

Articles

Molecular Modeling of Complexation of Alkyl Ammonium Ions by *p*-tert-Butylcalix[4]crown-6-ether

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The conformations and energies of *p*-tert-butylcalix[4]crown-6-ether (**1**) and its alkyl ammonium complexes have been simulated by AM1 semi-empirical quantum mechanics and molecular mechanics calculations using a variety of forcefields (MM2, MM+, CVFF). We performed molecular dynamics calculations to simulate the behavior of these complexes primarily focusing on the three representative conformations (cone, partial cone, 1,3-alternate) of host molecule **1**. When we performed AM1 semi-empirical and molecular mechanics calculations, the cone conformation was generally found 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. The complexation enthalpy calculations revealed that the alkyl ammonium cations having smaller and linear alkyl group showed the better complexation efficiencies when combined with *p*-tert-butylcalix[4]crown-6-ether, that is in satisfactory agreement with the experimental results.

Introduction

Since Pedersen^{1a} discovered crown ethers, the host-guest chemistry has been one of the most attracting research areas for last 30 years. The research efforts toward the development of a variety of synthetic receptors for the selective molecular recognition of many important guests are fruited in a lot of ingenious supramolecular systems both experimentally and theoretically.^{1b-d} More recently, the calixarenes² having both polar and nonpolar binding sites in their molecular framework are receiving much attention, and numerous attempts have been made to modify and endow unique binding characteristics to these versatile molecular systems.^{3,4}

Ungaro and Reinhoudt have synthesized calix[4]-crown ethers and related derivatives that have calix[4]arene moiety as a subcyclic unit of crown ether, and characterized their ion-binding properties toward alkali and alkaline earth metal cations.^{5,6} Several different host compounds based on the calix-crown framework, including selective chromoionophores for potassium ion⁷ and double-calix-crowns,⁸ have been prepared and their interesting ionophoric properties were investigated. Along with these efforts, a theoretical study of the stereochemical dependence of alkali metal ion complexation and liquid-liquid extraction of alkali cations by 1,3-dimethoxy-calix[4]crown-6 has been reported.⁹ Particularly, selective binding of organic ammonium guests attracts much research interests,¹⁰ which results in development of many sophisticated host systems.¹¹ Experimental data for the molecular recognition of butylamines by *p*-tert-butylcalix[4]-crown ethers has been reported, in which study the extraction efficiency decreases in the sequence *n*-Bu > *iso*-Bu > *sec*-Bu > *tert*-Bu.¹² More detailed study on the molecular recognition of alkyl and arylalkyl amines in dichloromethane and chloroform by calix[4]-crown ethers has been published.¹³

This report showed that the binding strength of alkyl amines with the host **1** generally decreased with the increasing size of the alkyl chain of the ammonium guests. Furthermore, ¹H NMR titration of compound **1** with alkyl or arylalkyl ammonium guests in CDCl₃ revealed that the primary binding site is the central part of the crown moiety.

In this study we have used three different kinds of molecular modeling software (HyperChem,¹⁴ InsightII/Discover,¹⁵ and Chem3D¹⁶) for the computer simulation of the complexation behaviors of the calix[4]crown-6 toward varying structures of representative alkyl ammonium ions. The main emphases of this research are: (1) trying to determine the most stable conformation of the calix[4]crown-6-ether among three representative conformations (cone, partial cone, and 1,3-alternate); (2) locating the most probable binding site of the host for the recognition of alkyl ammonium guest, *i.e.* either the crown-ether ring or the cavity region comprising of four benzene rings; and finally (3) determining the selectivity of the host for different alkyl ammonium guests with varying structural characteristics which are good model compounds for the biologically important organic amine guests.

Figure 1 shows the ChemDraw image of host **1**, in which

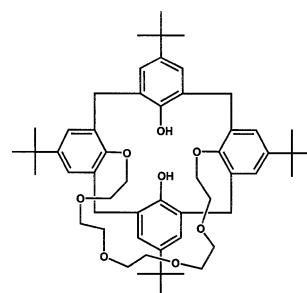


Figure 1. *p*-tert-Butylcalix[4]crown-6-ether (**1**).

hydrogen atoms are omitted for clarity except the hydrogen on hydroxy groups.

Computational Methods

Molecular Mechanics¹⁷ Calculations by MM+ and MM2 Forcefield. The initial structures of host and guest molecules were constructed by HyperChem.¹⁴ Initially, MM+ calculations were performed. In order to find optimized conformations, we executed conformational search by simulated annealing method, which is described below. We have adapted MM+ (HyperChem) and MM2 (Chem3D) forcefields to express the MM energies of calix[4]crown-6-ether host, alkylammonium cations, and complexes obtained thereof.

Conformational Search by Simulated Annealing. We have performed molecular dynamics (MD) calculations for 300 ps at 900 K constant temperature. The calculations used a time step of 1.0 fs. It was followed by 100 ps MD at 300 K constant temperature for the host and its complexes. MM calculations with steepest descent and Newton-Raphson (block-diagonal) methods were carried out to 0.001 kcal/mol gradient.

Semi-empirical Quantum Mechanical (AM1) Method.¹⁴ The conformations of the host and complexes obtained from MM calculations were fully 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[4]crown-6-ether); total charge=1, spin multiplicity=1 for cationic guests and complexes.

Molecular Mechanics Calculations by InsightII/Discover.¹⁵ The lowest energy conformers of host and complexes obtained from the previous HyperChem MD and MM runs were converted to MDL file formats, which were read by InsightII/Discover. We have adapted Consistent Valence Forcefield (CVFF) to express the MM energies of calix[4]crown-6-ether host, alkylammonium cations and complexes. The CVFF forcefield in Discover program was originally created for modeling peptides and proteins and has been extended to handle more general systems having similar functional groups. It is a Class I forcefield having some anharmonic and cross term enhancements. The 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 was carried out for 3 ns. Every 50 ps during the 3 ns snapshot were saved and the energies of these conformers were minimized to 0.01 kcal/mol gradient. The energy and structure of the lowest energy conformer from each search were then used for comparison with cone, partial cone, or 1,3-alternate conformers (see Figures 2 and 3 for the host, and Figure 4 for the host-guest complexes).

Absolute Gibbs Free Energy.¹⁵ 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. 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.

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, different conformations of host and the complexes of host 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.

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 forcefield (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 the 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.

Computers and Calculation Time. 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. Most of the InsightII/Discover MM (CVFF forcefield) calculations on this study are done on SGI Indy. Molecular dynamics (3 ns) simulation of *p-tert*-butylcalix[4]crown ether host normally took about 100 hours on this workstation and each free energy calculation required about 20 hours.

Results and Discussion

Conformational Characteristics of *p-tert*-Butylcalix[4]crown-6-ether. After we had performed high temperature molecular dynamics simulation using the unstable structure

Table 1. Energies (kcal/mol) of Three Different Host Conformations of Calix[4]crown-6-ether

Host 1 Conformation	Molecular modeling software						
	ΔH^b (AM1)	Relative ΔH (AM1)	Binding energy ^c (AM1)	MM (MM+)	MM (MM2)	MM (CVFF) ^d	ΔG^e
Cone	-329.48	0.00	-13887.80	-84.31	13.08	101.20	428.38
Partial cone	-319.40	10.07	-13879.48	-72.65	23.45	101.95	426.16
1,3-Alternate	-313.21	16.27	-13873.29	-68.47	26.60	114.02	436.14

^aError limits in AM1 and MM calculations are 0.001 kcal/mol. ^bEnthalpy of formation calculated by semi-empirical quantum mechanics (AM1) calculation. ^cBinding Energy of the AM1 calculation: Relative binding energies are same as relative enthalpies. ^dError limits in MM (CVFF) calculations are 0.01 kcal/mol. ^eError limits in absolute free energy calculations are 0.60 kcal/mol.

made from model build module in HyperChem, we could obtain many kinds of conformations on this molecule. But stable conformers on local minima could be categorized into three types of distinct structures. Host molecule **1** (Figure 1) can take three representative conformations of cone, partial cone (paco), 1,3-alternate form (Figures 2-3). Initially, we have performed MM+ molecular dynamics calculations for 300 ps at 900 K constant temperature. It was followed by 100 ps MD at 300 K constant temperature for each conformation of the host to remove any abnormal structure constrains. MM calculations with steepest descent and Newton-Raphson (block-diagonal) methods were carried out to 0.001 kcal/mol gradient. Finally AM1 semi-empirical quantum mechanics calculations were carried out for each of the cone, paco, 1,3-alternate conformers of **1**. MM and absolute free energy calculations were also carried out on SGI IRIS using the InsightII/Discover program.

As one sees the results in Table 1, the cone conformation is calculated to be the most stable regardless of calculation methods employed except for the InsightII/Discover. In the HyperChem calculation, the cone conformation is more stable than the partial cone about 10.07 kcal/mol in enthalpy (AM1) and 11.66 kcal/mol in MM+ energy. MM2 calculation using Chem3D shows similar difference between cone and partial cone conformations. The error limits in Tables 1 through 5 are the outputs from the molecular modeling programs. 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.

To compare the structural characteristics of the host **1** with the experimental crystal structure, we searched the structure **1** in Cambridge Structure Database. The calculated structure obtained in this study (Figure 2(b)) has similar conformation and structure features as the reported X-ray crystal structure¹⁸ (Figure 2(a)) of the host molecule **1**. The calculated structure exhibited somewhat expanded upper rim structure in underivatized phenol rings and more flattened crown ether moiety compared to the pleated form of the crystal structure.

Although the representative conformers in Figures 2-4 are carefully chosen, they might not be most stable structures. There could be lots of similar conformations in the error range of the minimum energy.

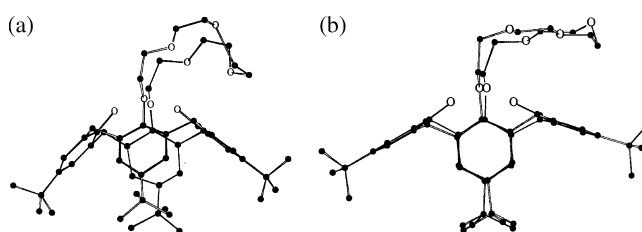


Figure 2. (a) X-ray crystal structure of **1**.¹⁸ (b) Calculated stable cone conformation of **1** from molecular modeling.

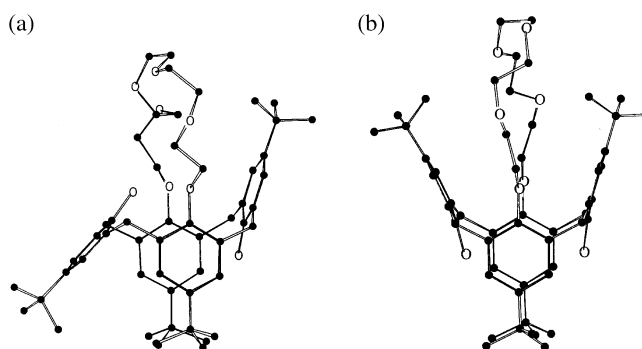


Figure 3. Calculated structures of (a) partial cone conformation of **1** and (b) 1,3-alternate conformation of **1**.

Complex Formation of Host with Alkylammonium Guests. The molecular dynamics, molecular mechanics, and AM1 semi-empirical quantum mechanics calculations were carried out for each of the four kinds of complexation mode of host(partial cone)/guest(cr), host(1,3-alternate)/guest(cr), host(cone)/guest(cr), and host(cone)/guest(bz) complexes of **1** and alkyl ammonium ions. (See Table 2 and Figures 2-4 for notations). For each complex we have performed MM+ MD calculations for 300 ps at 300 K constant temperature. Steepest descent and Newton-Raphson (block-diagonal) methods were carried out to 0.001 kcal/mol gradient for MM+ minimization with electrostatic interaction using the final structure obtained from MD. In AM1 calculations, steepest descent and Polak-Reviere (conjugate gradient) methods were also carried out to 0.001 kcal/mol gradient.

MM calculations were also carried out on SG IRIS using the InsightII/Discover program package. We have adapted CVFF forcefield to express the complex. Except as noted below, the default parameters supplied with the program

Table 2. AM1 Binding Energies (kcal/mol)^a of Complexes of Calix[4]crown-6-ether with Alkyl Ammonium Ions

Semi-empirical AM1 binding energy using HyperChem		Alkyl ammonium guest ^b					
		NH ₄ ⁺	Me	Et	<i>n</i> -Pr	<i>n</i> -Bu	<i>tert</i> -Bu
		-170.88	-447.85	-733.02	-1015.52	-1298.26	-1296.39
Host		Complexes with host					
-13889.55	Host(cone)+Guest(cr) ^c	-14121.96	-14392.08	-14672.63	-14954.67	-15236.74	-15230.30
	Host(cone)+Guest(bz) ^d	-14102.02	-14370.47	-14660.50	-14936.90	-15213.96	-15208.29
-13879.48	Host(paco)+Guest(cr)	-14114.66	-14379.95	-14665.33	-14945.01	-15227.97	-15223.29
-13873.30	Host(1,3-alt)+Guest(cr)	-14105.10	-14371.71	-14653.35	-14935.57	-15223.83	-15197.68

^aError limits in these calculations are 0.001 kcal/mol. ^bMe = methylammonium, Et = ethylammonium, *n*-Pr = *n*-propylammonium, *n*-Bu = *n*-butylammonium cation. ^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.

Table 3. Enthalpies (kcal/mol) of Different Complexes of Calix[4]crown-6-ether with Alkyl Ammonium Ions

Enthalpies (ΔH) ^a calculated from HyperChem AM1 method			Alkyl Ammonium guest					
			NH ₄ ⁺	Me	Et	<i>n</i> -Pr	<i>n</i> -Bu	<i>tert</i> -Bu
			150.53	148.65	138.57	131.17	123.53	125.40
Host			Complexes with host					
-329.47	Host(cone)	Guest(cr)	-240.47	-235.50	-240.95	-247.90	-254.88	-248.66
	Host(cone)	Guest(bz)	-220.53	-213.88	-228.82	-230.13	-232.10	-226.64
-319.40	Host(paco)	Guest(cr)	-233.17	-223.37	-233.65	-238.28	-246.10	-241.42
-313.21	Host(1,3-alt)	Guest(cr)	-223.58	-215.13	-221.68	-228.80	-241.97	-215.81
	Host(cone)+Guest (cr) complexation ^b		-61.52	-54.67	-50.04	-49.58	-48.92	-44.58
	Host(cone)+Guest (bz) complexation ^b		-36.90	-33.06	-37.91	-31.81	-26.15	-22.56
	Host(paco)+Guest (cr) complexation ^b		-54.22	-42.54	-42.75	-39.97	-40.15	-37.34
	Host(1,3-alt)+Guest (cr) complexation ^b		-44.63	-34.31	-30.77	-30.49	-36.01	-11.73

^aError limits in these calculations are 0.001 kcal/mol. ^bComplexation enthalpies = $\Delta H_{\text{Complex}} - \Delta H_{\text{Host(cone)}} - \Delta H_{\text{Guest}}$.

were used. The resulting structure was subjected to a conformational search in which 300 K constant temperature MD was carried out for 1 ns. Snapshots were saved for every 50 ps during the 1 ns, and the energies of these conformers were further minimized. The energy and structure of the lowest energy conformer from each search was then used for comparison with other conformers.

The results of semi-empirical AM1 binding energies and enthalpies (kcal/mol) of complexes of calix[4]crown-6-ether with alkyl ammonium ions are listed in Table 2 and 3.

In Tables 2 and 3, the relative differences of binding energies and enthalpies within identical guest cations are exactly same. For example, the difference is 19.94 (-14121.96 and -14102.02) kcal/mol for AM1 binding energies, and the difference in enthalpies is also 19.94 (-240.47 and -220.53) for NH₄⁺ (ammonium ion) cases. The enthalpy of formation (ΔH) is directly connected with the binding energy calculated from semi-empirical quantum mechanics.

When one compares the complexation enthalpies for the different types of combination in Table 3, the host in cone conformation has the better complexation efficiencies with the guest in the crown ether moiety (guest(cr) mode) for all kinds of the alkyl ammonium ions than with the guest in the calix[4]arene cavity (guest(bz) mode) complex. The reason why we compare the complexation enthalpies instead of ΔH is to cancel out the individual guest effects for the different

alkyl ammonium cations. The host(cone) + guest(cr) complex also found to be most stable among the three kinds of conformations (cone, partial cone, and 1,3-alternate). This result suggests that the host(cone) + guest(cr) combination is the most probable conformation for the complex formation (Figure 4). This result agrees well with the experimental data for the two phase solvent extraction of alkyl ammonium picrates.^{12,13} These studies showed that complexation occurs in the central part of crown periphery and that significant conformational reorganization of the calixarene moiety was induced upon complexation with butylammonium guests, and that *n*-butylammonium cation has much better complexation ability with calix[4]crown-6-ether (**1**) than *tert*-butylammonium ions. Calix[4]-crown-6-ether is known to have the characteristic ionophoric properties that complexes efficiently with alkyl ammonium ions by using suitable complementarities between host and guests. In this calculation, the stabilization by the electrostatic interaction of crown moiety of calix[4]-crown-6-ether with alkyl ammonium cation also seemed to be the principle factor of complexation of host with guest.

When one compares the calculated complexation enthalpies of **1**(cone) by two butylammonium guests in Table 3, *n*-butylammonium guest (-48.92 kcal/mol) has much better complexation ability over *tert*-butylammonium ion (-44.58 kcal/mol), which has a similar trend as the experimental

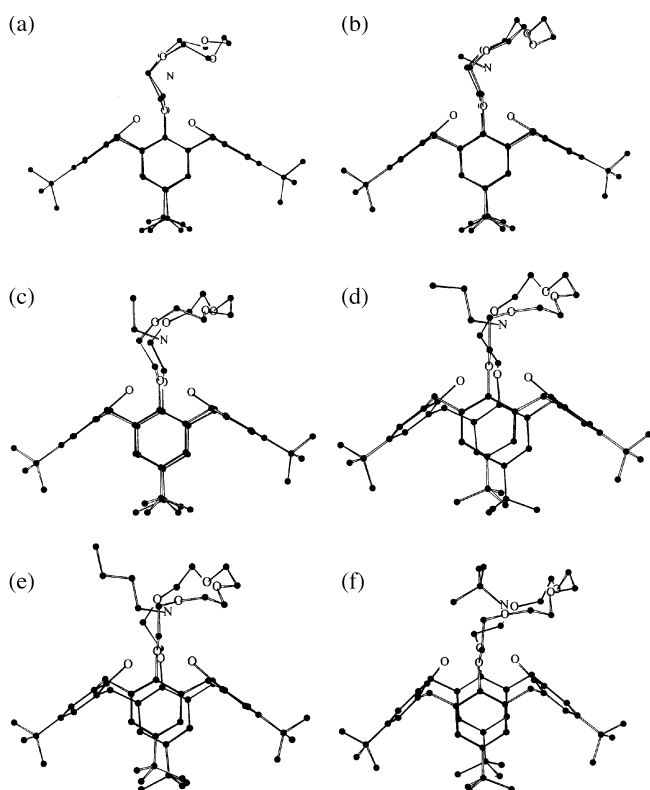


Figure 4. Calculated structures of cone-conformation of **1** complexed with (a) ammonium, (b) methylammonium, (c) ethylammonium, (d) *n*-propylammonium, (e) *n*-butylammonium, and (f) *tert*-butylammonium guest.

results.¹³ In that experiment, **1** exhibited pronounced discrimination behavior between varying structures of butylammonium picrates. That is the extraction efficiency decreases in the sequence *n*-Bu > *iso*-Bu > *sec*-Bu > *tert*-Bu. In Table

2, AM1 semi-empirical quantum mechanics calculations have already shown that cone conformation is most stable among three types of conformer. Therefore, we have concentrated our effort to the cone conformer of **1** obtained from AM1 method for the following CVFF forcefield calculations.

MM energies and absolute Gibbs energies calculated from InsightII/Discover of different complexes of **1** (cone) are reported in Tables 4 and 5. When one compares the complexation Gibbs energies for the different types of complexes for butylammonium guests in Table 5, *n*-butylammonium guest (-64.14 kcal/mol) exhibited again much larger binding affinity over *tert*-butylammonium ion (-52.70 kcal/mol). This result is again in parallel with the calculated results of enthalpies in Table 3 and the experimental extraction Gibbs energies (ΔG^0),¹³ although the magnitudes of free energy difference are not comparable due to different calculation environment (in vacuum) and experimental (in solution). The trend in different length of linear alkyl ammonium ions from methyl to *n*-butyl is not consistent with the result from AM1 calculation. One of the reasons for the discrepancy might be that no proper forcefield parameter in CVFF could be assigned on the crown ether moiety on this molecule.

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 steric interaction of crown ether moiety and calix[4]arene framework. The stabilization by the electrostatic interaction seemed to be the principle factor for the complexation of the calix[4]crown-6 host with the ammonium guests. To have an insight to this type of interaction in the present system, the Chem3D molecular structures for the complexes are depicted in Figure 4, without hydrogen atoms for the sake of clarity. As one looks at the guest ions in the complexes, the ammonium part of linear alkyl

Table 4. Energies (kcal/mol)^a of Different Complexes of Calix[4]crown-6-ether with Alkyl Ammonium Ions

MM (CVFF) ^b			Alkyl ammonium guest					
			NH ₄ ⁺	Me	Et	<i>n</i> -Pr	<i>n</i> -Bu	<i>tert</i> -Bu
			1.04	41.22	13.90	33.73	28.86	-93.94
Host			Complexes with host					
101.20	Host(cone)	Guest(cr)	44.41	87.27	58.39	78.55	71.72	-44.78
Host(cone)+Guest (cr) complexation ^f			-57.83	-55.15	-56.72	-56.38	-58.34	-52.04

^aError limits in these calculations are 0.01 kcal/mol. ^bForcefield in InsightII/Discover. ^cComplexation energies = $\Delta E_{\text{Complex}} - \Delta E_{\text{Host(cone)}} - \Delta E_{\text{Guest}}$.

Table 5. Absolute Gibbs Energies (kcal/mol)^a of Different Complexes of Calix[4]crown-6-ether

ΔG calculated			Alkyl ammonium guest					
			NH ₄ ⁺	Me	Et	<i>n</i> -Pr	<i>n</i> -Bu	<i>tert</i> -Bu
			13.88	59.48	40.96	67.78	70.31	-54.89
Host			Complexes with host					
428.38	Host(cone)	Guest(cr)	379.75	432.77	409.93	434.04	434.55	320.79
Host(cone)+Guest (cr) complexation ^b			-62.51	-55.09	-59.41	-62.12	-64.14	-52.70
Host+Guest extraction (ΔG^0) ^c			-9.74	-8.99	-9.09	-8.42	-7.96	-6.96

^aError limits in these calculations are 0.60 kcal/mol. ^bComplexation Gibbs Free Energies = $\Delta G_{\text{Complex}} - \Delta G_{\text{Host(cone)}} - \Delta G_{\text{Guest}}$. ^cTaken from reference 13.

ammonium cation is located inside of the crown-ether pocket and two hydroxyl groups in calix[4]arene except for the *tert*-butylammonium ion. And most of the oxygen atoms in the crown ether ring are within the hydrogen bonding distance (about 2.9-3.2 angstroms) from the nitrogen atom of alkyl ammonium guest. That observation suggests the possibility of the formation of multiple hydrogen bonding between the hydrogen atoms of ammonium group and the oxygen atoms of crown ether ring, even if the geometric requirement of the N-H...O angle for the hydrogen bond formation should also be satisfied. This confirms the stability of complex is mostly originating from the interaction between the crown ether moiety of calix[4]crown-6 host and the ammonium guests.

Conclusion

We performed AM1 semi-empirical and molecular mechanics calculations (MM2, MM+, CVFF) for the complexation of *p-tert*-butylcalix[4]arene 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) by all the employed calculation methods. The primary binding site for host **1** with alkyl ammonium guests was confirmed to be the central part of the crown moiety. The AM1 calculation results also suggest that the discrimination ability of the host toward the varying structures of alkyl ammonium ions. That is the complexation with smaller and less bulky alkyl ammonium cations showed the better complexation efficiencies.

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