

## DFT Study of *p*-*tert*-Butylcalix[6]aryl Ester Complexed with Alkylammonium Ions

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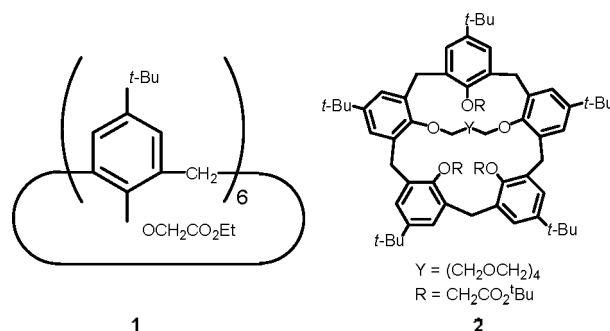
We have performed DFT B3LYP/6-31G(d,p) calculations to investigate the complexation behaviors of the ethyl ester derivative of *p*-*tert*-butylcalix[6]arene (**1**) toward a variety of alkylammonium ions. We have studied the binding sites of these host-guest complexes focusing on the *p*-*tert*-butylcalix[6]arene pocket (*endo*) of **1**. The smaller alkylammonium cations have the better complexation efficiency than the bulkier alkylammonium ions with the *p*-*tert*-butylcalix[6]aryl ester. The hydrogen-bonding of N-H...O is one of the important factors for the complexation behavior of the *p*-*tert*-butylcalix[6]aryl ester, in addition to the NH-aromatic  $\pi$ , CH-aromatic  $\pi$  and electrostatic interactions, and the steric hindrance of alkylammonium cation. The hydrogen-bonded distances and angles of N-H...O are reported for the complexes of the *p*-*tert*-butylcalix[6]aryl ester with various alkylammonium ions.

**Key Words:** DFT, B3LYP/6-31G(d,p), Calix[6]aryl ester, Alkylammonium ions, Hydrogen bond

### Introduction

The selective recognition of many important biogenic amines is one of the fundamental research interest in the field of the host-guest chemistry.<sup>1-3</sup> Calix[6]arene, a class of cyclic hexamers of phenol formaldehyde condensation product, seems to be more attractive for the design of larger organic guest ions, because they have larger cavities and therefore are expected to provide a more favorable versatile platform for the formation of inclusion complexes with many interesting guest molecules.<sup>4</sup> Even though some progress has been made on the design of suitably functionalized calixarene derivatives for the molecular recognition of amine and related compounds, a lot remains to be clarified.<sup>5,6</sup> For example, Shinkai *et al.* have reported that the trimethylammonium head group of some quaternary ammonium salt is predominantly included in the calixarene cavity via cation- $\pi$  interaction between  $\pi$ -base cavity of calix[6]arenes.<sup>7</sup> Ethyl ester derivatives of *p*-*tert*-butylcalix[6]arene (**1**) are known to have high affinity toward alkali metal ions, alkylammonium, and related cations.<sup>8,9</sup> Recently, 1,3-bridged calix[5]crown-6-ether (**2**) was investigated as a tool for the shape recognition of alkylammonium ions in focusing the *endo*-versus *exo*-cavity complexation.<sup>10,11</sup>

Various important computational approaches in a variety of interesting supramolecular system are published.<sup>12</sup> We have reported computer simulations on molecular recognition of alkylammonium ions by ethyl ester derivative of *p*-*tert*-butylcalix[6]arene (**1**) by using molecular mechanics (MM) and semi-empirical AM1 methods.<sup>13</sup> In that study, the *endo*-complex was reported as the most stable structure among different orientations of alkylammonium cations complexed inside the cone-shaped host. Complexes of aromatic ring with ammonium cations, which are very important in biological systems, were already studied using *ab initio* calculations.<sup>14,15</sup> *Endo*-calix complexations of alkylammonium cations by *p*-*tert*-calix[5]aryl ester have also been calculated by using the *ab initio* HF/6-31G method.<sup>16</sup>



**Scheme 1.** Chemical structures of (a) *p*-*tert*-butylcalix[6]aryl ethyl ester **1** and (b) 1,3-bridged *p*-*tert*-butylcalix[5]crown-6-ether **2**.

<sup>1</sup>H NMR complexation study of **1** with ethylammonium picrate guest suggests the conformational reorganization to the cone conformation has provoked upon the complex formation.<sup>17</sup> Also, an NMR study on complexation of ethylammonium ion by alkyl *p*-*tert*-butylcalix[6]aryl ester derivatives showed that the *endo*-type complexes are formed.<sup>18</sup>

In this paper, we have calculated the optimized energies and binding sites of calix[6]aryl ester (**1**) toward alkylammonium guests by using the DFT B3LYP/6-31G(d,p) calculation method, aiming to understand more deeply the complexational behavior of many related biologically interesting guests.

### Computational Methods

The initial structures of host **1** and alkylammonium guest molecules were constructed by HyperChem.<sup>19</sup> The lowest energy structures of host **1** and complexes obtained from the Molecular Mechanics (MM) and Molecular Dynamics calculations were re-optimized by using the AM1 semi-empirical quantum mechanical method.

The density functional theory (DFT)<sup>20,21</sup> methods are effective for the theoretical studies of supramolecular com-

plexes.<sup>22-26</sup> B3LYP, a version of the *DFT* method, which uses a Becke's three-parameter functional (B3) and a mixture of HF with *DFT* exchange terms associated with the gradient corrected correlation functional of Lee, Yang, and Parr (LYP).<sup>27</sup>

*DFT* B3LYP/6-31G(d,p) full optimizations of the structures of host **1** and its alkylammonium complexes obtained from AM1 semi-empirical method were performed to get the lowest energies and the stable structures by using Gaussian 03.<sup>28</sup>

## Results and Discussion

**Endo-Cone-type Complex.** Many different conformations (cone, a partial cone, three-[(1,2), (1,3), (1,4)]-alternates, three-[(1,2,3), (1,2,4), (1,3,5)]-alternates) are possible for calix[6]arene.<sup>17</sup> Without binding any alkylammonium guest, our calculations suggest that the 1,2,3-alternate conformational isomer of free host **1** is more stable than the cone analogue.<sup>13,29</sup> However, an NMR study on the complexation of ethylammonium or *n*-propylammonium cation by alkyl *p*-*tert*-butylcalix[6]aryl ester derivatives indicated that the guest is held tightly deep in the cone-shape aromatic cavity of calixarene, thus forming *endo*-type complex.<sup>18</sup> It was reported that, upon the complexation, the methyl and methylene protons in alkylammonium guest undergo upfield shifts by 2.6 and 2.9 ppm, respectively. The interaction of calixarene derivatives with primary alkylammonium ion is also reported to be originated from the complexation through a tripodal arrang

ement of  $N^+ - H \cdots O = C(\text{host})$  hydrogen bonds and  $R - NH_3^+ \cdots O = C(\text{host})$  charge dipole interaction.<sup>17</sup> The large upfield shifts observed are thought to arise from the so-called CH- $\pi$  interaction and indicate that the ethyl group side of the guest is embedded in the cavity and subject on the ring current of phenyl groups. The *endo*-type complexation may be caused predominantly by this interaction.<sup>18</sup> Therefore, we have focused our efforts to *endo*-cone-shaped complexes.

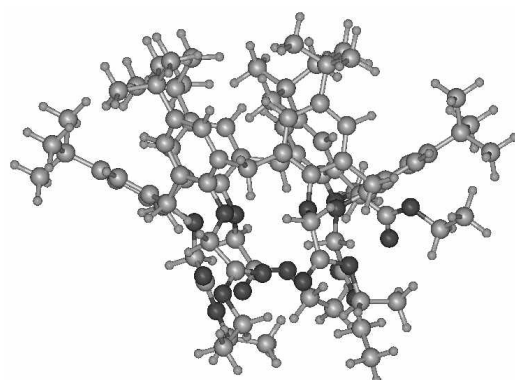
***DFT* B3LYP/6-31G(d,p) Calculations.** The *DFT* full optimizations were carried out for the *endo*-complexation mode of **1** by combining the cone conformer of host **1** with various alkylammonium cations. The results of B3LYP/6-31G(d,p) complexation energies of the complexes of calix[6]aryl ester (**1**) and 1,3-bridged *p*-*tert*-butylcalix[5]crown-6-ether (**2**)<sup>11</sup> with alkylammonium ions are listed in Table 1.

From Table 1, the more meaningful data than the absolute energies are the complexation energies ( $E_{\text{Complex}} - E_{\text{Host}} - E_{\text{Guest}}$ ). The smaller alkylammonium cations have the better complexation efficiency with *p*-*tert*-butylcalix[6]aryl ester than bulky alkylammonium ions. We can sort the complexation energies of nine alkylammonium complexes in Table 1 into three groups: the  $NH_4^+$ , methyl and ethyl ammonium complexes are 8 ~ 10 kcal/mol more stable than *n*-propyl, *iso*-propyl and *n*-butyl ammonium, and 20 ~ 30 kcal/mol more stable than the branched butyl ammonium analogues. One should note that in the gas phase it is natural that smaller cationic species such as  $NH_4^+$  should have higher binding energy than larger cationic species. However, in the presence

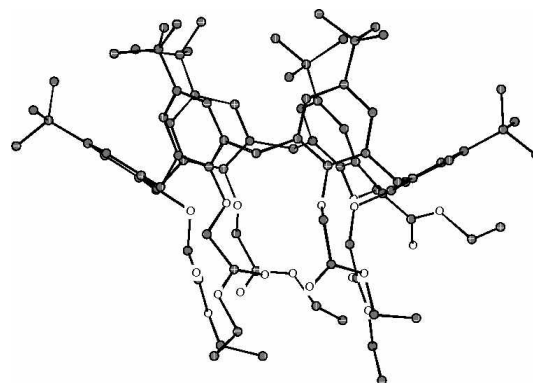
**Table 1.** *DFT* calculated complexation energies<sup>a</sup> of the *p*-*tert*-butylcalix[6]aryl ester (**1**) and 1,3-bridged *p*-*tert*-butylcalix[5]crown-6-ether (**2**) with alkylammonium ions

Guest <sup>b</sup>	$NH_4^+$	Me	Et	<i>n</i> -Pr	<i>iso</i> -Pr	<i>n</i> -Bu	<i>iso</i> -Bu	<i>sec</i> -Bu	<i>tert</i> -Bu
Cone-type <sup>c</sup> Host	<i>Endo</i> -Complexes with Cone-type Host								
<b>1</b>	-91.24	-89.77	-91.02	-82.52	-83.06	-79.59	-69.89	-73.42	-59.22
<b>2</b> <sup>d</sup>	-82.80	-73.56	-66.77	-66.56	-57.40	-65.22	-54.62	-49.11	-49.14

<sup>a</sup>Complexation energies (kcal/mol) =  $E_{\text{Complex}} - E_{\text{Host(cone)}} - E_{\text{Guest}}$ . <sup>b</sup>Me = methylammonium, Et = ethylammonium, *n*-Pr = *n*-propylammonium ion, *n*-Bu = *n*-butylammonium cation, etc. <sup>c</sup>The *DFT* B3LYP/6-31G(d,p) calculated energy of 1,2,3-alternate conformer of free host **1** was 7.16 kcal/mol more stable than the cone-type host **1**. However, we have chosen the cone-shaped host for the calculation of complexation energy relative to the *endo*-cone-type complex. Error limits in these calculations are about 0.01 kcal/mol. <sup>d</sup>Data are taken from the previously published reference 11.

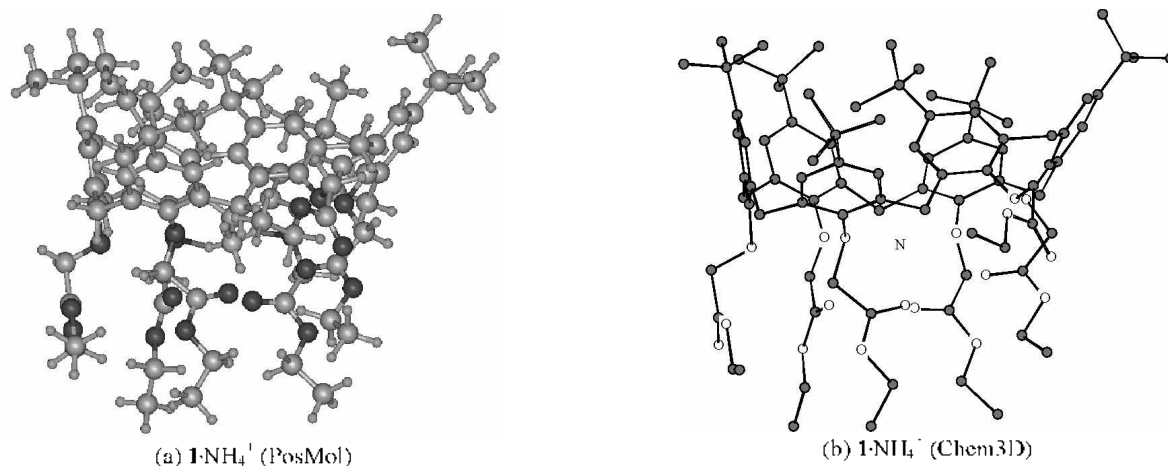


(a) Cone-type Host **1** (PosMol)

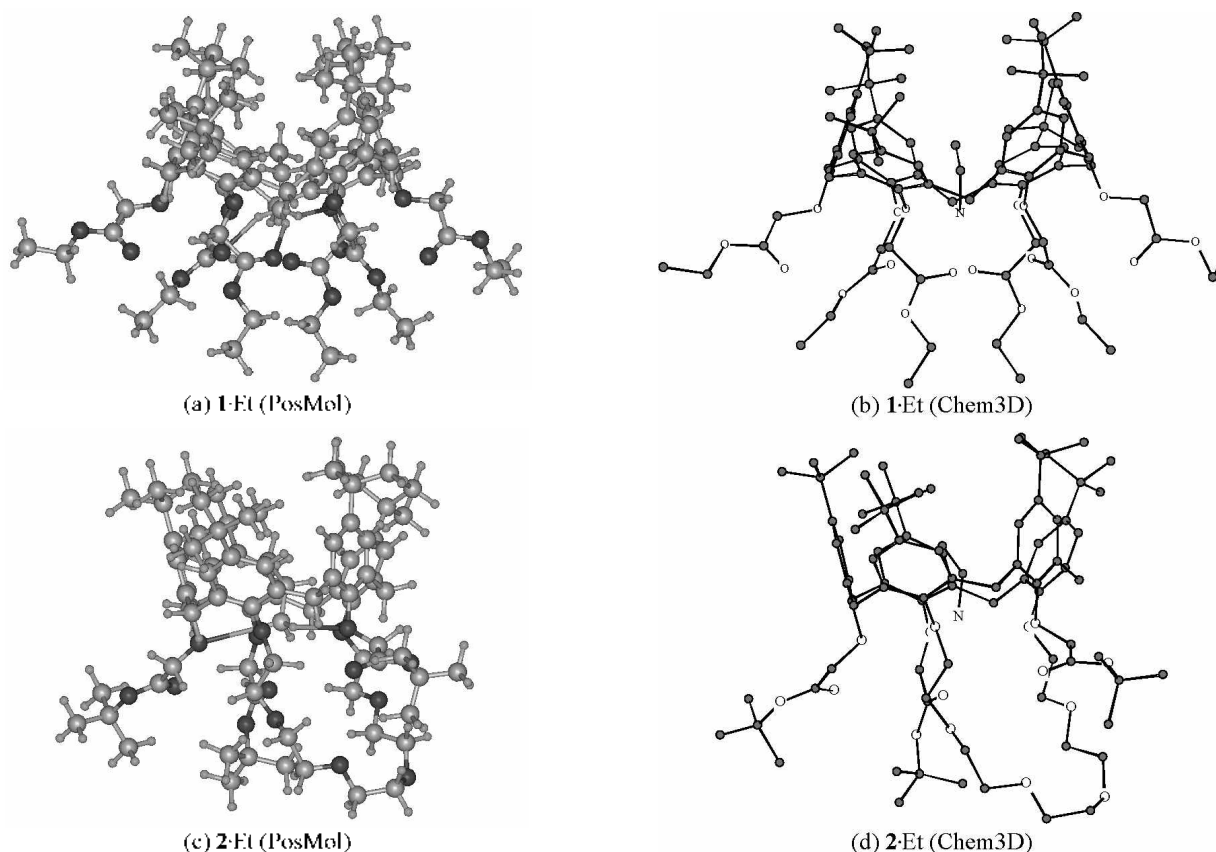


(b) Host **1** (Chem3D)

**Figure 1.** *DFT* calculated cone conformation of the free host **1**. Figure 1(a) shows all atoms by using PosMol<sup>31</sup> and Figure 1(b) is drawn by using Chem3D<sup>32</sup> without hydrogen atoms for clarity.



**Figure 2.** DFT calculated structures of the *endo*-cone-type ammonium complex (1-NH<sub>4</sub><sup>+</sup>). Figure 2(a) shows all atoms including the hydrogen bondings. Figure 2(b) is drawn without hydrogen atoms for clarity.

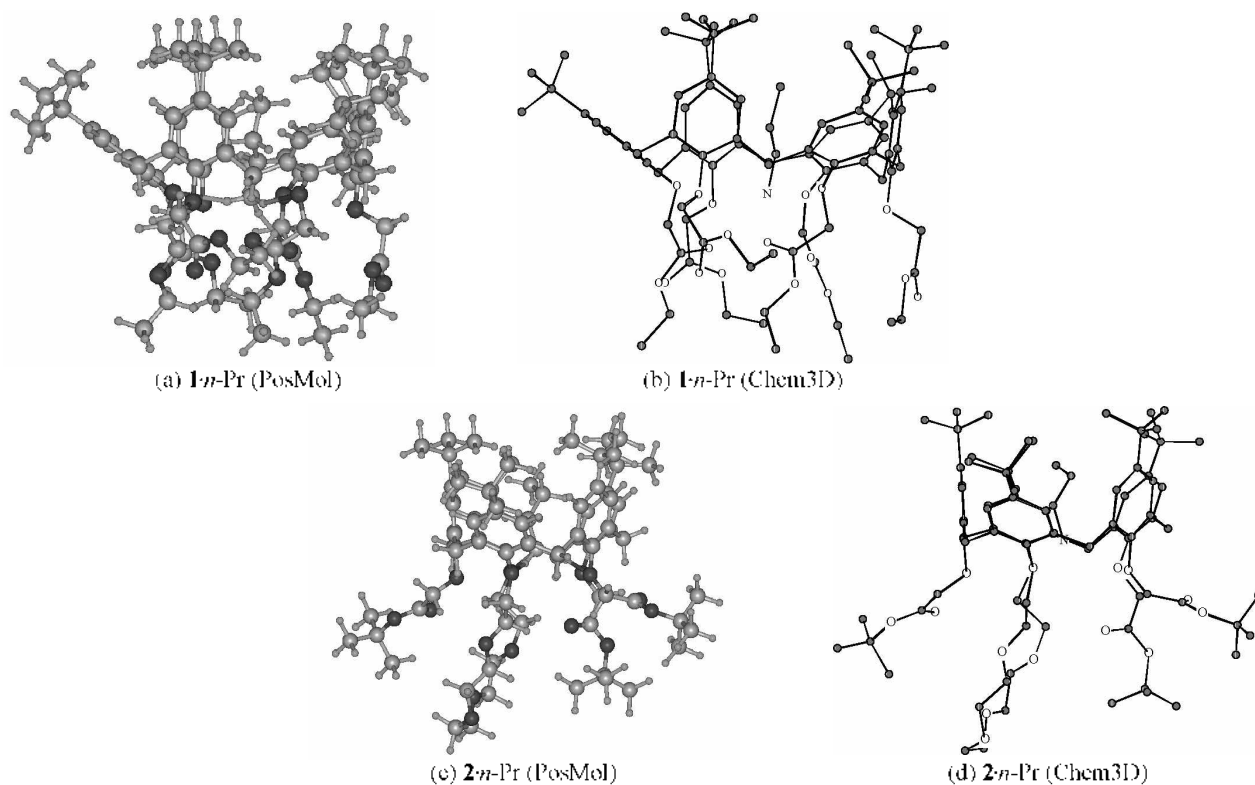


**Figure 3.** DFT calculated structures of the ethylammonium (CH<sub>3</sub>CH<sub>2</sub>NH<sub>3</sub><sup>+</sup>) complexes of **1** and **2**. (a) 1-Et (PosMol), (b) 1-Et (Chem3D), (c) 2-Et (PosMol), and (d) 2-Et (Chem3D).

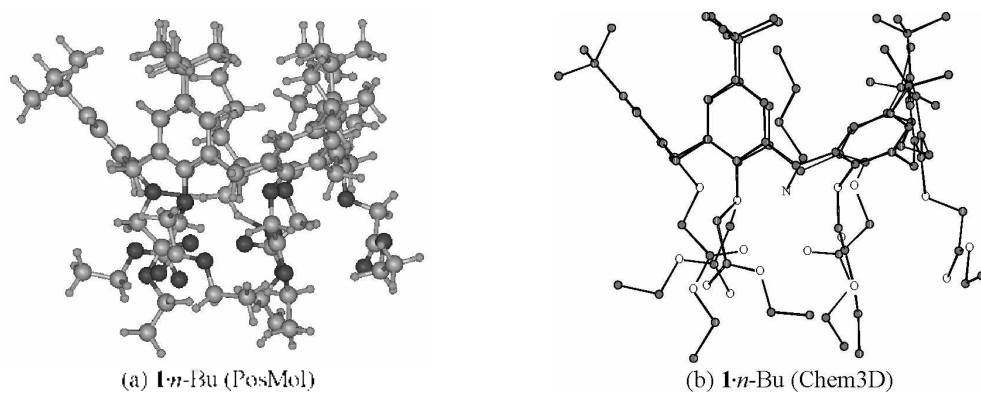
of solvents, a specific size of cations (rather than a smaller cation) would more selectively bind receptors.<sup>6d,30</sup>

Figures 1 to 6 show the DFT optimized structures of **1** and the *endo*-cone-type complexes of **1** with some of the alkylammonium cations. Figure 2(a) shows all atoms including the hydrogen bondings of ammonium complex (1-NH<sub>4</sub><sup>+</sup>) by using PosMol.<sup>31</sup> Figure 2(b) is drawn without hydrogen atoms for clarity by using Chem3D.<sup>32</sup> Figures 3(a) and 3(b) shows the ethylammonium (CH<sub>3</sub>CH<sub>2</sub>NH<sub>3</sub><sup>+</sup>) complexes of **1**,

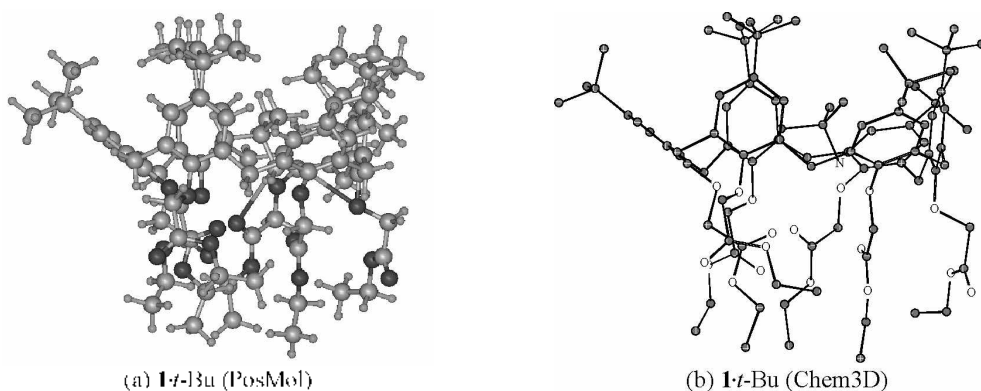
and Figures 3(c) and 3(d) shows the ethylammonium complexes of **2**. Addition to the NH<sub>2</sub>-aromatic  $\pi$ , CH<sub>2</sub>-aromatic  $\pi$  and electrostatic interactions, and the steric hindrance of alkylammonium cation, the hydrogen-bonding of N-H $\cdots$ O is one of the important factors for the complexation efficiency of the *p-tert*-butylcalix[6]aryl ester with varying structures of the guest ions. From the calculated structures, the distances from nitrogen atom in alkylammonium guest ion to oxygen atoms in a cone-shaped host **1** are reported in Table 2. The



**Figure 4.** *DFT* calculated structures of the *n*-propylammonium ( $\text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_3^+$ ) complex of **1** and **2**. (a) **1**-*n*-Pr (PosMol), (b) **1**-*n*-Pr (Chem3D), (c) **2**-*n*-Pr (PosMol), and (d) **2**-*n*-Pr (Chem3D).



**Figure 5.** *DFT* calculated structures of the *n*-butylammonium complex ( $1\text{-CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_3^+$ )



**Figure 6.** *DFT* calculated structures of the *tert*-butylammonium complex ( $1\text{-(CH}_3\text{)}_3\text{CNH}_3^+$ )

**Table 2.** DFT B3LYP/6-31G(d,p) Calculated Distances (Å) and Angles (N-H...O) of Hydrogen Bonds between **1** and alkylammonium ions

Complex	H-bond	1	2	3	Average
1-NH <sub>4</sub> <sup>+</sup>	N...O	3.078	3.173	3.276	3.176
	H...O	2.109	2.397	2.380	2.295
	N-H	1.032	1.023	1.024	1.026
	Angle	155.3	131.9	145.6	144.3
1-Me	N...O	2.930	3.206		3.068
	H...O	1.919	2.279		2.099
	N-H	1.032	1.026		1.029
	Angle	165.9	149.5		157.7
1-Et	N...O	2.964	3.011	3.393	3.123
	H...O	2.057	2.052	2.442	2.184
	N-H	1.030	1.031	1.023	1.028
	Angle	145.6	153.5	154.3	151.1
1-n-Pr	N...O	2.992	3.287		3.140
	H...O	2.064	2.308		2.186
	N-H	1.032	1.024		1.028
	Angle	148.4	159.5		153.9
1-iso-Pr	N...O	3.018	3.029	3.217	3.088
	H...O	2.109	2.110	2.354	2.191
	N-H	1.026	1.026	1.025	1.026
	Angle	146.6	147.8	141.2	145.2
1-n-Bu	N...O	2.957	3.135	3.149	3.080
	H...O	2.076	2.134	2.384	2.198
	N-H	1.027	1.026	1.026	1.026
	Angle	142.4	164.6	130.5	145.8
1-iso-Bu	N...O	3.049	3.063		3.056
	H...O	2.162	2.588		2.375
	N-H	1.022	1.026		1.024
	Angle	144.2	107.9		126.1
1-sec-Bu	N...O	3.161	3.332		3.247
	H...O	2.257	2.360		2.309
	N-H	1.024	1.027		1.026
	Angle	146.4	157.5		152.0
1-t-Bu	N...O	3.226			3.226
	H...O	2.302			2.302
	N-H	1.026			1.026
	Angle	149.1			149.1

**Table 3.** DFT Calculated (N...O) Distances (Å)<sup>a</sup> of Hydrogen Bonds between **2** and Alkylammonium Ions

Complex	1	2	3	Average
2-NH <sub>4</sub> <sup>+</sup>	2.746	2.777	2.790	2.771
2-Me	2.852	2.905	2.934	2.897
2-Et	2.784	2.840	2.972	2.865
2-n-Pr	2.863	2.877	2.881	2.874
2-iso-Pr	2.880	2.929	3.008	2.939
2-n-Bu	2.849	2.853	3.028	2.910
2-iso-Bu	2.857	2.943	2.951	2.917
2-sec-Bu	2.967	3.034		3.001
2-t-Bu	2.969	2.990		2.980

<sup>a</sup>Data are taken from the previously published reference 11.

unusual stability of the branched *iso*-propylammonium complex is originating from the three H-bonds of *iso*-propylammonium versus two H-bonds of the *n*-propylammonium analogue.

When one look at the hydrogen-bonding data of N...O in Table 2, the average distances (3.07-3.18 Å) of the smaller and linear alkylammonium-complexes are shorter than the values (3.23-3.25 Å) of the bulky *sec*- and *tert*-butylammonium-complexes. One of the N...O distances in *tert*-butylammonium-complex (3.749 Å) is out of the range of normal H-bond distance.<sup>33</sup> Therefore, this H-bond data is deleted from the Table 1. And the average distances (2.10-2.30 Å) of the H...O distances of the linear alkylammonium-complexes are shorter than the values (2.30-2.38 Å) of the branched butylammonium-complexes. For the host **1**, the binding site is the cavity consisted of six benzene rings which provide two types of NH-aromatic  $\pi$  and CH-aromatic  $\pi$  interactions.<sup>15</sup> When one compares the DFT calculated complexation energies of host **1** with previously reported host **2** in Table 1, *p*-*tert*-butylcalix[6]aryl ester (**1**) shows much better (9-25 kcal/mol) binding efficiencies toward alkylammonium ions than 1,3-bridged *p*-*tert*-butylcalix[5]crown-6-ether (**2**) having five benzene rings, although the average N...O distances (2.77-3.00 Å in Table 3)<sup>11</sup> of the complexes of **2** were shorter than the values (3.07-3.25 Å in Table 2) of **1**.

## Conclusion

We have performed DFT B3LYP/6-31G(d,p) calculations for the *endo*-complexation of the *p*-*tert*-butylcalix[6]aryl ethyl ester with a series of alkylammonium ions. Complexation with the smaller and linear alkylammonium ion usually shows the better complexation efficiency than the bulkier alkylammonium ion, and also displays shorter hydrogen-bond distances. Addition to the NH-aromatic  $\pi$ , CH-aromatic  $\pi$  and electrostatic interactions, and the steric hindrance of alkylammonium cation, the hydrogen-bonding of N-H...O is one of the important factors for the complexation efficiency of the *p*-*tert*-butylcalix[6]aryl ester with varying structures of the guest ions. DFT calculated complexation energies of *p*-*tert*-butylcalix[6]aryl ester (**1**) show better (9-25 kcal/mol) binding efficiencies toward alkylammonium ions than *p*-*tert*-butylcalix[5]crown-6-ether (**2**).

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