

***Ab Initio* Study of *p*-*tert*-Butylcalix[4]crown-6-ether Complexed with Alkyl Ammonium Cations**

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The conformations and energies of *p*-*tert*-butylcalix[4]crown-6-ether (**1**) and its alkyl ammonium complexes have been calculated by *ab initio* HF/6-31G quantum mechanics method. The cone conformation was found to be most stable for free host **1**. We have determined the binding site of these host-guest complexes focusing on the crown-6-ether or *p*-*tert*-butylcalix[4]arene pocket of the cone conformation of host molecule **1**. The primary binding site of host **1** for the recognition of alkyl ammonium guests was confirmed to be the central part of the crown moiety of cone conformation. The complexation energy calculations revealed that the ammonium cation without alkyl group showed the highest complexation efficiency when combined with host **1**, that is in satisfactory agreement with the experimental results.

Keywords : Calix[4]crown-6-ether, Alkylammonium, Complex. *Ab initio*. Host-guest.

Introduction

The calixarenes^{1,2} having both polar and nonpolar binding sites in their molecular framework have received much attention as a basic skeleton of supramolecular system, and numerous attempts have been made to modify and endow unique binding characteristics to these versatile molecular systems.^{3,4} Selective binding of biologically important organic ammonium guests attracts much research interests, which results in development of many sophisticated host systems.⁵⁻⁷

Various important computational approaches in a variety of interesting supramolecular system are published.⁸ Recently, Choe *et al.* reported computer simulations on molecular recognition of alkyl ammonium ions by ester derivatives of *p*-*tert*-butylcalix[6]arene.⁹ In that study, *endo*-cone calix[6]arene complex was reported as the most stable conformer among the different orientations of alkyl ammonium 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.¹⁰ The report shows that two types of NH-aromatic π and CH-aromatic π interactions in benzene ring are responsible for the binding. From analysis of the structures and energies, the π - σ^* through-space interactions are seen to be significant in both types of NH- π and CH- π interactions.¹¹ More recently, Kim *et al.* published a review report for theoretical studies of structures, spectra, and origin of interaction energies of molecular clusters of π -systems.¹²

We have also published the preliminary structures and energies of *p*-*tert*-butylcalix[4]crown-6-ether (**1**) and its alkyl ammonium complexes using AM1 semi-empirical quantum mechanics and molecular mechanics calculations using a variety of forcefields (MM2, MM+, CVFF).¹³ We have found that cone conformation is generally to be most stable for all the employed calculation methods. The primary

binding site of host **1** for the recognition of alkyl ammonium guests was confirmed to be the central part of the crown moiety, which is in satisfactory agreement with the experimental⁷ results.

In this study we have used *ab initio* HF/6-31G quantum mechanical method for the computer simulation of the complexation behaviors of the *p*-*tert*-butylcalix[4]crown-6-ether toward several alkyl ammonium ions. The main emphases of this research are trying to determine the most stable conformation of host (**1**), to locate the most probable binding site of the host for the recognition of alkyl ammonium guest, and to determine the selectivity of the host for different alkyl ammonium guests with varying structural characteristics. Figure 1(a) shows the sketch of host **1**, in which hydrogen atoms are omitted for clarity except the hydrogen on two hydroxyl groups.

Computational Methods

The initial structures of host molecule and host-guest complexes for *ab initio* HF/6-31G calculations were determined by InsightII/Discover.¹⁴ We have adapted Consistent Valence Forcefield (CVFF) to express the Molecular Mechanics (MM)¹⁵ energies of calix[4]crown-6-ether host, alkylammonium cations and complexes. Each structure was subjected to a conformational search in which 300 K constant temperature molecular dynamics was carried out for 3 ns. Structures for every 50 ps during the 3 ns snapshot were saved and the energies of these conformers were minimized to 0.01 kcal/mol gradient. Most of the InsightII/Discover MM calculations on this study are done on SGI Octane computer. Molecular dynamics (3 ns) simulation of *p*-*tert*-butylcalix[4]crown-6-ether host normally took about 20 hours on this workstation.

Ab initio HF/6-31G quantum mechanical calculation of host **1** or complexes with alkyl ammonium guest by Gaussian

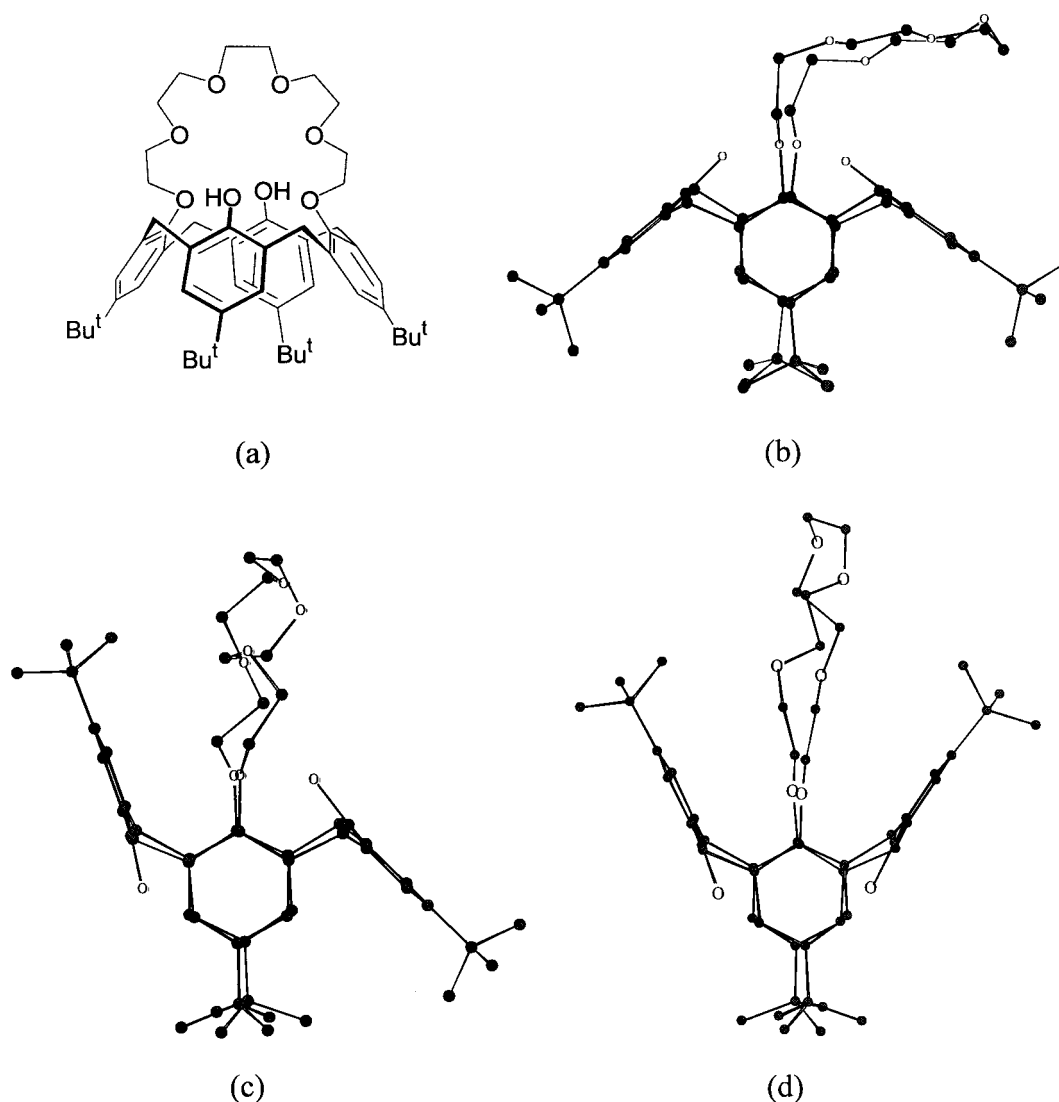


Figure 1. (a) Chemical structure of *p*-tert-butylcalix[4]crown-6-ether (**1**) in which hydrogen atoms are omitted for clarity except the hydrogen on 2 hydroxyl groups, (b) *ab initio* calculated structures of cone, (c) partial cone, and (d) 1,3-alternate conformation of host **1**.

98¹⁶ on Fujitsu VPP 5000 supercomputer (7GB RAM with 36000 MFLOPS CPU speed) at Okazaki National Research Institute of Japan took more than 100 hours to reach an optimum conformation with error limit of less than 0.001 kcal/mol (0.0000002 atomic unit (A.U.)). To our knowledge, *ab initio* HF/6-31G full optimizations for *p*-tert-butylcalix[4]crown-6-ether complexes with more than 135 atoms might not be precedent. *Ab initio* HF/6-31G* level optimization was not feasible due to insufficient memory. Generous time

allocation of the supercomputer should be appreciated to the research center for computational science in the Institute for Molecular Science of Japan.

Results and Discussion

Conformational Characteristics of *p*-tert-Butylcalix[4]-crown-6-ether. The minimized *ab initio* HF/6-31G energies were reported for three local minima of cone, partial cone,

Table 1. Energies^a of Calix[4]crown-6-ether for Different Calculation Methods

Host 1 Conformation	<i>Ab initio</i> (HF/6-31G)	Relative HF Energy	Relative AM1 Enthalpy ^b	Relative MM Energy ^b
Cone	-2685.7546	0.00	0.00	0.00
Partial cone	-2685.7191	22.25	10.07	11.66
1,3-Alternate	-2685.7197	21.90	16.27	15.88

^aError limits in these calculations are 0.00002 A.U. or 0.01 kcal/mol. Units for the *ab initio* total energies are in A.U. (Hartree) and units for relative values are in kcal/mol using conversion factor 1 A.U. = 627.50955 kcal/mol. ^bTaken from reference 13.

Table 2. *Ab initio* HF/6-31G Energies of Different Complexes of Calix[4]crown-6-ether with Alkyl Ammonium Ions

SCF Energies ^a calculated from Gaussian 98 HF/6-31G		Alkyl ammonium guest ^b				
		NH ₄ ⁺	Me	Et	<i>n</i> -Pr	
		-56.5159	-95.5388	-134.5658	-173.5862	
Host 1 (cone)	Complex	Complexes with Host				
-2685.7546	Host (cone)	Guest (cr) ^c	-2742.3914	-2781.3976	-2820.4232	-2859.4393
		Guest (bz) ^d	-2742.3557	-2781.3552	-2820.3774	-2859.3979
Host (cone) + Guest (cr) complexation ^e		-75.85	-65.37	-64.52	-61.81	
Host (cone) + Guest (bz) complexation ^e		-53.46	-38.77	-35.79	-35.81	
$\Delta G_{\text{complexation}}$ calculated by FDTI ^f		-62.51	-55.09	-59.41	-62.12	
$\Delta H_{\text{complexation}}$ calculated by AM1 ^g		-61.52	-54.67	-50.04	-49.58	

^aError limits in these calculations are about 0.00002 A.U. Units for the *ab initio* total energies are in A.U and units for complexation energies are in kcal/mol. ^bMe = methyl ammonium, Et = ethyl ammonium, *n*-Pr = *n*-propyl ammonium ion. ^cGuest (cr) conformation denotes that alkyl ammonium ion is contained inside of the crown-ether ring. ^dGuest (bz) means that alkyl ammonium ion is contained inside of the benzene rings. ^eComplexation energies (kcal/mol) = $E_{\text{Complex}} - E_{\text{Host (cone)}} - E_{\text{Guest}}$. ^f ΔG and ΔH complexation values (kcal/mol) are taken from reference 13.

and 1,3-alternate conformations of host 1 in Table 1.

Table 1 summarizes the relative stability of different conformations of host 1. The cone conformation is about 22

kcal/mol more stable than the partial cone or the 1,3-alternate conformation. The table also compares the relative stability of this host system for different calculation methods.

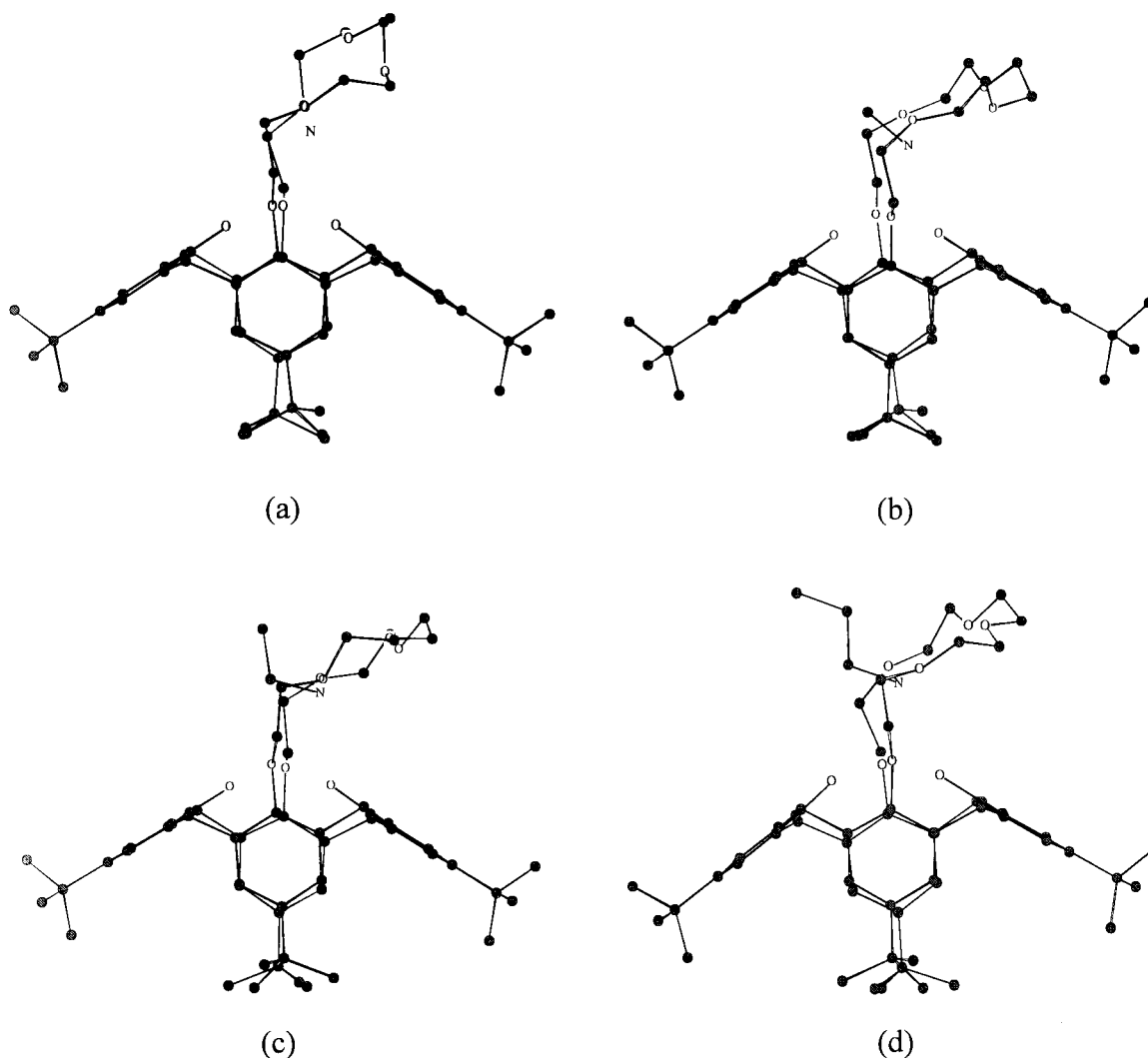


Figure 2. *Ab initio* calculated structures of cone conformation of 1 complexed in crown-ether ring with (a) ammonium, (b) methyl ammonium, (c) ethyl ammonium, and (d) *n*-propyl ammonium ion.

The calculations¹³ by molecular mechanics and semi-empirical (AM1) quantum mechanics in previous publication also have shown that the cone conformation is most stable. The *ab initio* HF/6-31G calculation result confirms the validity of the outcome of the less expensive MM and AM1 calculations. Figures 1(b)-(d) show the final structures for three representative conformations (cone, partial cone, 1,3-alternate) of host 1. Although the representative conformers for the host are carefully determined, they might be not most stable structures. There could be other conformations in the error ranges of the local minima.

Complex Formation of Host with Alkyl Ammonium Guests. The quantum mechanical full optimizations were also carried out for two kinds of complexation mode of 1, combining cone conformer of host 1 and two different locations of guest inside of host. The results of *ab initio* HF/6-31G energies of complexes of calix[4]crown-6-ether with alkyl ammonium ions are listed in Table 2.

When one compares the complexation energies for the different types of combination in Table 2, the host in cone conformation with the guest in the crown ether moiety (guest(cr) mode) has the higher complexation efficiencies for all kinds of the alkyl ammonium ions. The reason why we compare the complexation energies is to cancel out the individual guest effects for the different alkyl ammonium cations. When one compares the complexation energies for cone conformation, host(cone) + NH₄⁺(cr) complex (-75.85 kcal/mol) is found to be 22.39 kcal/mol more stable than the host(cone) + NH₄⁺(bz) complex (-53.46 kcal/mol). And the complexation energy (-65.37 kcal/mol) for host(cone) + CH₃NH₃⁺(cr) complex is found to be 10.48 kcal/mol less efficient than the host(cone) + NH₄⁺(cr) complex. These results show that complexation occurs in the central part of crown periphery and that ammonium cation without alkyl group has the better complexation efficiency with *p*-tert-butylcalix[4]crown-6-ether. Figure 2 shows the final struc-

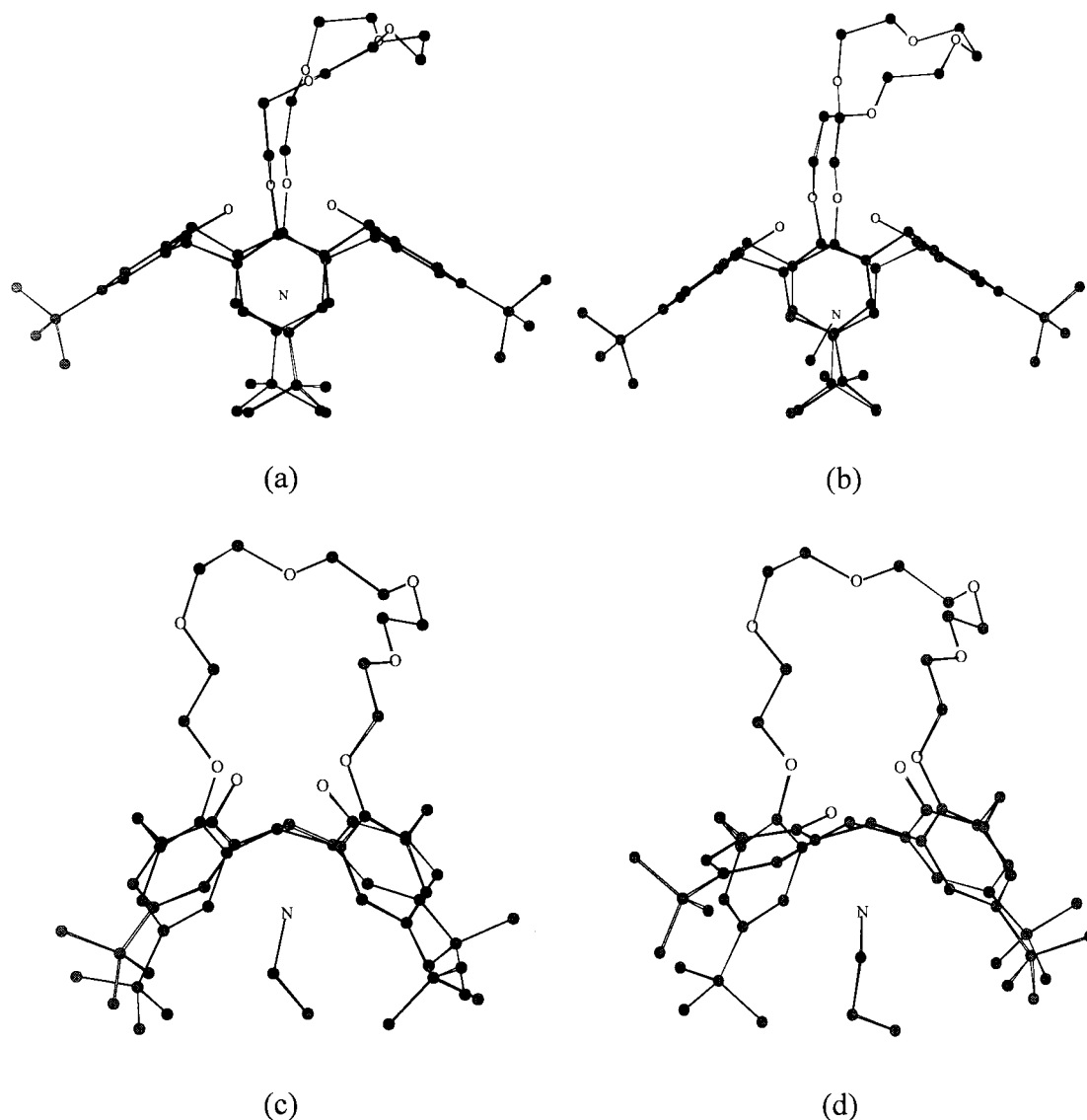


Figure 3. *Ab initio* calculated structures of cone conformation of 1 complexed in the calix[4]arene-cavity consisted of four benzene rings with (a) ammonium, (b) methyl ammonium, (c) ethyl ammonium, and (d) *n*-propyl ammonium ion.

Table 3. Distances^a from Nitrogen Atom in Ammonium Ion to Oxygen Atoms in Cone-shaped Calix[4]crown-6-ether

Distance (Angstrom)	Nitrogen to Ether Oxygen				Nitrogen to Hydroxyl Oxygen			
	N-O47 ^b	N-O48	N-O51	N-O54	N-O57	N-O60	N-O21	N-O44
NH ₄ ⁺	3.106	3.873	3.027	2.905	2.922	2.999	2.722	3.557
EtNH ₃ ⁺	3.259	4.142	2.888	3.356	2.939	3.011	2.788	3.861

^aThe distances which satisfy the hydrogen-bonding requirements of the quasi-linear N-H...O angle (close to 180°) and the distance (<3.2 Å) in each complex are listed as bold numeric characters. ^bSee Figure 4 for the numbering of oxygen as well as carbon atoms

tures of cone conformation of **1** complexed in crown-ether ring with alkyl ammonium ions. This result agrees well with the experimental data for the two-phase solvent extraction of alkyl ammonium picrates.⁷ Figure 3 shows the less stable structures of cone conformation of **1** complexed in the calix[4]arene cavity consisted of four benzene rings with alkyl ammonium ions.

For complexation of alkyl ammonium ions by ester derivatives of *p*-tert-butylcalix[6]arene, *endo*-cone calix[6]arene complex was reported as the most stable conformer among the different orientations of alkyl ammonium cations complexed inside of the cone-shaped host.⁹ For that *p*-tert-butylcalix[6]arene case, the most efficient binding site is a larger cavity consisted of six benzene rings which also provide two types of NH-aromatic π and CH-aromatic π interactions.¹¹ But in the present case of cone-shaped *p*-tert-butylcalix[4]crown-6-ether, the cavity size of calix[4]arene having four benzene rings is rather smaller for the accommodation of alkyl ammonium ions. Therefore, ammonium ions seem to prefer to the crown ether moiety (guest(cr) mode) by experiencing both the hydrogen-bonding and electrostatic interactions.

As has been already discussed, *p*-tert-butylcalix[4]-crown-6-ether has the characteristic ionophoric properties toward organic ammonium ions by utilizing the complementarities of hydrogen-bonding and the steric interaction of crown-6-ether moiety or calix[4]arene framework. The stabilization by the hydrogen-bonding, electrostatic interaction, and steric hindrance of alkyl ammonium cation with crown ether ring seemed to be the principle factors for the complexation of the *p*-tert-butylcalix[4]crown-6 host with varying structures of the alkyl ammonium guests. From the calculated structure, the distances from nitrogen atom in ammonium guest cation to eight oxygen atoms (six O's from crown ether ring and two O's from hydroxyl groups) in a cone-shaped host **1** are reported in Table 3.

Figure 4 shows the numbering of heavy atoms in the complex of cone conformation of **1** with ammonium ion complexed in crown-ether ring. Structure of Figure 4 was produced by POSMOL,¹⁸ which reads conveniently the output file of Gaussian 98. For the Figures of 1, 2, and 3, each structure read by POSMOL was saved as a Protein Data Bank (PDB) format to print a hardcopy of the three-dimensional molecular structure by Chem3D.¹⁹ In Table 3, six O's out of eight oxygen atoms are within 3.11 Å from the nitrogen atom of NH₄⁺ ion. However, for ethyl ammonium ion, only four O's out of eight oxygen atoms are within the

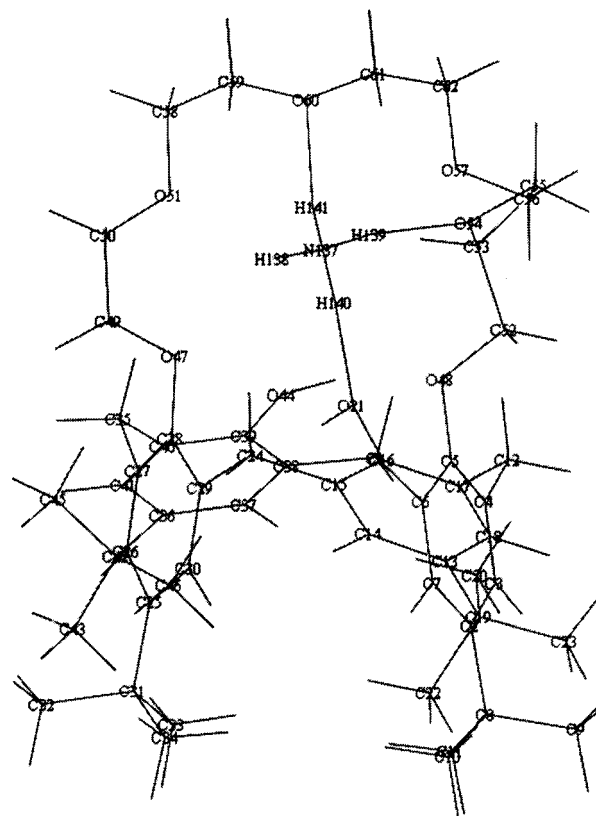


Figure 4. The numbering of heavy atoms in the cone conformation of **1** complexed in crown-ether ring with ammonium ion. Three out of four hydrogen atoms of ammonium ion show the H-bonds with oxygen atoms of host **1**.

distance, which reflects somewhat unfavorable interactions. Three out of four hydrogen atoms of ammonium ion show the formation of hydrogen-bonds with oxygen atoms of host **1**. Table 4 shows the angles between N-H...O in three H-bonds for the two complexes of ammonium and ethyl ammonium ions. These interactions and steric hindrance of alkyl group might be the major reasons for the higher complexation efficiency (~10 kcal/mol) for the NH₄⁺ ion compared to alkyl ammonium ion.

When one compares the host-guest complexation energies of the *ab initio* calculation with the results of previous calculation,¹³ ammonium ion having no alkyl group always has the highest complexation efficiencies among four kinds of the alkyl ammonium ions surveyed for three different calculation methods (See Table 2). The present *ab initio* result is again in parallel with the trend of the MM and AM1

Table 4. H-bond Angles^a from Nitrogen Atom in Ammonium Ion through Hydrogen Atom to Oxygen Atoms in Cone-shaped Calix[4]crown-6-ether

Angle (degree)	N-H...O				Nitrogen to Hydroxyl Oxygen
	Guest	N-H146-O51	N-H139-O54 ^b	N-H147-O57	
NH ₄ ⁺	—	168.7 ^o	—	160.9 ^o	150.1 ^o
EtNH ₃ ⁺	160.0 ^o	—	172.3 ^o	—	178.4 ^o

^aThe angles which satisfy the hydrogen-bonding requirements of the linear N-H...O angle (close to 180°) and the distance (< 3.2 Å) in each complex.

^bSee Figure 4 for the numbering of nitrogen, hydrogen, and oxygen atoms.

calculations as well as experimental extraction Gibbs energies (ΔG°),⁷ although the magnitudes of free energy difference are not comparable due to different conditions between calculation (in vacuum) and experimental environment (in solution).

Conclusion

We have performed *ab initio* HF/6-31G quantum mechanical calculations for the complexation of *p*-tert-butylcalix[4]crown-6-ether with varying alkyl ammonium ions. For the free host molecule, the cone conformation was found to be most stable among the three conformations (cone, partial cone, 1,3-alternate). The primary binding site for host **1** with alkyl ammonium guests was confirmed to be the central part of the crown moiety. These *ab initio* HF/6-31G calculations also duplicate the discrimination ability of the host toward the varying structures of alkyl ammonium ions. Complexation with ammonium ion without alkyl group shows the highest complexation efficiency. These *ab initio* HF/6-31G results are in satisfactory agreement with the results of preliminary publication¹³ which have used less expensive calculation methods such as molecular mechanics and semi-empirical quantum mechanics and also with experimental result.⁷

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