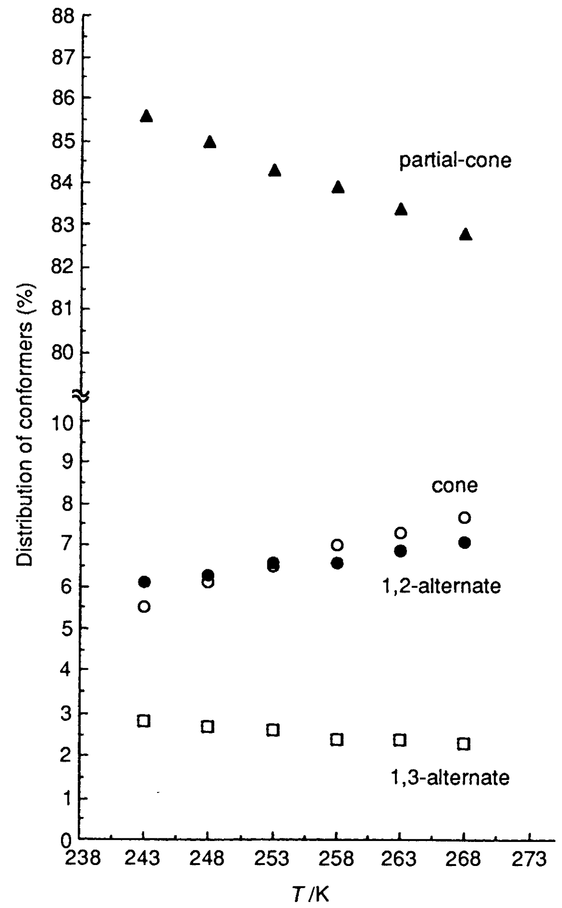

Fig. 5 Temperature dependence of the conformer distribution in **1b**

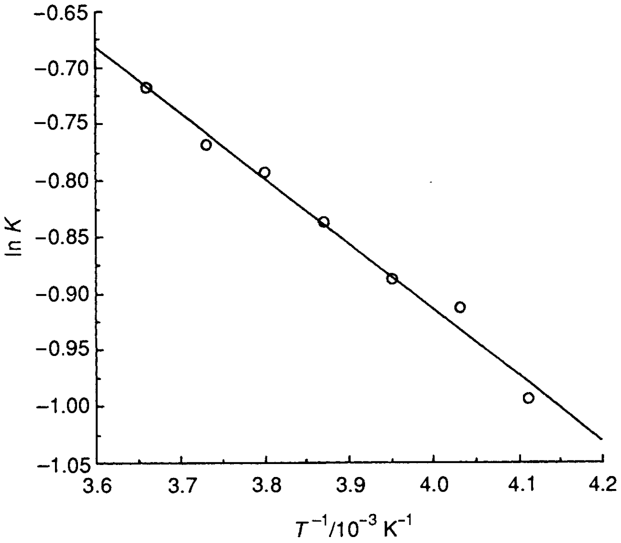

Fig. 6 van't Hoff plot for a partial cone **1a** $\rightleftharpoons$ cone **1a** equilibrium (where K = [cone **1a**]/[partial cone **1a**]): $\gamma = 0.994$. Plots for partial cone **1b** $\rightleftharpoons$ cone **1b**, partial cone **1b** $\rightleftharpoons$ 1,2-alternate **1b** and partial cone **1b** $\rightleftharpoons$ 1,3-alternate **1b** are not shown ($\gamma > 0.96$).

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* See the footnote on p. 2110.

Table 1 Thermodynamic parameters for the isomerization from partial cone

Calixarene	Isomerization	ΔH /kcal mol^{-1}	ΔS /cal mol^{-1} K^{-1}	ΔG/kcal mol^{-1} (T = 298 K)
1a	partial cone $\rightleftharpoons$ cone	1.15 ± 0.06	2.78 ± 0.23	0.32 ± 0.13
1b	partial cone $\rightleftharpoons$ cone	1.9 ± 0.1	2.4 ± 0.1	1.2 ± 0.3
1b	partial cone $\rightleftharpoons$ 1,2-alternate	0.97 ± 0.06	−1.2 ± 0.2	1.3 ± 0.1
1b	partial cone $\rightleftharpoons$ 1,3-alternate	−0.76 ± 0.11	−9.9 ± 0.4	2.2 ± 0.2

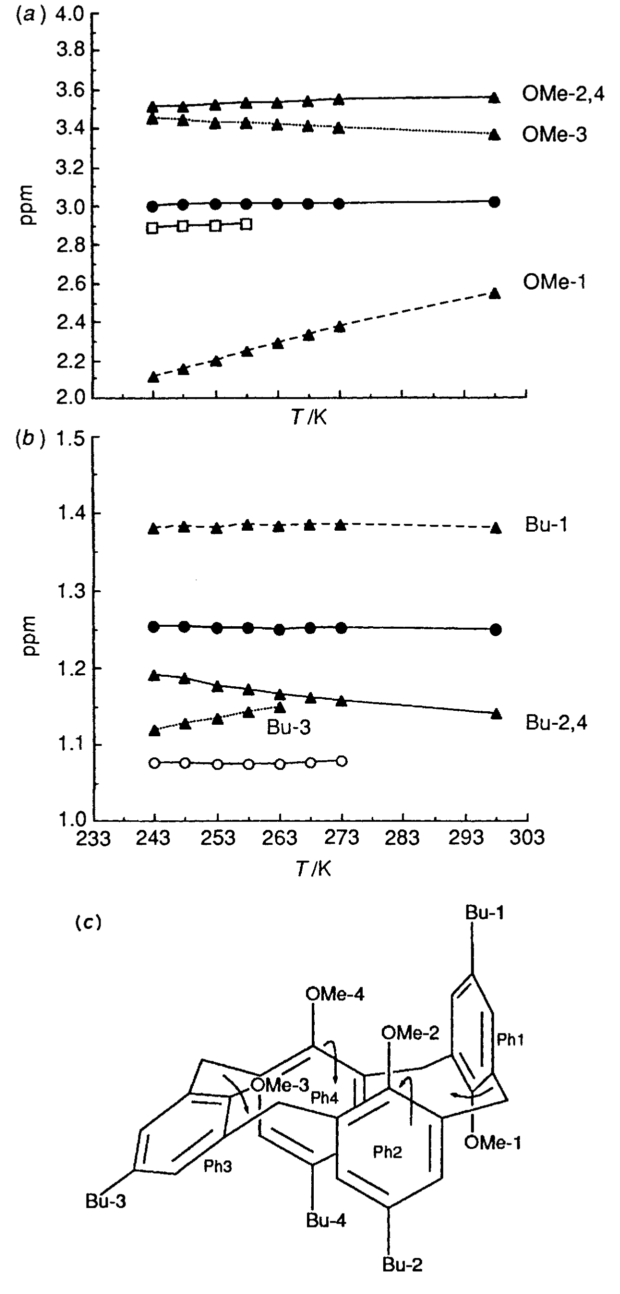

Fig. 7 Temperature dependence of the chemical shifts of (*a*) OMe and (*b*) *tert*-butyl protons in **1b** (250 MHz, $CDCl_3$): ○, cone; ▲, partial cone; ●, 1,2-alternate; □, 1,3-alternate; (*c*) assignment of OMe and *tert*-butyl in the partial cone.

group. In **1a** the 1,2- and 1,3-alternate conformers are not detected by ^{1}H NMR spectroscopy whereas in **1b** all of the four conformers are detected. This implies that 1,2-and 1,3-alternate **1b** are relatively more stabilized by the introduced *tert*-butyl groups. This problem will also be discussed later in connection with computational studies.

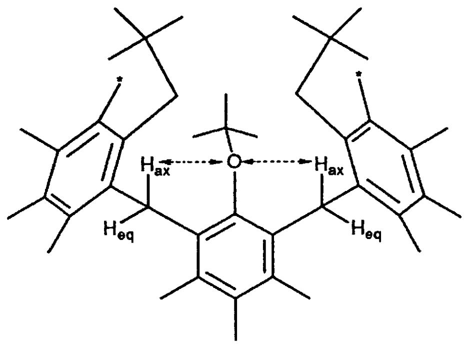

Fig. 9 Van der Waals repulsion expected for H_{ax} protons in methylene groups and OMe oxygens in the parallel phenol units

Computational Studies.—We estimated the energies and the structures for **1a** and **1b** by molecular mechanics calculations. The results obtained with MM3 are summarized in Table 2. As mentioned previously,[2,3,14] MM2 studies of **1a** predict that the order of the relative stability is 1,3-alternate (most stable) > partial cone > cone > 1,2-alternate (least stable). This order is not in line with the experimental findings that 1,2- and 1,3-alternate **1a** do not exist in a perceptible concentration level.* The MM3 calculation predicts, on the other hand, that the order of the relative stability is partial cone (most stable) > cone > 1,3-alternate > 1,2-alternate (least stable).† This order is exactly in accord with the experimental result. Provided that the conformer distribution in the present system is subject to the Boltzman distribution, one can obtain the conformer ratio as shown in Table 3 from the steric energies in Table 2 (see later for calculation of conformer distribution). Except for the slight disagreement between observed (determined by ^{1}H NMR spectroscopy) and calculated (determined by MM3) for 1,2-alternate **1b**, the computational results are in surprisingly good accord with the experimental results.

Examination of each energy term in Table 2 reveals that the energy terms for cone **1a** are mostly smaller or comparable to those for other three conformers. The exception is the van der Waals energy: the 1,4-energy arising from the interaction between the vicinal 1,4-atoms is also comparable to others whereas the energy arising from residual interactions is particularly large. Thus, the latter terms offsets the stabilization effect obtained by the accumulation of other energy terms. As shown in Fig. 8, the optimized structure for cone **1a** adopts C_{2v} symmetry: that is, two distal phenol units are flattened (the dihedral angles against the mean plane of the four methylene groups are 44.52°: Table 4) and residual two phenol units are

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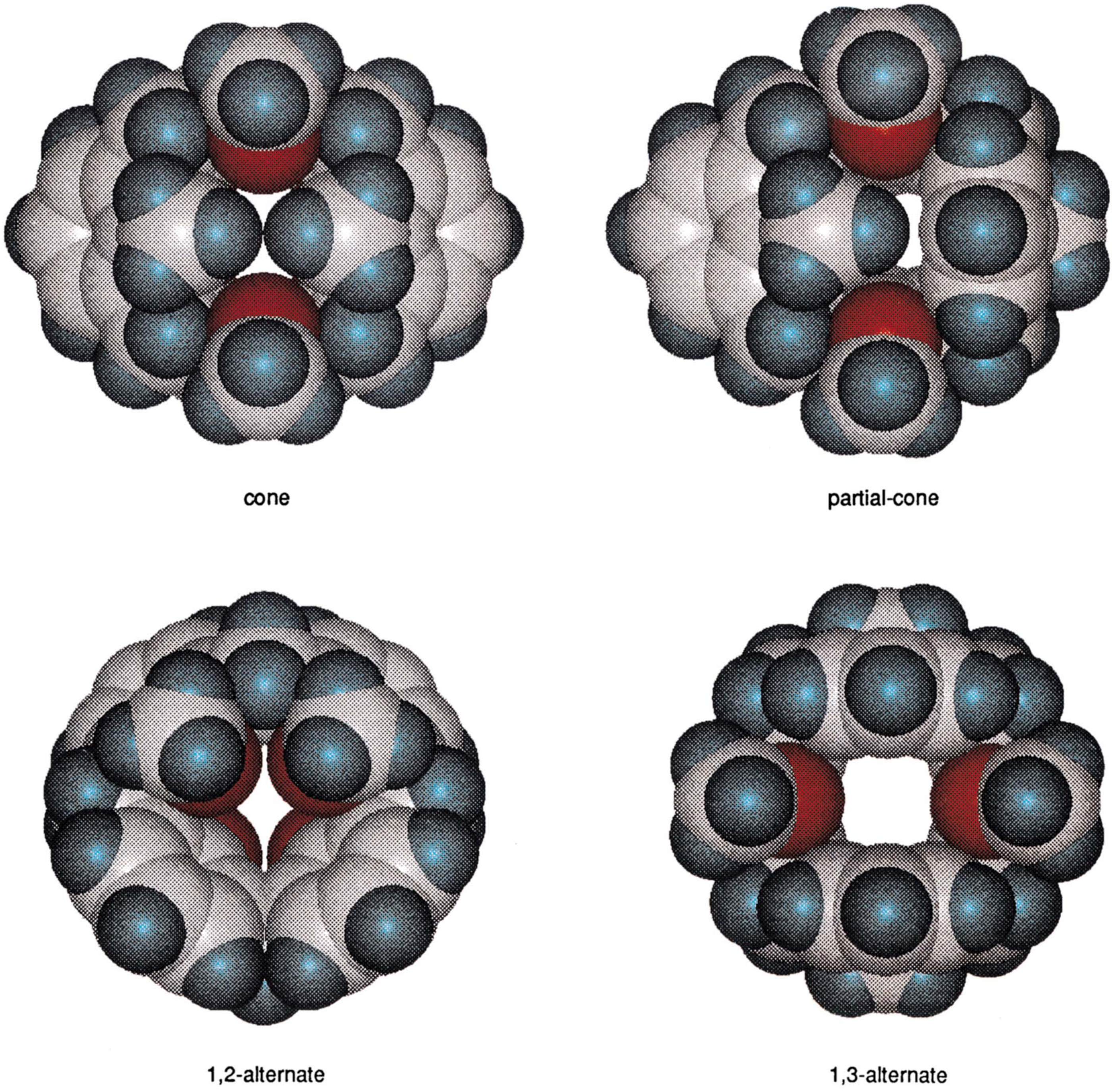
* It is known, however, that the 1,3-alternate conformer appears as the most stable one in an aqueous system: T. Nagasaki, K. Sisido, T. Arimura and S. Shinkai, *Tetrahedron*, 1992, **48**, 797 and J. L. Atwood and S. G. Bott, *Top. Inclusion Sci.*, 1991, **3**, 199.

† In the energy-optimized structure of partial cone **1a** (steric energy is 32.19 kcal mol^{-1}) the OMe group in the inversed phenol unit is turned outward. When the OMe group is turned inward, the steric energy is increased up to 34.35 kcal mol^{-1}. This value is larger than that for 1,3-alternate **1a** but still smaller than that for 1,2-alternate **1a**.



cone

partial-cone

1,2-alternate

1,3-alternate

Fig. 8 Optimized space-filling structures for four conformers in **1a** (top views from the side of the lower rim)

Table 2 MM3 Calculated energies (relative energy)/kcal of **1a** and **1b**

	1a				**1b**			
	Cone	Partial cone	1,2-Alternate	1,3-Alternate	Cone	Partial cone	1,2-Alternate	1,3-Alternate
Steric energy	32.46	32.19	36.29	33.69	43.16	41.66	47.74	43.12
	(0.27)	(0.00)	(4.10)	(1.50)	(1.50)	(0.00)	(6.08)	(1.46)
Symmetry	C_{2v}	C_s	C_{2h}	D_{2d}	C_{2v}	C_1	C_{2h}	D_{2d}
Compression	2.81	2.75	2.80	2.85	6.25	6.19	6.16	6.15
	(0.06)	(0.00)	(0.05)	(0.10)	(0.10)	(0.04)	(0.01)	(0.00)
Bending	5.68	5.67	7.02	5.89	9.82	9.71	11.18	10.05
	(0.01)	(0.00)	(1.35)	(0.22)	(0.11)	(0.00)	(1.47)	(0.34)
Bend–bend	−0.19	−0.20	−0.10	−0.20	−0.31	−0.31	−0.22	−0.30
	(0.01)	(0.00)	(0.10)	(0.00)	(0.00)	(0.00)	(0.09)	(0.01)
Stretch–bend	−0.61	−0.62	−0.51	−0.57	−0.79	−0.78	−0.68	−0.74
	(0.01)	(0.00)	(0.11)	(0.05)	(0.00)	(0.01)	(0.11)	(0.05)
Van der Waals 1,4[a]	28.58	28.80	28.39	28.58	45.20	45.13	45.00	45.29
	(0.19)	(0.41)	(0.00)	(0.19)	(0.20)	(0.13)	(0.00)	(0.29)
other[b]	−8.91	−10.24	−8.65	−10.02	−6.49	−8.88	−5.55	−9.17
	(1.33)	(0.00)	(1.59)	(0.22)	(2.68)	(0.29)	(3.62)	(0.00)
Torsional	−14.05	−13.21	−12.81	−13.61	−31.38	−30.60	−29.94	−30.78
	(0.00)	(0.84)	(1.24)	(0.44)	(0.00)	(0.78)	(1.44)	(0.60)
Torsion–stretch	0.00	0.00	0.00	0.00	−0.04	−0.03	−0.04	−0.04
	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.01)	(0.00)	(0.00)
Dipole–dipole	19.17	19.24	20.17	20.77	20.88	21.23	21.83	22.66
	(0.00)	(0.07)	(1.00)	(1.60)	(0.00)	(0.35)	(0.95)	(1.78)

[a] Van der Waals energy term arising from the interaction between vicinal 1,4-atoms. [b] Van der Waals energy term for non-bonding atom pairs except for 1,4-atoms.

Table 3 Observed and calculated distribution of conformers for **1a** and **1b** at 243 K

		Cone (%)	Partial cone (%)	1,2-Alternate (%)	1,3-Alternate (%)
1a	Observed	27.0	73.0	Nd[a]	Nd[a]
	Calculated	22.0	77.1	0.0	0.9
1b	Observed	5.5	85.6	6.1	2.8
	Calculated	2.2	96.7	0.0	1.2

[a] Nd denotes not detected by ^{1}H NMR spectroscopy (*i.e.*, less than 1%).

Table 4 MM3 Optimized structures of **1a** and **1b**

	1a				**1b**			
	Cone	Partial cone	1,2-Alternate	1,3-Alternate	Cone	Partial cone	1,2-Alternate	1,3-Alternate
Plane angle[a]/deg								
Ph1	83.32	−94.01	−63.80	−88.23	83.12	−91.89	−63.73	−87.99
Ph2	44.52	94.51	−63.80	88.07	44.50	88.68	−63.65	87.83
Ph3	83.32	32.27	63.80	−88.15	83.12	34.10	63.69	−87.87
Ph4	44.52	94.51	63.80	88.25	44.49	89.20	63.70	88.02
Angle/deg								
Ph1–CH_2–Ph2	113.4	113.6	114.2	115.1	113.5	114.9	114.5	115.0
Ph2–CH_2–Ph3	113.4	113.6	119.4	115.1	113.5	114.1	119.4	115.1
Ph3–CH_2–Ph4	113.4	113.6	114.2	115.1	113.5	114.4	114.5	115.1
Ph4–CH_2–Ph1	113.4	113.6	119.4	115.1	113.5	114.4	119.4	115.2
Distance[b]/Å								
C(1,2)–C(3,4)	7.19	7.16	6.71	7.18	7.18	7.19	6.69	7.18
C(2,3)–C(4,1)	7.19	7.16	7.70	7.18	7.17	7.14	7.70	7.17

[a] Dihedral angle between the phenyl plane and the mean plane of four methylene carbons. [b] Distance between two distal methylene carbons: C(*x*,*y*) indicates the methylene carbon connecting Ph*x* and Ph*y* (see Scheme 3).

more or less parallel to each other (the dihedral angles are 83.32°: Table 4). In this structure, four H_{ax} protons in the $ArCH_2Ar$ methylene groups and two oxygens in the parallel phenol units experience significant van der Walls repulsion (Fig. 9). This tells us that the cone skeleton is basically stable but four substituents concentrated on the narrow lower rim destabilize cone **1a**. The destabilization for 1,3-alternate **1a** is induced by the dipole–dipole interaction term. The 1,2-alternate is the least stable of the four conformers because of several energy terms such as the bending term, van der Waals term (other than 1,4), torsional term and dipole–dipole interaction term. The unfavourable terms are related to the basic metacyclophane structure with a 1,2-alternate conformation.[6]

The optimized structures for **1a** are illustrated in Fig. 8 and their structural parameters are summarized in Table 4. These parameters reproduce well the X-ray structures of calix[4]arene-based conformers reported so far.[3,14,15,20–25] To compare the difference in the basic skeleton of four conformers we made superimposed illustrations (Fig. 10). It can be seen from Fig. 10 that the framework of the 16-membered ring for cone, partial cone and 1,3-alternate is more or less similar whereas that for 1,2-alternate is quite different. In the former three conformers, for example, the four $ArCH_2Ar$ bond angles are almost equal (113.4–115.2°). However, in the 1,2-alternate, the two $ArCH_2Ar$ bond angles connecting two *syn* phenol units are expanded (119.4° for **1a** and **1b**) while those connecting two *anti* phenol units are relatively narrowed (114.2° for **1a** and 114.5° for **1b**). As a result, 1,2-alternate adopts a lozenge-shape. The difference is also reflected by the distances between two distal $ArCH_2Ar$ methylene carbons. In the former three conformers the distances are almost constant (7.14–7.19 Å) whereas in the 1,2-alternate the distances are different by 1 Å. These structural characteristics of the 1,2-alternate conformation are surprisingly similar to those of the X-ray structure reported by Bott *et al.*[23] (the sole example for the 1,2-alternate calix[4]arene; the 1,2-alternate conformation is immobilized by a bound metal ion). We consider that the distortion in the framework of 1,2-alternates is reflected by the large bending term in Table 2. It is seen from Table 4 that four phenol units in the 1,2-alternate are significantly flattened, the dihedral angles between a phenyl ring and the mean plane of the four methylene groups being 63.69–63.80 (or −63.65 to −63.80). Presumably, the *syn* phenol units flattened into the narrow calix[4]arene annulus cause serious steric repulsion and extend the $ArCH_2Ar$ bond angles.

Introduction of bulky *tert*-butyl groups into the *para* positions affects the relative stability of four conformers. How do four conformers relax the steric crowding increased by the *tert*-butyl groups? Careful examination of the structural parameters in Table 4 reveals that four phenol units in cone, 1,2-alternate and 1,3-alternate are slightly flattened (by 0.1–0.2°; *e.g.*, from 83.32° for cone **1a** to 83.12° for cone **1b**) by introduction of the *tert*-butyl groups. As mentioned above, cone **1a** and 1,2-alternate **1a** are already sterically crowded and strained. Hence, even though *tert*-butyl groups are introduced, they cannot change the structures further. That is, it is difficult for these two conformers to relax the steric crowding by the conformational change and as a result, they undergo the serious steric destabilization. As shown in Table 2, cone **1b** and 1,2-alternate **1b** are more destabilized (relative to partial cone **1b**) than cone **1a** and 1,2-alternate **1a** (relative to partial cone **1a**). On the other hand, four phenol units in 1,3-alternates are more or less parallel to each other, so that the *para* positions are more separated than those in other three conformers. This means that in 1,3-alternate **1b** the increased steric crowding can be relaxed by a smaller conformational change. In fact, the steric energy difference between 1,3-alternate **1b** and partial cone **1b** (1.46 kcal mol^{-1}) is almost equal to that between 1,3-alternate **1a** and partial cone **1a** (1.50 kcal mol^{-1}).

Here, we compare the foregoing computational results on introduction of *tert*-butyl groups with the experimental results (Table 1). The computational results predict that the steric energy difference between cone and partial cone increases from 0.27 kcal mol^{-1} for **1a** to 1.50 kcal mol^{-1} for **1b**.* The experimental results show a good agreement: the ΔG value at 298 K increases from 0.32 ± 0.13 kcal mol^{-1} for **1a** to 1.2 ± 0.3 kcal mol^{-1} for **1b**. On the other hand, a satisfactory agreement is not seen for 1,2-alternates. In ^1H NMR spectroscopy 1,2-alternate **1a** is not detected whereas 1,2-alternate **1b** exists in a concentration of 6.1% at 243 K. Therefore, the energy difference between the 1,2-alternate and partial cone must become smaller when *tert*-butyl groups are introduced. However, the computational results predict that 1,2-alternate **1b** should be more destabilized than 1,2-alternate **1a** (relative to each partial cone counterpart). We consider that the discrepancy stems from unknown factors which are not taken into account by MM3 (*e.g.*, solvent effects).

The structural changes observed for partial cones are quite different (Scheme 3 and Table 4). When *tert*-butyl groups are introduced into the *para* positions, two phenol units proximal to an inversed phenol units (Ph2 and Ph4) are flattened by 5–6° whereas an inversed phenol unit (Ph1) and a so-called 'flattened' phenol unit distal to the inversed phenol unit (Ph3) are raised by *ca.* 2°. The rotation of the former two phenol units to the *endo*-annulus direction occurs synchronously with the rotation of the latter two phenol units to the *exo*-annulus direction. This motion is very compatible with the change in the ^1H NMR spectra. By introduction of the *tert*-butyl groups, δ values for the OMe protons shift to higher magnetic field: in $CDCl_3$ at 243 K, δ 3.02, 3.58 and 3.70 for **1a** and δ 2.11, 3.45 and 3.51 for **1b**. These results provide an important clue to explain why partial cones appear as the most stable conformer. In partial cone conformers, the steric distortion induced by *O*- (on the lower rim) or *para*-substituents (on the upper rim) is readily relaxed by the change in the basic calix[4]arene skeleton. In other words, partial cone conformers have an energy minimum with the flattened potential energy surface. The sensitivity of the δ values in ^1H NMR spectroscopy (Fig. 7) and the significant line-broadening at the high temperature region (Fig. 3) also support this conclusion.

Conclusions

From the combined NMR spectroscopy and molecular mechanics studies we learned that MM3 is a useful tool to reproduce several conformational characteristics of tetramethoxycalix[4]arenes: the relative stability of the four conformers can be predicted and the influence of the *tert*-butyl groups introduced into the *para*- positions is readily understood. The unexpected bonus is the finding that partial cones feature the flattened potential energy surface through which they can relax the steric distortion induced by the introduced substituents. The finding now provides an unequivocal answer for the question, why do partial cones frequently appear as the most stable conformer? We must admit, however, that in the present study the solvent effect is not yet taken into account. We have found that solvent effects sometimes influence the relative stability of the four conformers.[2] We believe that further elaboration of the computational studies will eventually disclose the conformational characteristics of calix[4]arenes and related compounds.

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* In the present MM3 calculation, aided by full matrix Newton–Raphson minimization method, the harmonic vibrational frequencies are evaluated for stationary points, and are used to calculate vibrational contributions to the thermodynamic functions. The Gibbs free energies are calculated by using standard statistical-mechanical equations as implemented in MM3: J.-H. Lii and N. L. Allinger, *J. Am. Chem. Soc.*, 1989, **111**, 8566.

For the equilibrium, partial cone **1a** $\rightleftharpoons$ cone **1a**, we obtained ΔG = 0.75 kcal mol^{-1}, ΔH = 0.37 kcal mol^{-1} and ΔS = −1.28 cal mol^{-1} K^{-1}. The calculated ΔG shows a good agreement with the experimental ΔG, but the calculated ΔS is negative whereas the experimental ΔS is positive (Table 1). This disagreement may be caused by some factors which are not taken into account in the present system (*e.g.*, solvent effects). We could not estimate the thermodynamic parameters for **1b** because of the limitation for the maximum number of atoms in the present program (see the Experimental section).

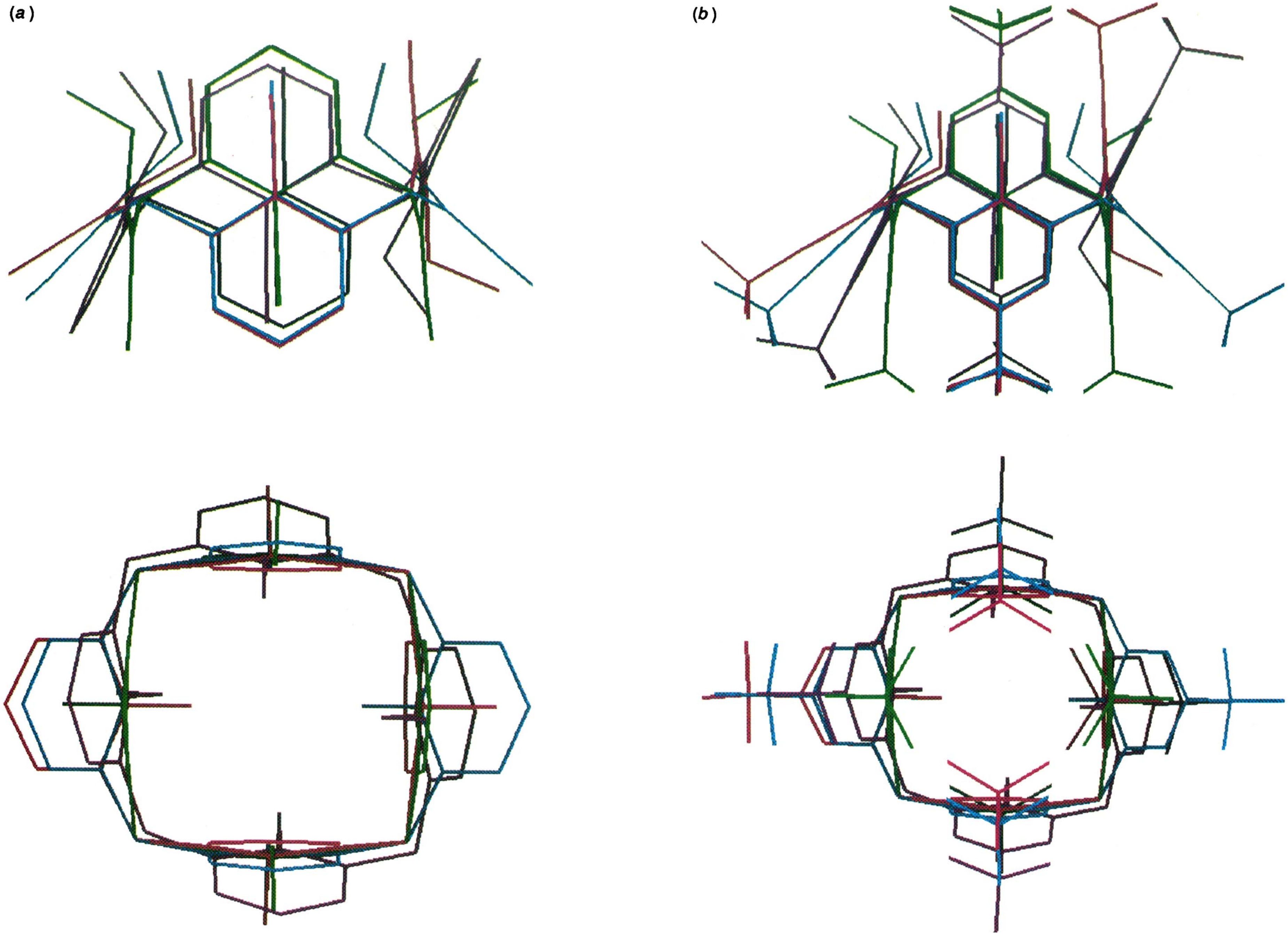

Fig. 10 Superimposed structures for (*a*) **1a** and (*b*) **1b**: cone, blue; partial cone, red; 1,2-alternate, purple and 1,3-alternate, green. Root-mean-square distance of the geometry of four corresponding methylene carbons is 0.01–0.03 Å for cones, partial cones and 1,3-alternates, 0.25 Å for 1,2-alternates.

Experimental

Procedure for the Synthesis of the Tetramethyl Ethers (**1a**, **b**).—Tetramethyl ethers **1a**, **b** were prepared as described in the previous paper[14] (*J* values are given in Hz). Here we describe the synthesis of 25,26,27,28-tetramethoxycalix[4]arene (**1a**). Calix[4]arene (1.0 g, 2.36 mmol) was treated with 60% oil-dispersed NaH (1.5 g, 37.5 mmol) in THF (40 cm^3)–DMF (4 cm^3) and CH_3I (17.6 g, 124 mmol) was added dropwise. The reaction mixture was refluxed for 7 h under nitrogen. After decomposition of the excess of NaH with methanol (5 cm^3), the mixture was diluted with water (500 cm^3) and extracted with chloroform (150 cm^3 × 2). The organic layer was separated and dried over $MgSO_4$. The solution was evaporated to dryness, the residue being recrystallized from chloroform–hexane: white crystals (0.71 g, 63%), m.p. 240–242 °C (Found: C, 79.4; H, 6.7. $C_{32}H_{32}O_4$ requires C, 79.97; H, 6.71%); δ_H(250 MHz; $CDCl_3$; 243 K; Me_4Si) partial cone: 3.02 (3 H, s, OCH_3), 3.16, 4.08 (4 H, H_{AB}, *J* 13.6, $ArCH_2Ar$), 3.58 (3 H, s, OCH_3), 3.69, 3.74 (4 H, H_{AB}, *J* 13.4, $ArCH_2Ar$), 3.70 (6 H, s, OCH_3), 6.43–7.33 (12 H, m, Ar-H); cone: 3.23, 4.37 (8 H, H_{AB}, *J* 13.1, $ArCH_2Ar$), 3.85 (12 H, s, OCH_3), 6.5–6.9 (12 H, m, Ar-H).

Calculations of the Thermodynamic Parameters.—In this study, we presumed that partial cone is the universal intermediate for interconversion among four isomers. The conformer distribution was determined by ^1H NMR spectroscopy as a function of medium temperature. The thermodynamic parameters were determined from the slope ($= -\Delta H/R$) and the intercept ($= \Delta S/R$) of van't Hoff plots (ln K *vs.* T^{-1}). In all cases the correlative coefficients are better than 0.96.

MM3 Calculations.—MM3 calculations[26] were performed on a UNIX workstation system: SUN 4/2GX—IRIS 4D/35G. All aromatic carbons in phenol units were treated as a conjugated π-system. The atom type for oxygens of the phenol unit was set to 6. All parameters used in these calculations are default values. Energy optimization was carried out using a full matrix Newton–Raphson method for **1a** and a block diagonal Newton–Raphson method for **1b** owing to the limitation in the original program. Full matrix minimization for 1,3-alternate **1a** produced unreliable results owing to some numerical problems within MM3 program. Therefore, the result of the block diagonal minimization is retained for this conformer. The structures for each conformer reported in this paper are those of the lowest energy minima obtained by grid search for the rotation of all substituents using BIGSTRN-3 program[27] with MM2 force field as the pre-optimizer.

Calculations of the Conformer Distribution.—The theoretical conformer distribution was estimated from the final steric energies obtained from the MM3 calculation: the corresponding ΔG values could not be determined because of the program limitations for the maximum number of atoms (up to 80 atoms for full matrix Newton–Raphson minimization). We used a modified equation for Boltzman population, including the contribution arising from the entropy of mixing, *i.e.* degeneracy of the conformational potential energy surface.

Miscellaneous.—The ^1H NMR apparatus used here was a Bruker AC250P spectrophotometer. A molecular modelling system, ANCHOR-II[28] was used to create the initial structures for grid search, and MOL-GRAPH[29] was used for the analysis and drawing of the molecular shapes (*e.g.*, Figs. 8 and 10).

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