Computer Simulations on Molecular Recognition of Alkylamines by Ester Derivatives of *p-tert*-Butylcalix[6]arene

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Received October 2, 1999

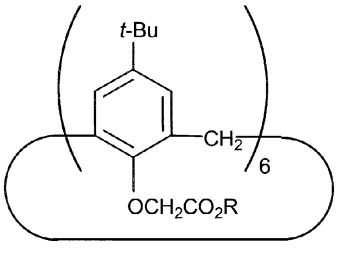
In this study we have performed computer simulations to investigate the complexation behaviors of the ester derivatives of *p-tert*-butylcalix[6]arene toward a variety of alkyl ammonium ions. Using the Finite Difference Thermodynamic Integration (FDTI) method in Discover we have calculated the absolute and relative Gibbs free energy of the different alkyl ammonium ions complexed with the alkyl *p-tert*-butylcalix[6]aryl acetates. Semi-empirical AM1 method was used for calculating enthalpy of formation. CVFF and MM+ forcefield for molecular mechanics calculations were adapted to express the complexation energies of the hosts. The local charges used to calculate electrostatic energy term in MM+ were estimated using AM1 semi-empirical quantum mechanics methods. Molecular dynamics were performed to simulate the behavior of these complexes. Most stable conformation is found to be 1,2,3-alternate for uncomplexed alkyl *p-tert*-butylcalix[6]aryl ester host, and cone-type conformation for host-guest complexes. Among the different orientations of alkyl ammonium cations complexed inside the cone-shape host, *endo*-cone complex is calculated as the most stable conformer. Ethyl *p-tert*-butylcalix[6]aryl ester (**2**) showed better complexation efficiency toward alkylamines than methyl *p-tert*-butylcalix[6]aryl ester (**1**) and this calculation result agrees well with the reported experimental data.

Introduction

Numerous attempts have been made to design new host systems which can selectively interact the target guest and perform intriguing molecular recognition processes.[1-3] The selective recognition of many important biogenic amines is one of the fundamental research interest in the field of the biomimetic chemistry.[4,5] Particularly, selective binding of organic ammonium guests attracts much research interests, which results in development of many sophisticated host systems.[6] Calix[6]arenes, a class of cyclic hexamers of phenol formaldehyde condensation product, seem 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.[7]

Ester derivatives of *p-tert*-butylcalix[6]arene are known to have high affinity toward alkali metal ions, alkylammonium, and related cations.[8,9] 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.[10,11] 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-π interaction between π-base cavity of calix[6]arenes.[12] More recently, ^{1}H NMR complexation studies of ethyl ester **2** with ethylammonium picrate guests suggest the conformational reorganization into cone conformation has provoked upon complex formation.[13] Also, NMR study on complexation of ethylammonium ion by alkyl *p-tert*-butylcalix[6]aryl ester derivatives showed that the *endo*-type complexes are formed.[14]

In the molecular modeling study of calixaryl derivatives, conformational analysis of *p-tert*-butylcalix[6]arene symmetrically tetra-substituted with pyridine pendant groups has been studied by molecular mechanics calculations.[15] Grootenhuis calculated the structural, energetical, and acid-base properties of calix[4]arenes using molecular mechanics programs such as AMBER, MM2P, QUANTA/CHARMm.[16] Wipff *et al*. reported the molecular dynamics calculation of calixarene amine derivatives containing metal cation or organic molecule.[17] Shinkai group have calculated the relative stabilities of four different conformations (cone; partial cone; 1,2-alternate; 1,3-alternate) of several homologs of calix[4]arene using MM3 molecular modeling software, and reported quantitatively the similar trend with the relative free energies obtained from the NMR spectroscopic data.[18] In this paper, we have simulated the conformational and the molecular recognition behavior toward alkylammonium guests of calix[6]arene-based ester derivatives, aiming to understand more deeply the complexational behavior and to develop more elaborate host for biogenic amines as well as many related biologically interesting guests.



1 R = Me

2 R = Et

Computational Methods

Molecular Mechanics[19] **Calculations by InsightII/ Discover**.[20] The initial structures of host and guest molecules were constructed by InsightII/Discover on Silicon Graphics IRIS workstation. We have adapted CVFF forcefield to express the MM energies of calix[6]arene hosts, alkylammonium cations and complexes. The molecular dynamics (MD) and free energy simulation studies used a time step of 1.0 fs. The initial structure was subjected to a conformational search in which 300 K constant temperature MD were carried out for 3 ns. Every 50 ps during the 3 ns snapshot was saved and the energies of these conformers were minimized to 0.001 kcal/mol gradient. The energy and structure of the lowest energy conformer from each search was then used for comparison with other up/down conformers (see Figure 1 for host, and Figure 2 for host-guest complex).

Absolute Gibbs Free Energy.[20] The technique of absolute free energy is general and can be applied in transparent manner to systems in a vacuum or in solution, under any conditions of volume and/or temperature. This approach is a special case of thermodynamic integration (TI) approach to free energy calculations, which is itself a general method for computing the change in free energy upon going from one thermodynamic state to another. Absolute free energy simply constrains one of these states to be a model system for which the absolute free energy is known analytically. By integrating from a known, albeit model, state to the final real state, the absolute free energy becomes the sum of the numerically computed thermodynamic integration step and the analytical absolute free energy of the model state. These calculations have been carried out on guests, hosts and the complexes of calixarene with guest. All free energy simulations in this work were carried out with the default settings: $\Delta\lambda = 0.005$ (the spacing between windows); 6 windows were used to go from the initial to the final state, quadrature points = 6 (the number of Gauss-Legendre quadrature points), sampling = 10 (the frequency at which $e^{-\Delta H/kT}$ is sampled). In each window equilibration was carried out for 100,000 steps (100 ps) followed by data collection for 100,000 steps. The model implement in Discover program is an ideal solid. That is, the atoms in system are constrained harmonically to a lattice (analogous to a solid) and do not interact with each other (analogous to the ideal gas). The absolute free energy technique is primarily used to evaluate the free energy of different conformation of the same molecule. As in any physical measurement, there are both systematic and random sources of error in the calculation of free energies. A major source of systematic errors in these calculations is lack of convergence (that is, failure to equilibrate long enough to active thermodynamic equilibration at each λ value) and insufficient sampling of configurational space. Other sources of systematic error include inaccuracies in the force field (both in functional form and the parameters) and quantum mechanical effects. Random errors are a natural consequence of free energy calculations. The statistical distribution of states available to a molecule at a given temperature is precisely what defines its entropy. Measuring entropy is an inherently statistical process that can be quantified with standard random error analysis procedures. A detailed theory will be left in the reference.[20]

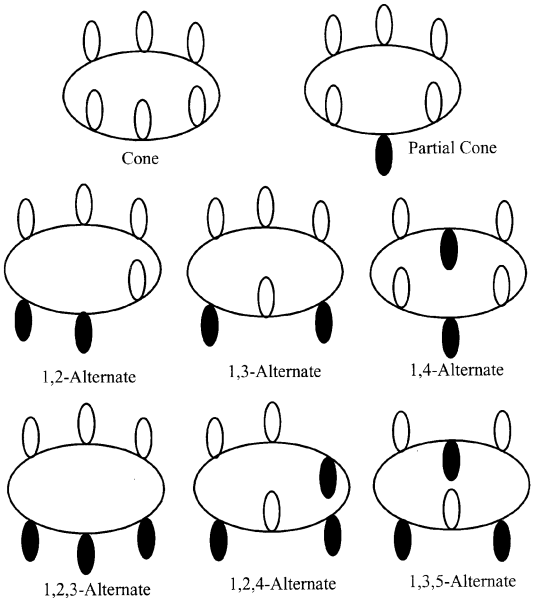


Figure 1. Conformations of calix[6]arene: cone, a partial cone, [(1,2), (1,3), (1,4)]-alternate, [(1,2,3), (1,2,4), (1,3,5)]-alternate. White ellipse denotes benzyl ring is up, black means down.

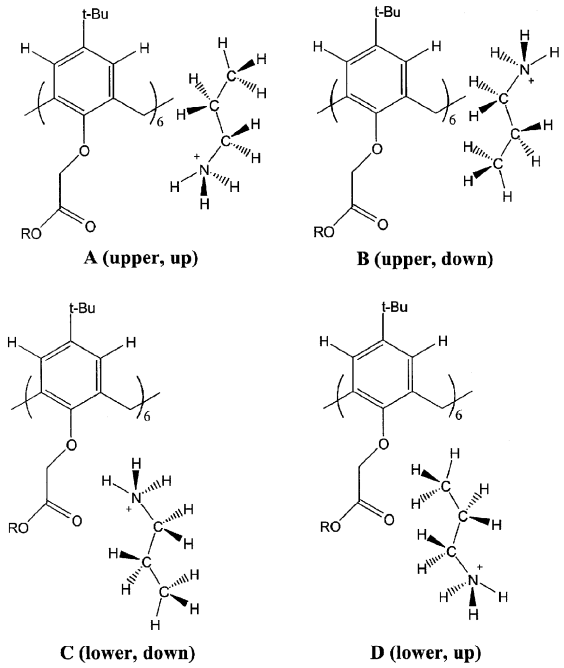


Figure 2. Complex conformations of alkyl *p-tert*-butylcalix-[6]aryl acetate with *n*-propyl ammonium cation; **A**(upper, up) conformation denotes that alkylammonium ion is contained in upper rim (in 6 benzene rings), and that alkyl group of the guest cation is up, etc.

Determination of Relative Binding Free Energy (ΔG).[20] We have calculated the relative Gibbs free energy of the dif-

$$\begin{array}{ccccc} & & \Delta G_1 & & \\ \text{Host} & + & \text{guest}_1 & \rightarrow & \text{Host•guest}_1 \\ & \Delta G_3 \downarrow & & & \downarrow \Delta G_4 \\ \text{Host} & + & \text{guest}_2 & \rightarrow & \text{Host•guest}_2 \\ & & \Delta G_2 & & \end{array}$$

Scheme 1. Thermodynamic cycle used to determine the relative free energy of binding between two-host guest complexes.

ferent alkyl ammonium ion complexation with calix[6]aryl hosts using the Finite Difference Thermodynamic Integration (FDTI) method (a free energy perturbation method[21]), which is similar to the procedure for the absolute free energy calculations.

By using FDTI to obtain the Gibbs free energy change between two states, relative binding free energies can be calculated from the thermodynamic cycle shown in Scheme 1.

$$\Delta\Delta G = \Delta G_2 - \Delta G_1 = \Delta G_4 - \Delta G_3$$

Here the desired free energy change is depicted by the horizontal arrows, where guest 1 and guest 2 move from far to bind to the host; the relative binding free energy is $\Delta G_2 - \Delta G_1$. In general, this event occurs on much too long a time scale to be effectively simulated with current techniques. Instead, the unphysical process depicted by the vertical arrows is simulated, *i.e.* guest 1 is mutated to guest 2 in vacuum and in the host to obtain ΔG_3 and ΔG_4. Taking advantage of the fact that the free energy change between two states is independent of the path taken to go from one state to the other, the relative binding free energy can then be calculated as $\Delta G_4 - \Delta G_3$. One often uses the calculated $\Delta G_4 - \Delta G_3$ values to compare with the experimentally observed $\Delta G_2 - \Delta G_1$ values to validate a theoretical model, or to predict relative binding free energies of a set of host-guest complexes if their experimental data are not available. These free energy simulations were carried out with the same settings as the absolute free energy calculation except warping[20] different atoms in two systems.

Semi-empirical Quantum Mechanical (AM1) Method. The lowest energy conformers of host and complexes obtained from the previous Discover MD and MM were re-optimized to estimate the binding energy and the enthalpy of formation of the compounds using AM1 semi-empirical quantum mechanics method of the HyperChem. The default semi-empirical options (Restricted Hartree Fock (RHF) spin pairing) were used except the followings: total charge = 0, spin multiplicity = 1 for neutral host (*p-tert*-butylcalix[6]aryl ester); total charge = 1, spin multiplicity = 1 for cationic guests and complexes.

Molecular Mechanics[19] **Calculations by MM+ Forcefield with AM1 Charge**. Using the structures and local charges determined by the AM1 semi-empirical quantum mechanics method, MM+ calculations with electrostatic interaction were performed. Initially, steepest descent was carried out to ~0.1 kcal gradient, followed by Newton-Raphson (block-diagonal) methods to 0.001 kcal gradient.

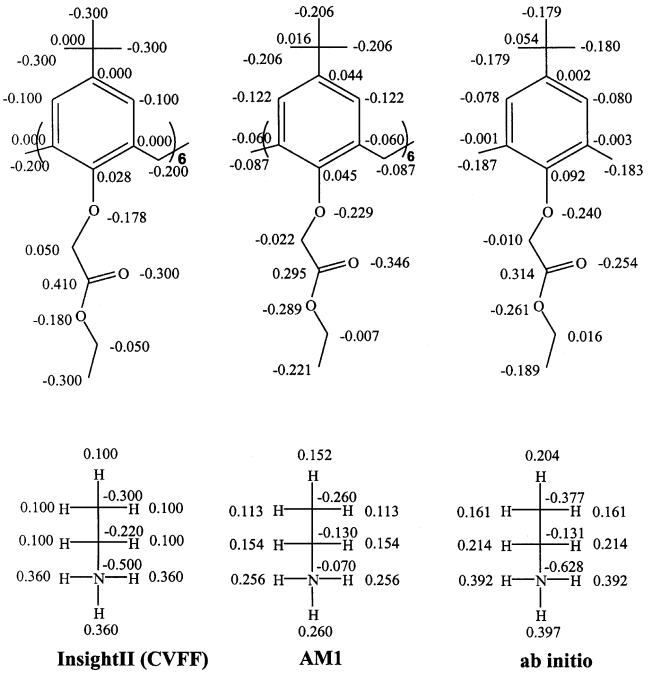


Figure 3. Partial charges of host **2** without hydrogens, and ethylammonium cation guest for three different methods. For ab initio case, the charges of guest cation was calculated by 6-31G** method and a ring of host **2** was done by STO-3G.

Partial Atomic Charges.[23] Figure 3 shows the partial atomic charges in a ring of *p-tert*-butylcalix[6]aryl host and those of propyl ammonium cation by three different methods (CVFF, AM1, and ab initio).

Conformational Search by Simulated Annealing. We have performed MD calculations for 300 ps at 900 K constant temperature. It was followed by 50 ps MD at 300 K constant temperature for hosts and complexes. MM calculations with steepest descent and Newton-Raphson (block-diagonal) methods were carried out to 0.001 kcal/mole gradient.

Computers and Calculation Time. Most of the InsightII/Discover MM (CVFF forcefield) calculations on this paper are done on SGI Indy. Molecular dynamics (3 ns) simulation of an alkyl *p-tert*-butylcalix[6]aryl ester derivative normally took about 100 hours on this workstation and each free energy calculation requires about 20 hours. Semi-empirical quantum mechanical (AM1) optimization of a host or complex on workstation or on Pentium PC took more than 10 days to reach a gradient of less than 0.001 kcal/mol.

Results and Discussion

Conformational Characteristics of Calix[6]arene. 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 (See Figure 1). Initially, the host **2** was considered for the calculations of energies for some of the representative conformations (cone, partial cone, and 1,2,3-alternate) using the method of confor-

Table 1. Energies (kcal/mol) of Different Conformations for Host **2**

Host **2**	Calculated Values with Discover(CVFF)[20]			
Conformation	ΔG^a	Relative ΔG	MM[b]	Relative MM
cone	712.23	9.13	173.94	9.91
partial cone	715.62	12.52	173.50	9.47
1,2-alternate	714.02	10.88	174.15	10.12
1,2,3-alternate	703.10	0.00	164.03	0.00

[a]Error limits in absolute free energy calculations are 0.60 kcal/mol. [b]Error limits in MM calculations are 0.01 kcal/mol

mational search by simulated annealing described in computational method section.

The error limits in Table 1 through 6 are the outputs from the molecular modeling programs. And the probable errors might be several times of these error limits when one calculates the energies repeatedly. The detailed explanation about errors in free energy calculation is written in computational section.

Without binding the alkyl ammonium guest, our calculation suggests that the 1,2,3-alternate conformer is most stable in vacuum for the calculated Gibbs free energy. Table 1 shows that 1,2,3-alternate conformer is 9.13 kcal/mol more stable than cone, and 12.52 kcal/mol more stable than partial cone. The NMR study on alkyl *p-tert*-butylcalix[6]aryl ester derivatives showed that 1,2,3-alternate conformer is found to be most stable in solution.[14] This experimental observation is in line with our calculation results. Figure 4 shows the calculated structure of 1,2,3-alternate conformer of **2**. The initial structures of guest molecules were constructed by InsightII/ Discover[20] on Silicon Graphics IRIS workstation.

Complex Formation of Host and Guest. The different conformers of hosts are known to form the cone conformation when they bind with alkyl ammonium cations.[14] Therefore, we focused the cone conformers for the complexation with the guest ions. Initially, the four kinds of complex formation were considered for the calculations of energies for different orientations (upper or lower rim, up or down direction of alkylammonium) of guests inside the cavity of calixarene host. The MD calculations for 300 ps at 300 K constant temperature were carried out for **A**) upper rim and up cation, **B**) upper rim and down cation, **C**) lower rim and up cation, and **D**) lower rim and down cation complexes of hosts and alkyl ammonium ion. (See Figure 2 for the notation.) The roughly minimized structure was subjected to a conformational search, in which 300 K constant temperature MD were carried out for 3 ns. Every 50 ps during the 1 ns, snapshot of the structure was saved and the energies of these conformers were minimized to 0.001 kcal/mol or less gradient. The energy and structure of the lowest energy conformer from each search were then used for comparison with other up/down conformers for the same size. Table 2 shows the energies of complexes of ethyl ester (**2**) with *n*-propylammonium cation for different orientations of guest inside the cavity of calixarene host. If we allow more dynamical condition of higher temperature and/or longer time period, the less stable complex [***B*** (upper, down) or ***D*** (lower, up)] normally converts to more stable conformation [***A*** (upper, up) or ***C*** (lower, down)]. Here we will call ***A*** (upper, up)-type complex as global minimum conformation which may not be the true minimum, and call ***C*** (lower, down)-type as the local minimum structure. Since *p-tert*-butylcalix[6]aryl esters are very flexible, there are a lot of variations in the ***A*** (upper, up)-type complex.

Endo*-Cone-type Complex**. As one compares the calculated free energies (ΔG) of the complexes in Table 2, *endo*-cone-shaped ***A (upper, up) complex is most stable compared ***C*** (lower, down) complex or 1,2,3-alternate type complex. The NMR study on the complexation of ethylammonium or *n*-propylammonium (*n*-Pr) cation by alkyl *p-tert*-butylcalix[6]aryl ester derivatives also indicated that the guest is held tightly deep in the cone-shape aromatic cavity of calixarene, thus forming *endo*-type ***A*** (upper, up) complex.[14] It was reported that, upon 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 arrangement of N^+-H···O=C(host) hydro-

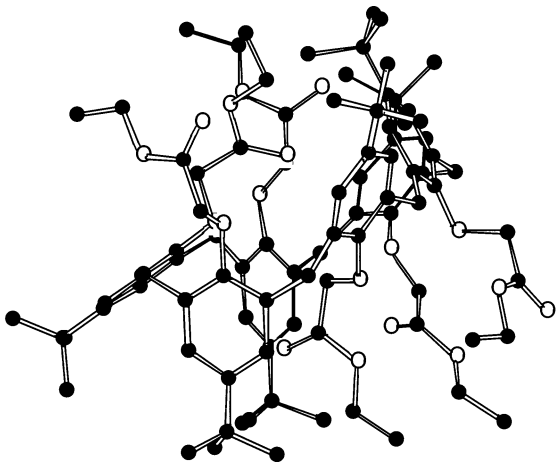


Figure 4. 1,2,3-Alternate conformation of **2** without guest cation: side view without hydrogen.

Table 2. Energies (kcal/mol) of *endo*-Cone-type Complex **2**·*n*-Pr for Different Orientations of Guest Inside the Host **2**

Host **2**	Complex	Calculation Method[c]			
conformation	**2**·n-Pr (position,direction)[a]	ΔG (CVFF)	MM (CVFF)	ΔH (AM1)	MM+ (AM1)
cone	***A*** (upper,up)	713.39	143.30	-643.96	-193.92
	B (upper,down)	unstable[b]	unstable[b]	-630.00	unstable[b]
	C (lower,down)	727.20	155.30	-635.78	-185.00
	D (lower,up)		unstable[b]		
1,2,3-alternate	Middle	unstable[b]	unstable[b]	-618.00	-169.00

[a]See Figure 2 for notation of ***A***, ***B***, ***C***, and ***D***. [b]This conformation of complex was too easily transformed to more stable structure in MM calculation even without MD. [c]Error limits in absolute free energy, in MM and in AM1 calculations are 0.60 kcal/mol, 0.01 kcal/mol, and 0.001 kcal/mol, respectively.

Table 3. MM Energies[a] (kcal/mol) of Hosts, Alkylammonium Cations, and Complexes

MM Energy		Alkylammonium Guest[b]								
		NH_4^+	Me	Et	*n*-Pr	*iso*-Pr	*n*-Bu	*iso*-Bu	*sec*-Bu	*tert*-Bu
		1.04	41.22	13.90	33.73	-31.07	28.86	35.78	-1.65	-93.94
Host		Complexes with Host								
$\mathbf{1}_{(cone)}$	202.92	148.66	187.60	160.60	179.37	112.53	173.03	180.03	143.65	52.80
$\mathbf{2}_{(cone)}$	173.94	113.40	153.12	123.50	143.40	80.58	138.06	144.74	112.78	19.20
$\mathbf{1}_{(cone)}$ Complexation[c]		-55.29	-56.53	-56.22	-57.28	-59.32	-58.75	-58.66	-57.61	-56.18
$\mathbf{2}_{(cone)}$ Complexation[c]		-61.58	-62.04	-64.34	-64.27	-62.29	-64.74	-64.98	-59.51	-60.80

[a]Error limits in these calculations are 0.01 kcal/mol. [b]Me = Methyl ammonium, Et = Ethyl ammonium, *n*-Pr = *n*-propyl ammonium cation, *etc*. [c]Complexation energy = $E_{Complex}-E_{Host}-E_{Guest}$.

gen bonds and R-$NH_3^+\cdots$O=C(host) charge dipole interaction.[13] Due to this type of primary interaction in the complex, the alkylammonium guest has two possible orientations to assume, either head-up or head-down with respect to the cone cavity. The large upfield shifts observed are thought to arise from the so-called CH-π interaction and indicate that the ethyl group side of the guest is embedded in the cavity and subject to the ring current of phenyl groups (See Figure 2A). The *endo*-type complexation may be caused predominantly by this interaction.[14]

Therefore, we have focused our efforts to *endo*-cone-shaped ***A*** (upper, up) complexes. The preliminary determined structures were subjected to a conformational search using InsightII/Discover, in which 300 K constant temperature MD were carried out for 3 ns. Every 50 ps during the 3 ns snapshot was saved and the energies of these 61 conformers were minimized to 0.001 kcal/mol gradient or less. The lowest energy values from these MD/MM optimizations are presented in Table 3.

From the Table 3, the more meaningful data than MM energy are the complexation energies ($E_{Complex}-E_{Host}-E_{Guest}$). The result obtained suggests that the ethyl *p-tert*-butylcalix[6]aryl ester (**2**) showed much better complexation efficiency toward all the tested alkylamines than methyl *p-tert*-butylcalix[6]aryl ester (**1**). This calculated outcome is also very similar to the reported experimental results.[24] Figure 5 shows the calculated structure of *endo*-cone-type Complex of **2** with propyl ammonium cation.

Absolute Gibbs Free Energy. The free energies of the optimized conformers were calculated using the optimized structures obtained from the above MM (CVFF) routine by the absolute free energy calculation method in Discover[20] program. Gibbs free energies of host, alkylammonium ions and complexes of *p-tert*-butylcalix[6]aryl esters with the cations are listed in Table 4.

In Table 3 and 4, individual guest effect will be cancelled out by comparing the complexation energies for different alkyl ammonium cations. Table 4 shows that ethyl ester (**2**) gives better complexation efficiency toward alkylamines than methyl ester (**1**). Trends of these Gibbs free energy calculations in vacuum agree fairly well with the published experimental results (Table 5) for the extraction of alkylammonium picrates with ester derivatives of calix[6]arenes in

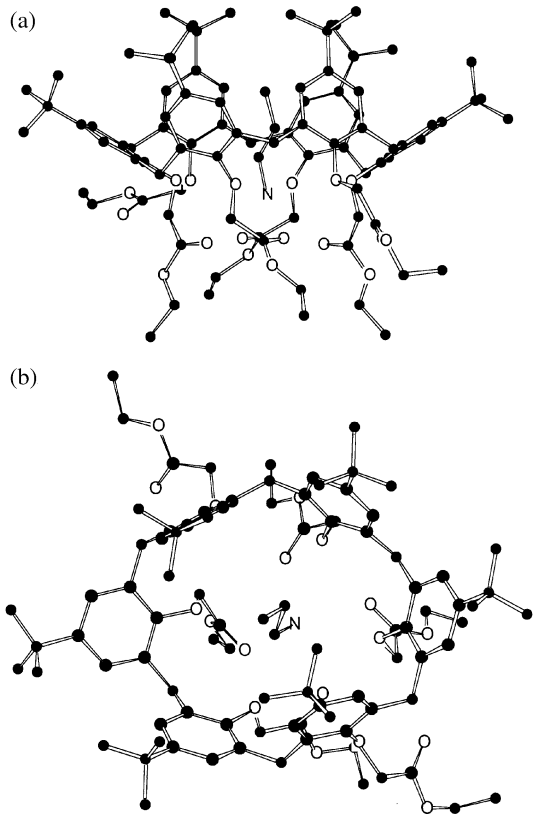


Figure 5. Conformation of **2** & propyl ammonium complex: (a) side view without hydrogen. (b) top view without hydrogen.

solution.[9(b),24] When one compares the calculated complexation energies of $\mathbf{2}_{(cone)}$ by various butyl ammonium guests in Table 4, *n*-butyl ammonium guest (-70.39 kcal/mol) has much better complexation ability over *tert*-butyl ammonium (-59.62 kcal/mol), which is also similar trend as the experimental $\Delta G_{Extraction}$ in Table 5. The different magnitudes in trends for the two cases may be due to the different environment such as solvent.

Determination of Relative Binding Free Energy (ΔG). Using the Finite Difference Thermodynamic Integration (FDTI) method in Discover[20] we have calculated the relative binding Gibbs free energy of the different alkyl ammonium ion complexation with calix[6]arenes.

The independent calculations of relative free energies

Table 4. Absolute Free Energies (kcal/mol)[a] of Hosts, Alkylammonium Cations, and Complexes

ΔG_{calc}		Alkylammonium Guest								
		NH_4^+	Me	Et	*n*-Pr	*iso*-Pr	*n*-Bu	*iso*-Bu	*sec*-Bu	*tert*-Bu
		13.88	59.48	40.96	67.78	3.35	70.31	77.30	39.48	-54.89
Host		Complexes of host with guest								
1$_{(cone)}$	698.98	655.95	703.87	681.89	707.95	645.68	708.95	714.5	680.69	591.53
2$_{(cone)}$	712.23	666.19	711.01	685.19	713.39	652.56	712.15	720.79	685.97	597.72
1$_{(cone)}$ Complexation[b]		-56.91	-54.59	-58.05	-58.81	-56.65	-60.34	-61.78	-57.77	-52.56
2$_{(cone)}$ Complexation[b]		-59.92	-60.70	-68.00	-66.62	-63.02	-70.39	-68.74	-65.74	-59.62

[a]Error limits in these calculations are 0.10 kcal/mol for guest and 0.60 kcal/mol for host and complex. [b]Complexation free energy = $\Delta G_{Complex} - \Delta G_{Host} - \Delta G_{Guest}$.

Table 5. Experimental Thermodynamic Quantities (ΔG in kcal/mol)[24] for the Extraction of Alkylammonium Picrates with Ester Derivatives of Calix[6]arenes in CH_2Cl_2

$\Delta G_{Extraction}$	Complexes of host with guest								
Host	NH_4^+	Me	Et	*n*-Pr	*iso*-Pr	*n*-Bu	*iso*-Bu	*Sec*-Bu	*tert*-Bu
1	-6.50	-8.25	-8.51	-7.67		-7.34	-7.04	-6.93	-6.59
2	-7.87	-10.30	-10.58	-9.48		-8.80	-8.40	-8.29	-7.53

Table 6. Relative Free Energies (kcal/mol)

$\Delta\Delta G_{Calc}$(CVFF)	System			
	$NH_4^+ \rightarrow$Me	Me $\rightarrow$ Et	Et$\rightarrow$ *n*-Pr	*n*-Pr $\rightarrow$ *n*-Bu
6-1. Alkylammonium Cations				
Guest	45.98	-18.98	31.47	7.00
6-2. Complexes of Host with guest				
Host **1**$_{(cone)}$	56.56	-12.02	35.76	7.16
Host **2**$_{(cone)}$	54.82	-12.86	35.22	7.23

[a]Error limits in these calculations are 0.10 kcal/mol for guest and 0.60 kcal/mol for host.

(Table 6) agree pretty well with absolute free energies calculations (Table 4). For example, on the $NH_4^+ \rightarrow$ Me System, the difference (45.98 kcal/mol) in guest is approximately equal to the absolute free energy (59.48 kcal/mol) of methylammonium cation minus the value of ammonium cation (13.88 kcal/mol); the difference (54.82 kcal/mol) in complex of Host **2**$_{(cone)}$ is about same to the absolute free energy (711.01 kcal/mol) of methylammonium complex minus the value of ammonium complex (666.19 kcal/mol).

Although the calculations are performed under quite different conditions of vacuum from the experimental results obtained by the two phase solvent extractions, we believe that the present simulations provide a general and useful explanation to the molecular recognition behavior of the calix[6]arene derivatives toward alkylamines.

Conclusion

Using the Finite Difference Thermodynamic Integration (FDTI) method in Discover we have calculated the absolute and relative Gibbs free energy of the different alkyl ammonium ion complexation with the alkyl *p-tert*-butylcalix[6]-aryl esters. Semi-empirical AM1 method in HyperChem was used for calculating enthalpy of formation. We have adapted CVFF (in Discover) and MM+ (in HyperChem) forcefields for molecular mechanics calculations to express the complexation energy of the hosts. Most stable conformation is 1,2,3-alternate for uncomplexed free calix[6]arene host. Optimum structure of host-guest complex is found to be cone-type conformation. Among the different orientations of alkyl ammonium cations inside the cone-shape host, *endo*-cone complex is calculated as the most stable structure . Ethyl *p-tert*-butylcalix[6]aryl ester (**2**) showed better complexation efficiency toward alkylamines than methyl *p-tert*-butylcalix[6]aryl ester (**1**), that agrees well with experimental observations.

Acknowledgment. This research was supported by the Chung-Ang University special research grants in 1997.

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23. As one see the Figure 3, the partial charges in three separate methods are different. A lot of care should be taken when electrostatic interaction is included in energy calculation. In HyperChem 4.5, unusual bond angles and nonplanar aromatic rings are commonly observed in MM+ minimized structure when not enough time of molecular dynamics are performed. Those kinds of strange structure would give incorrect total MM energy in which tremendous contribution of electrostatic interaction energy will compensate the unstable bond or ring strains. Normally more than 100 ps of dynamics simulation with 300 K is recommended.
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