

Ab Initio Study of the Conformational Isomers of Tetraethyl and Triethyl Esters of Calix[4]arene

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In this study we have performed *ab initio* computer simulations to investigate the conformational characteristics of the tetraethyl (**1**) and triethyl ester (**2**) of *p-tert*-butylcalix[4]arene. The structures of different conformational isomers for each compound have been optimized using *ab initio* RHF/6-31G methods. After optimization, B3LYP/6-31+G(d,p) single point calculations of the final structures are done to include the effect of electron correlation and the basis set with diffuse function and polarization function. Relative stability of tetraethyl ester (**1**) of *p-tert*-butylcalix[4]arene is in following order: cone (most stable) > partial cone > 1,3-alternate > 1,2-alternate isomer. Relative stability of triethyl ester (**2**) of *p-tert*-butylcalix[4]arene is in following order: cone (most stable) > 2-partial cone > 1-partial cone > 3-partial cone ~ 1,3-alternate ~ 1,2-alternate isomer.

Key Words : *Ab initio* calculation, HF/6-31G, Calix[4]arene esters, Conformational isomer, Cone

Introduction

There are four possible conformational isomers 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.^{1,2} 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.³⁻⁷

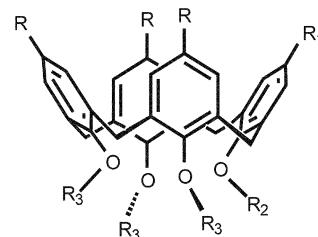
The relative stabilities of four different conformations of the tetramethoxycalix[4]arene (**3** and **4**) have been calculated using MM3 molecular modeling software, and the trend (in the order of partial cone (most stable) > cone > 1,2-alternate ~ 1,3-alternate) is consistent with the relative free energies obtained from the NMR spectroscopic data.⁶ 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 **4**.⁷

We have published a series of calculations for the relative stabilities on the conformers of *p-tert*-butylcalix[4]crown-6-ether by *ab initio* RHF/6-31G method, which showed that the cone conformation is generally the most stable.⁸ We have also reported the conformational behavior of tetramethoxycalix[4]arenes using *ab initio* RHF/6-31G and 6-31G** calculations.⁹ Trends in relative stabilities of tetramethoxycalix[4]arene **3** and tetramethoxy-*p-tert*-butylcalix[4]arene **4** are found to be similar in following order: partial cone (most stable) > cone > 1,3-alternate > 1,2-alternate.⁹ The results of the most stable conformation of partial cone agree well with the reported NMR experimental data.⁶

The main emphasis of this research is determining the relative stability of different conformational isomers for the tetraethyl (**1**) and triethyl ester (**2**) of the calix[4]arene 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 conformational isomers and supramolecular functions.

Since calix[4]quinone and calix[4]hydroquinone have recently been very useful chemical substance in making organic nanotubes and silver nanowires,¹⁰ it would be interesting to investigate the conformational characteristics of calix[4]arene systems as a building block of nano-materials.



	R	R ₁	R ₂	R ₃
1	<i>tert</i> -Bu		CH ₂ CO ₂ CH ₂ CH ₃	
2	<i>tert</i> -Bu	H	H	CH ₂ CO ₂ CH ₂ CH ₃
3	<i>tert</i> -Bu			CH ₃
4	H			CH ₃

Scheme 1. Chemical structures of calix[4]arene derivatives.

Computational Methods

The initial structures of *p-tert*-butylcalix[4]arene derivatives were constructed by HyperChem.¹¹ In order to find optimized conformations, we executed conformational search by simulated annealing method, which has been described in previous publication.^{8a} The structures of tetraethyl (**1**) and

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triethyl ester (**2**) of *t*-butylcalix[4]arenes obtained from MM/MD calculations were fully re-optimized to estimate the binding energies and the enthalpies of formation for the compounds using AM1 method. In order to confirm that the structures are in the local minima, we have calculated the normal mode frequencies of the optimized conformational isomers of **1** and **2**. Each vibrational spectrum shows no negative value of frequency, which suggests that the optimized structure is really in minimum point. In the previous publication¹² of *ab initio* RHF/6-31G study of vibrational spectrum of *p*-*tert*-butylcalix[4]crown-6-ether, the optimized structure is also confirmed to be in the minimum point.

RHF/6-31G optimizations of **1** and **2** followed by B3LYP/6-31+G(d,p) single point calculations of the structures using Gaussian 98 on Fujitsu VPP 5000 supercomputer took more than 100 hours to reach an optimum structure with error limit of less than 0.001 kcal/mol (2×10^{-6} atomic unit (A.U.)) for each conformational isomer. The large portions of the computations were carried out with use of the computer facilities at the Research Center for Computational Science of The Okazaki National Research Institutes in Japan.

Results and Discussion

Conformational Characteristics of Tetraethyl Ester (1) of *p*-*tert*-Butylcalix[4]arene. 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.¹³ Substitution of all the phenolic protons of a calix[4]arene by

a bulky alkyl group generally leads to conformationally rigid products. However, when the substituent is small such as a methyl group, the resulting methyl ether is no longer rigid and any anisole ring can rotate *via* oxygen-through-the-annulus to give a mixture of the four possible conformers.⁹ Reinhoudt group summarized the calculated results on conformational distribution and obtained the Boltzmann distribution for the tetramethoxy-*p*-*tert*-butylcalix[4]arene **4**.⁷ Tetraethyl ether of *p*-*tert*-butylcalix[4]arene is much less conformationally mobile than tetramethyl ether **4**. And tetrapropyl and tetrabenzyl ether of *p*-*tert*-butylcalix[4]arene are conformationally fixed.

The RHF/6-31G optimizations without any constraint followed by B3LYP/6-31+G(d,p) single point calculations were carried out for the different conformational isomers of tetraethyl ester of *p*-*tert*-butylcalix[4]arene **1**: cone, partial-cone, 1,2-alternate, and 1,3-alternate. The results of RHF/6-31G optimized energies and B3LYP/6-31+G(d,p) energies are listed in Table 1, which reports the *ab initio* absolute energies (in atomic unit) and relative values (in kcal/mol) of **1**. The relative stabilities calculated from less reliable AM1 semi-empirical and MM+ methods are also reported for comparison in Table 1.

Ab initio calculation results suggest that cone-shaped structure is most stable among the various conformational isomers of **1** in following order: cone > partial-cone > 1,3-alternate > 1,2-alternate. B3LYP/6-31+G(d,p) single point energy reports that the cone isomer is slightly (0.097 kcal/mol) more stable than partial cone, and 5.72 kcal/mol more stable than 1,3-alternate analogue. AM1 semi-empirical and MM+ methods report different values, but the overall trends

Table 1. Calculated energies^a of tetraethyl ester of calix[4]arene (**1**)

Method \ Conformation	Cone	Paco	1,2-Alt	1,3-Alt
HF/6-31G Optimized	-3215.7004	-3215.6990	-3215.6847	-3215.6913
HF/6-31G (relative)	0.0000	0.8964	9.8769	5.7200
B3LYP/6-31+G(d,p) single point	-3237.4807	-3237.4806	-3237.4639	-3237.4717
B3LYP/6-31+G(d,p) (relative)	0.0000	0.0969	10.5750	5.6724
AM1 Optimized (relative)	0.0000	5.1728	13.4640	9.6755
MM+ Optimized (relative)	0.0000	3.5600	12.6100	13.4900

^aError limits in these calculations are about 2×10^{-5} A.U. or 0.01 kcal/mol. *Ab initio* energies were written as A.U. The relative energies were reported as kcal/mol using conversion factor: 1 A.U. = 627.50955 kcal/mol.

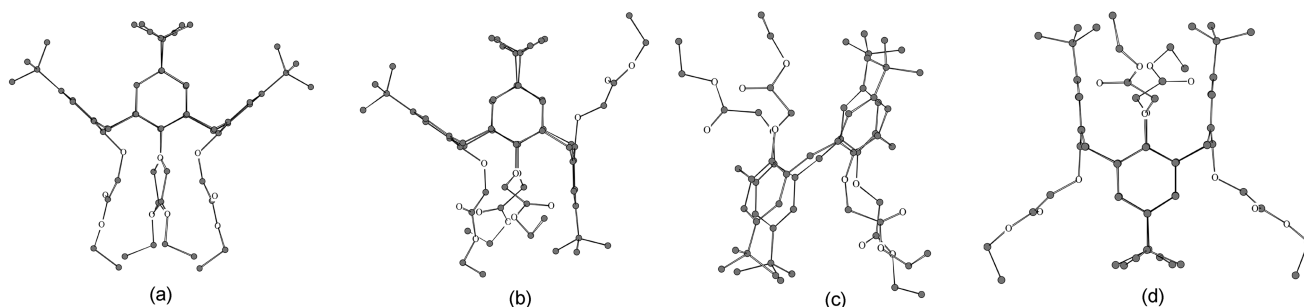


Figure 1. Structures of tetraethyl ester of *tert*-butylcalix[4]arene (**1**): (a) cone, (b) partial cone, (c) 1,2-alternate, and (d) 1,3-alternate conformational isomer. Hydrogen atoms are omitted for clarity.

Table 2. Calculated energies^a triethyl ester of calix[4]arene (**2**)

Method \ Conformation	Cone	1-Paco ^b	2-Paco ^c	3-Paco ^d	1,2-Alt	1,3-Alt
HF/6-31G Optimized	-2755.0960	-2755.0880	-2755.0940	-2755.0800	-2755.0790	-2755.0810
HF/6-31G (relative)	0.0000	5.0201	1.2550	10.0402	10.6677	9.4126
B3LYP/6-31+G(d,p) single point	-2773.7275	-2773.7202	-2773.7268	-2773.7173	-2773.7151	-2773.7132
B3LYP/6-31+G(d,p) (relative)	0.0000	4.6090	0.4680	6.4168	7.7898	8.9958
AM1 Optimized (relative)	0.0000	6.1375	6.4653	7.4690	8.1127	10.7625
MM+ Optimized (relative)	0.0000	8.8500	4.7400	10.5340	4.4000	8.0200

^aError limits in these calculations are also about 2×10^{-5} A.U. or 0.01 kcal/mol. See Table 1. ^bPartial cone of **2** with an inverted phenol ring. See 2(b). ^cPartial cone of **2** with an inverted ring which is just next of phenol ring. See Figure 2(c). ^dPartial cone of **2** with an inverted ring which is opposite side of phenol ring. See Figure 2(d).

of the relative stabilities are very similar to the *ab initio* methods. The major factor for relative stability is coming from the electrostatic interactions of the ester groups in the lower rim of tetraethyl ester of *p-tert*-butylcalix[4]arene.

An interesting thing to mention about the MM+ optimized cone-shaped structure of **1** is that the planes of four benzene rings show significantly different dihedral angles for opposite rings. Two opposite rings are almost parallel and the other opposite planes are almost perpendicular, whereas *ab initio* optimized structure displays a little closer to C_{4v} symmetry.

Conformational Characteristics of Triethyl Ester (2**) of *p-tert*-Butylcalix[4]arene.** It is very interesting to know what kind of influence to the relative stabilities for the different conformational isomers of *p-tert*-butylcalix[4]arene will be made by the substitution of one of the four long-bulky rings in **1** with the original debutylated phenol group. The phenol ring with R₁=H and R₂=H of **2** is movable through the annulus of upper or lower rim. However, other three rings with R=*tert*-butyl and R₃=CH₂CO₂CH₂CH₃ are too long and bulky, the steric hindrance will not permit the rotation through the annulus. The number of distinct conformational isomers for **2** is increased to six (cone, 1-partial-cone, 2-partial-cone, 3-partial-cone, 1,2-alternate, and 1,3-alternate).

The RHF/6-31G optimizations without any constraint followed by B3LYP/6-31+G(d,p) single point calculations were carried out for the six different conformational isomers of triethyl ester (**2**) of *p-tert*-butylcalix[4]arene. The results of RHF/6-31G optimized energies and B3LYP/6-31+G(d,p) energies are listed in Table 2, which reports the *ab initio* absolute energies (in atomic unit) and relative values (in kcal/mol) of **2**. The relative stabilities calculated from AM1 semi-empirical and MM+ methods are also reported for comparison in Table 2.

Ab initio calculation results suggest that cone-shaped structure is most stable among the various conformational isomers of **2** in following order: cone > 2-partial-cone > 1-partial-cone > 3-partial-cone ~ 1,3-alternate ~ 1,2-alternate. B3LYP/6-31+G(d,p) single point energies reports that the cone conformational isomer is 0.46 kcal/mol more stable than 2-partial-cone, 4.61 kcal/mol more stable than 1-partial-cone, and 6.42 kcal/mol more stable than 3-partial-cone analogue. Figure 2 shows the calculated stable structures of triethyl ester of *tert*-butylcalix[4]arene **2**.

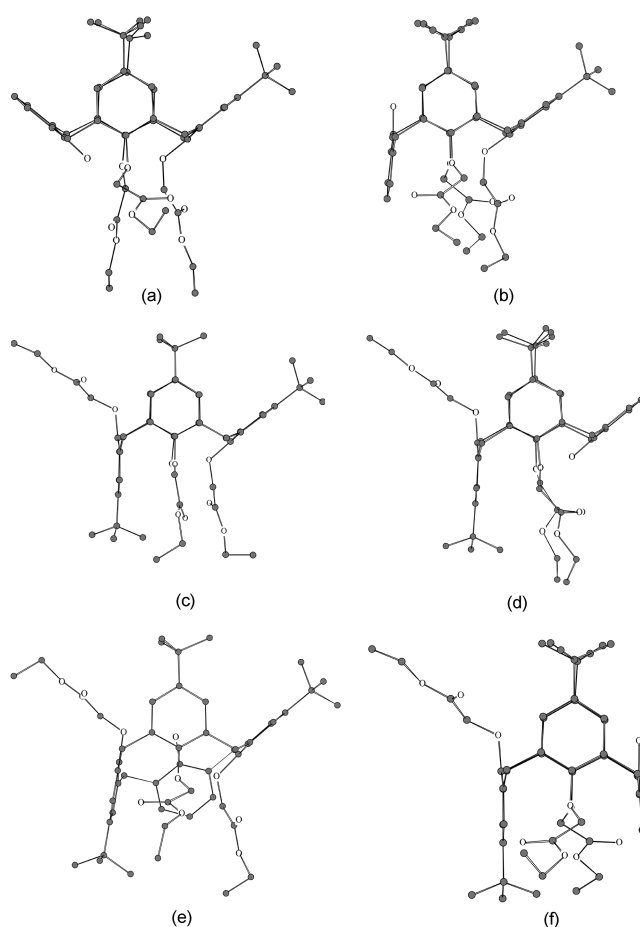


Figure 2. Structures of triethyl ester of *p-tert*-butylcalix[4]arene (**2**): (a) cone, (b) 1-partial cone, (c) 2-partial cone, (d) 3-partial cone, (e) 1,2-alternate, and (f) 1,3-alternate conformational isomer. Hydrogen atoms are omitted for clarity.

The reasons of the best stability of cone conformation (Figure 2(a)) of **2** are coming from the hydrogen bonding between the hydrogen of the hydroxyl group and the adjacent ether oxygen, and from no steric hindrance of phenol ring which has no *p-tert*-butyl group on the upper rim. The next most stable isomer (2-partial cone) of Figure 2(c) shows a strong hydrogen-bonding between the hydrogen of the O-H group and two oxygen's (one from ether oxygen and another one from the C=O group in the ethyl ester branch). The 1-partial-cone isomer is less stable than 2-

partial-cone analogue, since OH group of the inverted phenol ring in the Figure 2(b) of 1-partial cone has no hydrogen-bond with the oxygen's of the adjacent rings. The 3-partial-cone isomer is less stable than 2-partial cone, since the bulky *tert*-butyl group of an inverted *p-tert*-butylbenzene ring in the Figure 2(d) of 3-partial cone makes steric interference with two ethyl ester groups of the adjacent rings.

In both **1** and **2** calix[4]aryl esters, the electrostatic interactions of the ester groups in the lower rim of ethyl esters of *p-tert*-butylcalix[4]arene are major factors for the relative stabilities. In triethyl ester (**2**), the hydrogen-bonding between the hydrogen of the O-H group and oxygen atom is another strong influence to the stabilities of conformational isomers. The present simulation performed by *ab initio* calculation provides a general and useful explanation to the relative stabilities of the different conformational isomers of quite large and relatively complicated molecules of the tetra- and tri-ethyl esters of *p-tert*-butylcalix[4]arene.

Conclusion

Using the *ab initio* RHF/6-31G and B3LYP/6-31+G(d,p) methods we have calculated the absolute and relative energies of the different conformational isomers of the tetraethyl (**1**) and triethyl ester (**2**) of *t*-butylcalix[4]arenes. Relative stability of tetraethyl ester (**1**) of *p-tert*-butylcalix[4]arene is in following order: cone (most stable) > partial cone > 1,3-alternate > 1,2-alternate. Relative stability of triethyl ester (**2**) of *p-tert*-butylcalix[4]arene is in following order: cone (most stable) > 2-partial cone > 1-partial cone > 3-partial cone ~ 1,3-alternate ~ 1,2-alternate. The electrostatic interactions of the ester groups in the lower rim of *p-tert*-butylcalix[4]aryl esters (**1** and **2**) and the hydrogen-bonding between the hydrogen of the O-H group and oxygen atom in **2** are major factors for the relative stabilities of conformational isomers.

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