

## Ab Initio Study of the Conformations of Tetramethoxycalix[4]arenes

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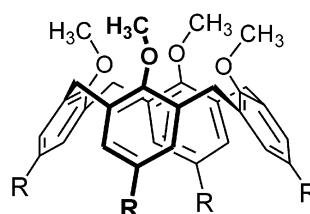
In this study we have performed *ab initio* computer simulations to investigate the conformational characteristics of the tetramethoxycalix[4]arenes (**1** and **2**). The structures of four types (cone, partial cone, 1,2-alternate, and 1,3-alternate) of conformers for each compound have been optimized using *ab initio* RHF/6-31G and 6-31G\*\* methods. General trends in relative stabilities of tetramethyl ether derivatives of calix[4]arene **1** and *p*-*tert*-butylcalix[4]arene **2** are similar and decrease in following order: partial cone (most stable) > cone > 1,3-alternate > 1,2-alternate. The calculated results of the most stable conformation of partial cone structure agree with the reported NMR experimental observations.

**Key Words** : *Ab initio* calculation, RHF/6-31G\*\*, Calix[4]arene, Conformations, Partial cone

### Introduction

Calix[4]arenes are macrocyclic molecules which are receiving increasing attention in the fields of supramolecular chemistry.<sup>1</sup> They can selectively interact with a variety of ionic and molecular guests by performing intriguing molecular recognition processes.<sup>2</sup> There are four possible conformations in various derivatives of calix[4]arenes due to the inhibition of O-annulus rotations by the presence of bulky substituents larger than ethyl groups on phenol moiety. Several studies have been reported in which the relative stability of the calix[4]arene conformations are determined by experiments and theoretical calculation methods of molecular mechanics.<sup>3-7</sup>

Grootenhuis calculated the structural, energetical, and acid-base properties of calix[4]arenes using molecular mechanics programs such as AMBER, MM2P, QUANTA/CHARMm.<sup>3</sup> Wipff *et al.* reported the molecular dynamics calculations of calix[4]arene amide derivatives containing metal cation or organic molecule as guests.<sup>5</sup> Shinkai group have calculated the relative stabilities of four different conformations of the tetramethoxycalix[4]arene (**1** and **2**) using MM3<sup>8</sup> molecular modeling software, and reported quantitatively the trend (in the order of partial cone (most stable) > cone > 1,2-alternate ~ 1,3-alternate) consistent with the relative free energies obtained from the NMR spectroscopic data.<sup>6</sup> More recently, Reinhoudt group have also reported the calculated and experimental results on conformational distribution of tetramethyl ether derivative of *p*-*tert*-butylcalix[4]arene **2**.<sup>7</sup> They summarized the previously calculated results on conformational distribution and obtained the Boltzmann distribution from the published minimized energies and compared them with the experimental results. We have published a series of calculations for the relative stabilities on the conformers of *p*-*tert*-butylcalix[4]crown-6-ether and its alkyl ammonium complexes by *ab initio* RHF/6-31G, which showed that the cone



**1** : R = H

**2** : R = *tert*-Bu

**Scheme 1.** Chemical structures of **1** and **2**.

conformation is generally the most stable.<sup>9</sup>

Since calix[4]quinone and calix[4]hydroquinone have recently been very useful chemical substance in making organic nanotubes and silver nanowires,<sup>10</sup> it would be interesting to investigate the conformations of calix[4]arene systems.

In this paper, we have simulated the conformational behavior of tetramethoxycalix[4]arenes **1** and **2** using *ab initio* RHF/6-31G and 6-31G\*\* calculations. The main emphasis of this research is determining the relative stability of different conformations for the calix[4]arene derivatives with varying structural characteristics by accurate *ab initio* calculations. The calculation results might provide a basis for the utilization of these interesting molecular frameworks of calix[4]arenes for the design of other functional ionophores having various conformers.

### Computational Methods

The initial structures of calix[4]arene derivatives were constructed by HyperChem.<sup>11</sup> In order to find optimized conformations, we executed conformational search by simulated annealing method, which has been described in previous publication.<sup>9a</sup> The structures of tetramethoxycalix[4]arenes **1** and **2** obtained from MM/MD calculations were fully re-optimized using *ab initio* methods to estimate the absolute and relative energies for the different conformations.

RHF/6-31G and 6-31G\*\* optimizations of calix[4]arenes **1** and **2** by Gaussian 98 on Fujitsu VPP 5000 supercomputer

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(13GB RAM with 36000 MFLOPS CPU speed) at Okazaki National Research Institute of Japan took more than 50 hours to reach an optimum conformation with error limit of less than 0.001 kcal/mol ( $2 \times 10^{-7}$  atomic unit (A.U.)) for each conformer. Generous time allocation of the super-computer should be appreciated to the research center for computational science in the Institute for Molecular Science of Japan.

## Results and Discussion

**Conformational Characteristics of Tetramethoxycalix[4]arenes.** The *ab initio* quantum mechanical full optimizations without any constraint were carried out for the different conformers of tetramethoxycalix[4]arene **1** and **2**: cone, partial-cone, 1,2-alternate, and 1,3-alternate conformers.

It is well known that the unmodified calix[4]arene-25,26,27,28-tetraols form strong intramolecular hydrogen bonds among OH groups and rendering the cone conformer to be the most stable.<sup>13</sup> However, in *O*-methylated tetramethoxycalix[4]arenes the cone conformer is no longer the most stable due to the absence of intramolecular hydrogen

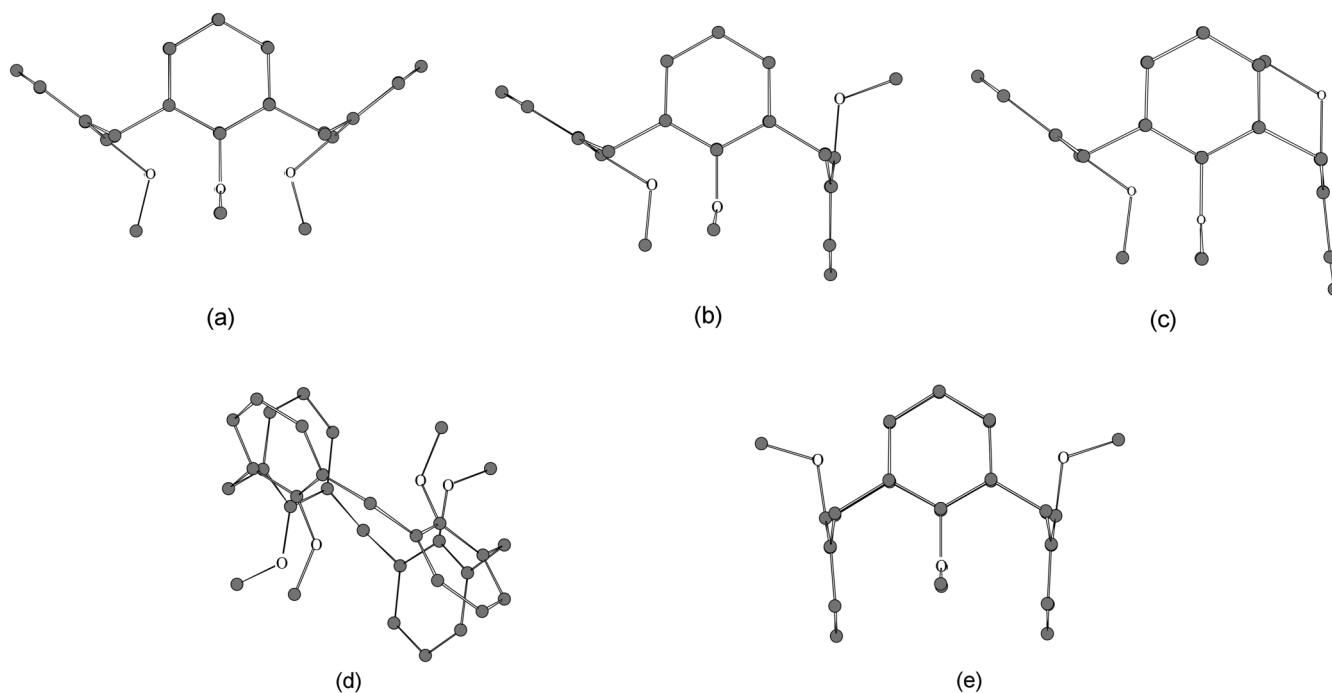
bonds. In this case, the methoxy moieties of tetramethoxycalix[4]arene can either point into the annulus of the calix[4]arene or point outward. In most publications, the conformational energies were calculated using only one representative of every conformation: a conformation with all methoxy moieties pointing outward.<sup>6a</sup> The high-field position of some of the methoxy signals of **2** in the NMR spectrum obtained in CDCl<sub>3</sub> indicates that the methoxy groups of the 1,2-alt and 1,3-alt, and one of the methoxy groups of the partial cone is, at least part of the time, pointing inward.<sup>7</sup> Reinhoudt group took all possible methoxy in/out conformations into account for the tetramethoxy-*p*-*tert*-butylcalix[4]arene **2**.<sup>7</sup> They summarized the calculated results on conformational distribution and obtained the Boltzmann distribution from the minimized potential energies and quantum mechanical vibrational free energies as well as the zero point correction energy. The result indicated that the conformers other than partial cone stayed in methoxy "out" conformations. Therefore, in this study, methoxy in/out conformations are taken into account only for the partial cone conformation for both **1** and **2**.

### Minimized Energies and Optimized Structures of

**Table 1.** *Ab Initio* Relative Energy (kcal/mol)<sup>a</sup> of Tetramethoxycalix[4]arene **1**

Conformation	Cone	Paco (out) <sup>b</sup>	Paco (in) <sup>c</sup>	1,2-Alt	1,3-Alt
HF/6-31G (kcal/mol)	1.81	0.00	4.16	7.98	2.84
HF/6-31G** (kcal/mol)	0.31	0.00	5.71	5.85	3.15
NMR CDCl <sub>3</sub> (Experimental) <sup>d</sup>	0.32	0.00	e	e	e

<sup>a</sup>Error limits in these calculations are about 0.01 kcal/mol. <sup>b</sup>Partial cone with all four methoxy groups "out" conformation. See Figure 1(b). <sup>c</sup>Partial cone with the conformation at which the methoxy group of the inverted anisole ring is "in" position. See Figure 1(c). <sup>d</sup>Taken from reference 6a. <sup>e</sup><sup>1</sup>H NMR signals (3.02, 3.58, and 3.70 ppm) at 243 K assigned to the OMe protons in partial cone conformer indicate "methoxy out" position. "Not observed"



**Figure 1.** Conformations of tetramethoxycalix[4]arene **1**: (a) cone, (b) partial cone (methoxy out), (c) partial cone (methoxy in), (d) 1,2-alternate, and (e) 1,3-alternate.

**Table 2.** *Ab Initio* Relative Energy (kcal/mol)<sup>a</sup> of Tetramethoxy-*p-tert*-butylcalix[4]arene **2**

Conformation	Cone	Paco (out)	Paco (in)	1,2-Alt	1,3-Alt
HF/6-31G (kcal/mol)	1.29	0.00	3.16	6.62	4.15
HF/6-31G** (kcal/mol)	-0.34	0.00	5.48	4.82	3.76
NMR CDCl <sub>3</sub> (Experimental) <sup>b</sup>	1.20	0.00 <sup>d</sup>		1.30	2.20
NMR CD <sub>2</sub> Cl <sub>2</sub> (Experimental) <sup>c</sup>	0.70	0.00 <sup>d</sup>		1.30	1.50

<sup>a</sup>Error limits in these calculations are about 0.01 kcal/mol. <sup>b</sup>Taken from reference 6a. <sup>1</sup>H NMR signals (2.10, 3.45, 3.50 (2x) ppm) at 243 K assigned to the OMe protons in partial-cone conformer indicate "methoxy out" position. <sup>c</sup>Taken from reference 7. Paco (methoxy in) is most likely the conformation observed in chloroform solution, based on the high-field position of one ( $\delta = 1.99$  ppm) of the three of the methoxy signals (1.99, 2.48 (2x), 3.46 ppm) in the <sup>1</sup>H NMR spectrum at 243 K.<sup>4,12</sup> Paco (methoxy out) is the conformation found in the solid state.<sup>4</sup> <sup>d</sup>Experimental results<sup>4,6a,7,12</sup> indicate different orientations (out or in) of the methoxy group of the inverted anisole ring. Therefore, we have placed the value in the middle of the two columns.

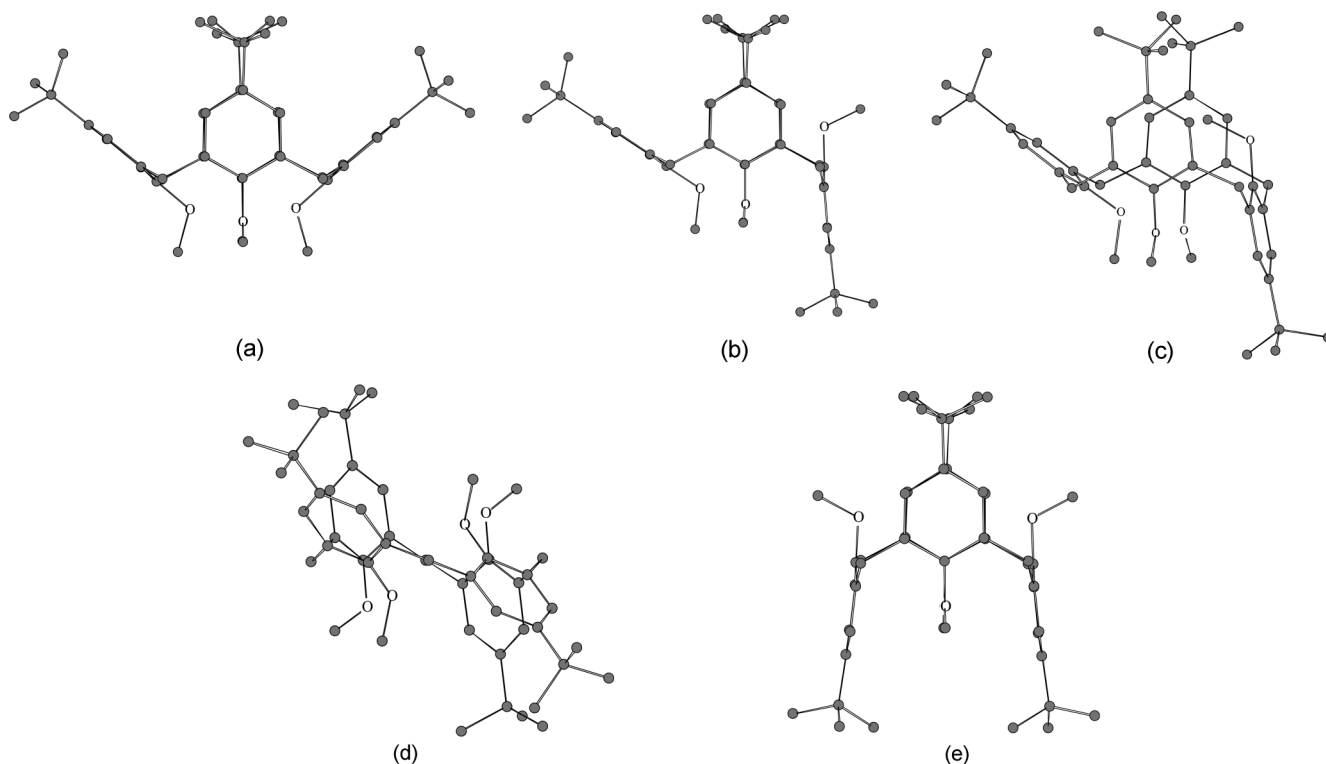
**Tetramethoxycalix[4]arenes.** The results of RHF/6-31G energies calculated for the conformers of tetramethoxycalix[4]arene **1** without *tert*-butyl groups are listed in Table 1, which reports the relative energies of conformers in kcal/mol and compares with experimental values<sup>6a</sup> obtained from NMR.

Calculation results suggest that partial cone conformer is most stable among the various conformers of tetramethoxycalix[4]arene **1** in following order: partial-cone (methoxy out) > cone > 1,3-alternate > partial-cone (methoxy in) > 1,2-alternate. Table 1 shows that the partial cone (methoxy out) conformer is 0.31 kcal/mol more stable than cone, and 4.16 kcal/mol more stable than partial-cone (methoxy in) analogue. The NMR study on tetramethoxycalix[4]arene **1** showed that partial cone conformer is found to be most stable in solution.<sup>6</sup> Shinkai group have also calculated the relative stabilities of four different conformations of the

tetramethoxycalix[4]arene (**1** and **2**) using MM3 molecular modeling software, and reported quantitatively the similar trend (in the order of partial cone (most stable) > cone > 1,2-alternate ~ 1,3-alternate) with the relative free energies obtained from the NMR spectroscopic data.<sup>6</sup> Figure 1 shows the calculated stable conformations of tetramethoxycalix[4]arene **1**.

The results of RHF minimized energies for the conformers of tetramethoxy-*p-tert*-butylcalix[4]arene **2** are listed in Tables 2, which reports the relative energies of conformers in kcal/mol for both 6-31G and 6-31G\*\* calculations and comparison with experimental values<sup>6a,7</sup> obtained from NMR spectroscopy.

For tetramethoxy-*p-tert*-butylcalix[4]arene **2**, the present RHF/6-31G calculations again suggest that partial cone "out" conformer is most stable and decreases in following order: partial cone (out) > cone > partial cone (in) > 1,3-



**Figure 2.** Conformations of tetramethoxy-*p-tert*-butylcalix[4]arene **2**: (a) cone, (b) partial cone (methoxy out), (c) partial cone (methoxy in), (d) 1,2-alternate, and (e) 1,3-alternate.

alternate > 1,2-alternate. The results of most stable conformation for partial cone calculated by RHF/6-31G agree with the reported experimental data,<sup>6a,7</sup> while RHF/6-31G\*\* calculation shows a little different order in relative stabilities. However, if we count the observable degeneracy number of conformations, the probability of finding partial-cone conformer will be four times the value of finding cone conformer. Therefore, the 0.34 kcal less stable partial-cone conformer (methoxy out) has about twice more population (65.5%) than cone analog (34.5%). In this case, the populations of 1,2-Alt, 1,3-Alt, and partial-cone (methoxy in) conformation are negligible. Boltzmann distributions for each conformation are calculated with the following degeneracy numbers<sup>7</sup>: Cone: 2; Paco: 8; 1,2-Alt: 4; 1,3-Alt: 2 at a temperature of 243 K which is used in NMR experiment.<sup>6a,7</sup>

Figure 2. shows the optimized conformations of tetramethoxy-*p-tert*-butylcalix[4]arene **2**.

Although the calculations are performed under quite different conditions of vacuum without any solvent molecules from the experimental results referenced, we believe that the present simulations performed by *ab initio* calculation provide a general and useful explanation to the conformational behavior of quite large and relatively complicated molecules of the tetramethoxycalix[4]arenes.

### Conclusion

Using the *ab initio* RHF/6-31G and 6-31G\*\* methods we have calculated the relative energies of the different conformations of the tetramethoxycalix[4]arene (**1** and **2**). Trends in relative stabilities of tetramethoxycalix[4]arene **1** and tetramethoxy-*p-tert*-butylcalix[4]arene **2** are found to be similar in following order: partial cone (most stable) > cone > 1,3-alternate > 1,2-alternate. The results of the most stable conformation of partial cone agree well with the reported NMR experimental data. The partial-cone conformer with methoxy "out" was calculated about 5 kcal/mol more stable than the partial-cone (methoxy "in") analog in vacuum.

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