STUDY ON THE CONFORMATIONS OF *p*-(NITRO)METHOXYCALIX[4]ARENE AND *p*-(*tert*-BUTYL)METHOXYCALIX[4]ARENE USING HIGH LEVEL *AB INITIO* METHOD

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ABSTRACT

Ab initio calculations have been performed in order to investigate the conformational characteristics of p-(nitro)methoxycalix[4]arene and p-(tert-butyl)methoxycalix[4]arene. The structures of four types (cone, partial cone, 1,2-alternate and 1,3-alternate) of conformers for each compound have been optimized by ab initio method at the restricted Møller-Plesset fourth-order perturbation (RMP4) level of theory using 6-311G and 6-311G++(d,p) basis sets. General trends in relative stabilities of p-(nitro)methoxycalix[4]arene and p-(tert-butyl)methoxycalix[4]arene are similar and decrease in following order: partial cone > 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.

Keywords: *ab initio, RMP4, conformational characteristics, p-(nitro)methoxycalix[4]arene, p-(tert-butyl)methoxycalix[4]arene*

INTRODUCTION

Calix[4]arenes are macrocyclic compounds which are increasingly being used as building blocks in supramolecular chemistry [1-2]. One interesting property of calix[4]arenes is that they can exist in four extreme conformations, designated cone, partial cone, 1,2-alternate and 1,3-alternate, due to the inhibition of *O*-annulus rotations by the presence of bulky substituents larger than ethyl groups on phenol moiety [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.

Grootenhuis *et al*. calculated the structural, energetical and acid-base properties of calix[4]arene using molecular mechanics programs such as AMBER, MM2P, QUANTA/CHARMm [3]. Shinkai group have calculated the relative stabilities of four different conformations of the methoxycalix[4]arene 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 [4]. 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 [5].

Since calix[4]quinone and calix[4]hydroquinone have recently been very useful chemical substance in making organic nanotubes and silver nanowires [6], it would be interesting to investigate the conformational characteristics of calix[4]arene systems as a building block of nanomaterials. The cone conformation has a cavity which has inspired the use of calix[4]arenes as host molecules and potential enzyme mimics [1-2].

In this paper, we have calculated the conformational behavior of *p*-(nitro)methoxycalix[4] arene and p-(*tert*-butyl)methoxycalix[4]arene using high level *ab initio* RMP4/6-311G and RMP4/6-311G++(d,p) calculations. The main emphasis of this research is determining the relative stability of different conformational isomers for p-(nitro)methoxycalix[4] arene and p-(*tert*-butyl)methoxycalix[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.

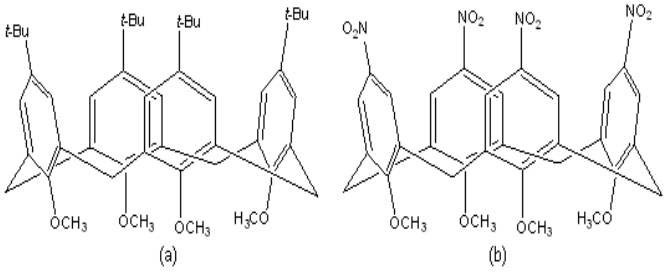

Figure 1. Molecular structures of p-(*tert*-butyl)methoxy calix[4]arene (a) and p-(nitro)methoxycalix[4]arene (b)

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COMPUTATIONAL METHODS

The initial structures of calix[4]arene were constructed by HyperChem 7.5 program [7]. In order to find optimized conformations, we executed conformational search by Molecular Mechanics Molecular Dynamics (MM MD) simulation using BIO+ force fields. The structures of calix[4]arene obtained from MM MD calculations were fully re-optimized by *ab initio* methods to estimate the absolute and relative energies for the different conformations.

We have carried out geometry optimizations at the restricted Møller-Plesset fourth-order perturbation (RMP4) level of theory using 6-311G and 6-311G++(d,p) basis sets. The calculations have been performed with the GAUSSIAN 03 program [8] on linux-based cluster computer took more than 400 hours to reach an optimum conformation with error limit of less than 0.001 kcal/mol for each conformer.

RESULT AND DISCUSSION

Conformational characteristics

The *ab initio* quantum mechanical full optimizations without any constraint were carried out for the different conformers of p-(nitro)methoxycalix[4]arene and p-(*tert*-butyl)methoxycalix[4]arene: 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 [9]. However, in *O*-methylated methoxycalix[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 methoxycalix[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 [4]. The high-field position of some of the methoxy signals of p-(*tert*-butyl)methoxycalix[4]arene in the NMR spectrum obtained in $CDCl_3$ indicates that the methoxy groups of the 1,2-alternate and 1,3-alternate and one of the methoxy groups of the partial cone is, at least part of the time, pointing inward. Reinhoudt group took all possible methoxy in/out conformations into account for the p-(*tert*-butyl)methoxycalix[4]arene [5]. 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 p-(nitro)methoxycalix[4]arene and p-(*tert*-butyl)methoxycalix[4]arene.

Minimized Energies and Optimized Structures

The results of RMP4 calculated energies for the conformers of p-(nitro)methoxycalix[4]arene are listed in Table 1, which reports the relative energies of conformers in kcal/mol and compares with experimental values obtained from NMR [4]. Calculation results suggest that partial cone conformer is most stable among the various conformers of p-(nitro)methoxycalix[4]arene in following order: partial cone (methoxy out) > cone > 1,3-alternate

Table 1. *Ab initio* relative energy (kcal/mol)[a] of p-(nitro)methoxycalix[4]arene

Methods	cone	paco (out)[b]	paco (in)[c]	1,2-alt	1,3-alt
RMP4/6-311G (kcal/mol)	0.56	0.00	4.63	7.87	2.91
RMP4/6-311G++(d,p) (kcal/mol)	0.33	0.00	5.42	5.76	3.14
NMR $CDCl_3$ (experimental)[d]	0.32	0.00	*e*	*e*	*e*

[a]Error limits in these calculations are about 0.001 kcal/mol. [b]Partial cone with all four methoxy groups "out" conformation, see Figure 2(b). [c]Partial cone with the conformation at which the methoxy group of the inverted anisole ring is "in" position, see Figure 2(c). [d]Taken from reference [4], ^{1}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. [e]Not observed.

Table 2. *Ab initio* relative energy (kcal/mol)[a] of p-(*tert*-butyl)methoxycalix[4]arene

Methods	cone	paco (out)	paco (in)	1,2-alt	1,3-alt
RMP4/6-311G (kcal/mol)	-0.31	0.00	5.48	4.82	3.76
RMP4/6-311G++(d,p) (kcal/mol)	1.14	0.00	3.16	6.62	4.15
NMR $CDCl_3$ (experimental)[b]	1.20	0.00[d]		1.30	2.10
NMR CD_2Cl_2 (experimental)[c]	1.10	0.00[d]		1.30	1.70

[a]Error limits in these calculations are about 0.001 kcal/mol. [b]Taken from reference [4], ^{1}H NMR signals (2.10, 3.45, 3.50 ppm) at 243 K assigned to the OMe protons in partial cone conformer indicate "methoxy out" position. [c]Taken from reference [5], Paco (methoxy in) is most likely the conformation observed in chloroform solution, based on the high-field position of one (δ = 1.99 ppm) of the three of the methoxy signals (1.99, 2.48, 3.46 ppm) in the ^{1}H NMR spectrum at 243 K. [d]Experimental results 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.

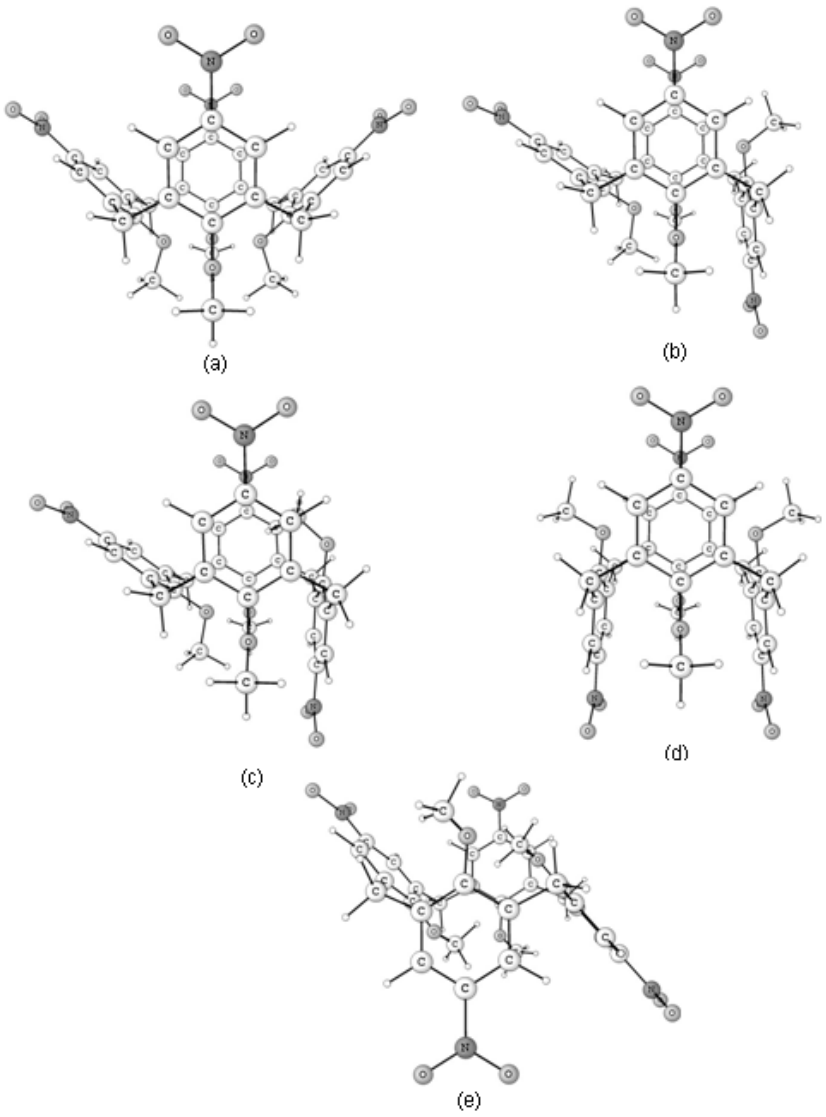

Figure 2. Conformations of p-(nitro)methoxycalix[4]arene 1: (a) cone, (b) partial cone (methoxy out), (c) partial cone (methoxy in), (d) 1,3-alternate and (e) 1,2-alternate

> partial-cone (methoxy in) > 1,2-alternate. Table 1 shows that the partial cone (methoxy out) conformer is 0.33 kcal/mol more stable than cone and 5.42 kcal/mol more stable than partial cone (methoxy in) analogue for RMP4/6-311G++(d,p) calculations. The NMR study on p-(nitro)methoxycalix[4]arene showed that partial cone conformer is found to be most stable in solution [4, 10-11]. Figure 2 shows the calculated stable conformations of p-(nitro)methoxycalix[4]arene.

The results of RMP4 minimized energies for the conformers of p-(*tert*-butyl)methoxycalix[4]arene are listed in Tables 2, which reports the relative energies of conformers in kcal/mol for both 6-311G and 6-311G++(d,p) calculations and comparison with experimental values obtained from NMR spectroscopy [4-5]. For p-(*tert*-butyl)methoxycalix[4]arene, the present RMP4/6-311G++(d,p) 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-alternate > 1,2-alternate. The results of most stable conformation for partial cone calculated by RMP4/6-311G++(d,p) agree with the reported experimental data [4-5], while RMP4/6-311G 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 0.31 kcal/mol 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-alternate, 1,3-alternate and partial cone (methoxy in) conformation are negligible. Boltzmann distributions for each conformation are calculated with the following

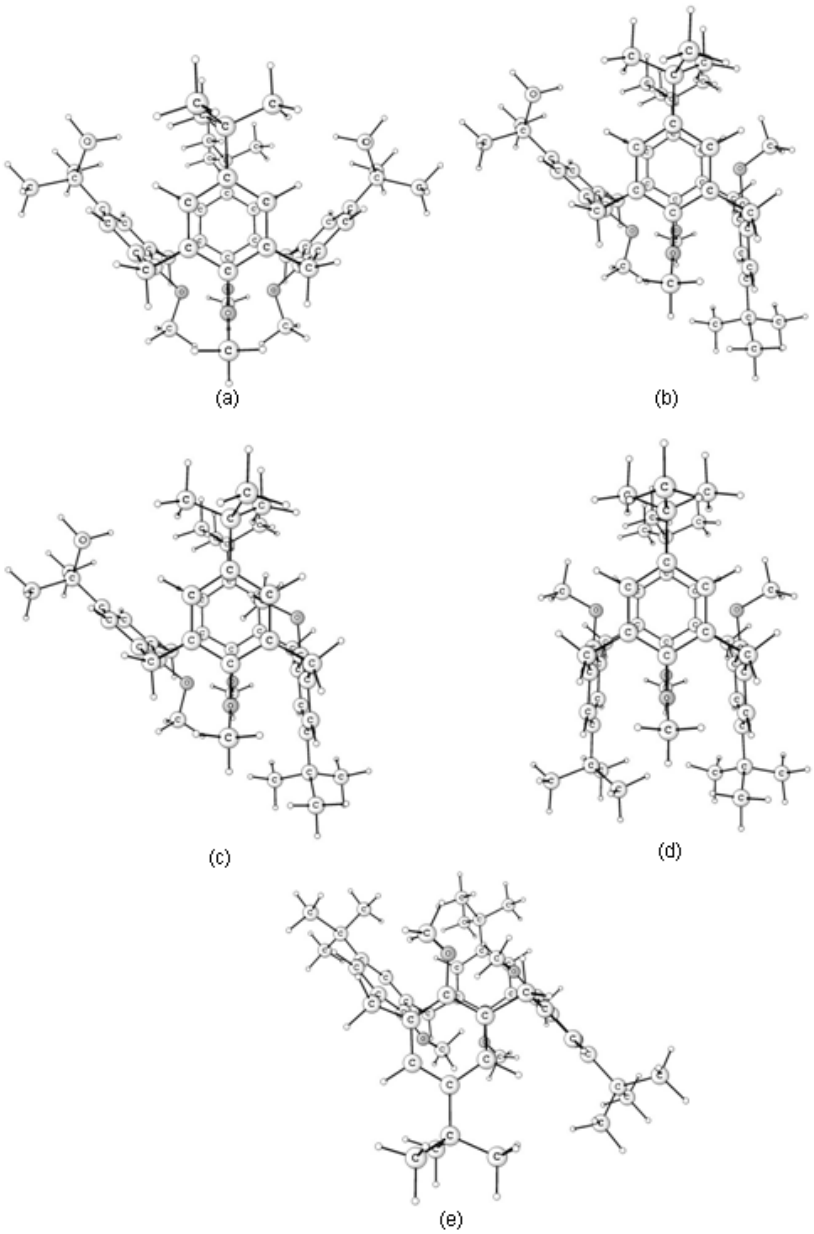

Figure 3. Conformations of p-(*tert*-butyl)methoxycalix[4]arene: (a) cone, (b) partial cone (methoxy out), (c) partial cone (methoxy in), (d) 1,3-alternate and (e) 1,2-alternate

degeneracy numbers: cone: 2; partial cone: 8; 1,2-alternate: 4; 1,3-alternate: 2 at a temperature of 243 K which is used in NMR experiment [4-5]. Figure 3 shows the optimized conformations of p-(*tert*-butyl)methoxy calix[4]arene.

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 calculations performed by *ab initio* calculation provide a general and useful explanation to the conformational behavior of quite large and relatively complicated molecules of the methoxycalix[4]arenes.

CONCLUSION

Using the high level *ab initio* RMP4/6-311G and RMP4/6-311G++(d,p) methods we have calculated the relative energies of the different conformations of p-(nitro)methoxycalix[4]arene and p-(*tert*-butyl)methoxy calix[4]arene. Trends in relative stabilities of p-(nitro)methoxycalix[4]arene and p-(*tert*-butyl)methoxy calix[4]arene are found to be similar in following order: partial cone > 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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