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

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The structures and energies of *p-tert*-butylcalix[4]crown-6-ether (**1**) in various conformers and their alkyl ammonium complexes have been calculated by *ab initio* HF/6-31G quantum mechanics method. We have tried to obtain the relative affinity of partial-cone and 1,3-alternate conformers of **1** for alkyl ammonium guests by comparison with its cone-shaped analogue. We have also calculated the relative complexation efficiency of these host-guest complexes focusing on the binding sites of crown-6-ether moiety or benzene-rings pocket of the host molecule **1**. These calculations revealed that the crown moiety has better complexation efficiency than upper rim part of calix[4]arene that is in similar trend to the cone-shaped complexes.

Keywords : Calix[4]crown-6-ether, Partial cone, 1,3-Alternate, Alkyl ammonium ions, Molecular recognition.

Introduction

The molecular design of synthetic receptors for the selective recognition of many important guests has been ever increasing active research area in supramolecular chemistry field.[1] The calixarenes[2,3] having well-defined molecular framework are particularly attractive as a basic skeleton for new supramolecular systems and a variety of compounds have been prepared to endow unique binding characteristics to these versatile molecular systems.[4,5] Particularly, selective binding of organic ammonium guests of biologically important functions attracted much research interests,[6] which results in development of many interesting host systems from calixarenes.[7] Of these calix[4]-crown ethers revealed selective molecular recognition and sensing behavior toward many of important amine guests.[8,9]

Recently, there has been much progress in the computational approaches in supramolecular chemistry, which may lead to the microscopic insight into the structural and thermodynamical features involved in the processes of molecular recognition and supramolecular organization.[1d] Wipff *et al.* have performed computational studies on a series of important ionophores derived from calixarenes.[9] We have reported preliminary AM1 semi-empirical quantum mechanics and molecular mechanics calculations using a variety of forcefields (MM2, MM+, CVFF) for the alkyl ammonium complexes on three different conformations (cone, partial cone, 1,3-alternate) of *p-tert*-butylcalix[4]crown-6-ether (**1**).[11] We have also studied the structures and energies of the cone-shaped host **1** and its alkyl ammonium complexes using *ab initio* HF/6-31G quantum mechanics.[12] By a series of calculations 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.[11] The complexation energy calculations also revealed that the ammonium cation without alkyl group showed the highest complexation efficiency when combined with host **1**. These results are in satisfactory agreement with the preliminary AM1 semi-empirical quantum mechanics and molecular mechanics calculations as well as with the experimental[9] results.

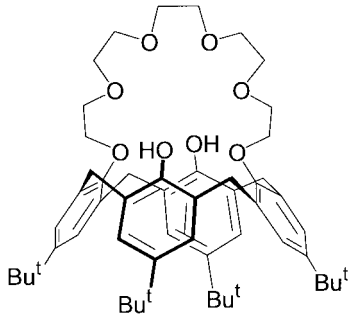

Figure 1. Structure of *p-tert*-butylcalix[4]crown-6-ether (**1**). In order to focus the crown-ether moiety, all of the conformers in Figures 1 through 5 show the upper rim of calixarene in the lower position.

In this paper we report the *ab initio* calculation of the conformers of *p-tert*-butylcalix[4]arene complexed with simple alkyl ammonium guests. The main emphases of this study are trying to determine the relative binding affinity toward alkyl ammonium guests of partial-cone and 1,3-alternate conformations compared to its cone-shaped analogue along with the complexation efficiency of these host-guest complexes focusing on the binding site of crown-6-ether or benzene-rings pocket of the host molecule **1** using *ab initio* HF/6-31G quantum mechanics.

Computational Methods

The initial structures of host molecule and host-guest

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Table 1. *Ab initio* HF/6-31G Energies (A.U.)[a] of Complexes of Calix[4]crown-6-ether with Alkyl Ammonium Ions

HF/6-31G energies calculated from Gaussian 98			Alkyl ammonium guest[b,c]							
			NH_4^+		Me		Et		*n*-Pr	
			-56.5159		-95.5388		-134.5658		-173.5862	
Host **1**[c]	Complex conformation		HF/6-31G Absolute and relative energies[a] of complexes with host **1**							
-2685.7546	Host (cone)[c]	Guest(cr)[d]	-2742.3914	0.0000	-2781.3976	0.0000	-2820.4232	0.0000	-2859.4393	0.0000
		Guest(bz)[e]	-2742.3557	0.0357	-2781.3552	0.0424	-2820.3774	0.0458	-2859.3979	0.0414
-2685.7191	Host (paco)[f]	Guest(cr)	-2742.3758	0.0155	-2781.3872	0.0104	-2820.4052	0.0179	-2859.4165	0.0228
		Guest(bz)	-2742.3328	0.0586	-2781.3489	0.0486	-2820.3714	0.0518	-2859.3903	0.0490
-2685.7197	Host (1,3-alt)[f]	Guest(cr)	-2742.3584	0.0330	-2781.3541	0.0435	-2820.3733	0.0499	-2859.3236	0.1157
		Guest(bz)	-2742.3117	0.0797	-2781.3152	0.0824	-2820.3513	0.0719	-2859.3717	0.0676

[a]Units are in Hartree (Atomic Unit). Error limits in these calculations are 0.00002 A.U. [b]Me = methyl ammonium, Et = ethyl ammonium, *n*-Pr = *n*-propyl ammonium ion. [c]Data for the free hosts and the cone-shaped complexes are taken from the previous publication.[12] [d]Guest(cr) conformation denotes that alkyl ammonium ion is contained inside of the crown-6-ether moiety. [e]Guest(bz) means that alkyl ammonium ion is contained inside of upper rim consisted of benzene rings. [f]paco and 1,3-alt denote partial cone and 1,3-alternate conformation, respectively.

Table 2. *Ab initio* Energies (kcal/mol)[a] of Complexes of Calix[4]crown-6-ether with alkyl Ammonium Ions

Ab initio HF/6-31G energies (kcal/mol)			Alkyl ammonium guest[b,c]			
			NH_4^+	Me	Et	*n*-Pr
			-35464.26	-59951.51	-84441.30	-108927.01
Host **1**[c]	Complex conformation		HF/6-31G relative energies[a] of complexes			
-1685336.67	Host(cone)[c]	Guest(cr)[d]	0.00	0.00	0.00	0.00
		Guest(bz)[e]	22.39	26.60	28.74	26.00
-1685314.42	Host(paco)[f]	Guest(cr)	9.76	6.55	11.26	14.33
		Guest(bz)	36.76	30.52	32.52	30.78
-1685314.77	Host(1,3-alt)[f]	Guest(cr)	20.68	27.32	31.28	72.60[g]
		Guest(bz)	50.02	51.72	45.11	42.41

[a]Units are in kcal/mol using conversion factor 1 A.U. = 627.5096 kcal/mol. Error limits in these calculations are 0.001 kcal/mol. [b-f]Other footnotes are same as Table 1. [g]This conformer was so unstable that further *ab initio* geometry optimization would convert it from 1,3-alternate complex to partial cone analogue due to the steric hindrance of *n*-propyl group in the ammonium cation.

complexes for *ab initio* HF/6-31G calculations were determined by InsightII/Discover.[13,14] 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. Every 50 ps during the 3 ns snapshot were saved and the energies of these conformers were minimized to 0.01 kcal/mol gradient.

Semi-empirical Quantum Mechanical (AM1) Method. 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 6.03.[16] 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.

***Ab initio* Quantum Mechanical (HF/6-31G) Method**. *Ab initio* HF/6-31G quantum mechanical calculation of the host **1** or its complexes by Gaussian 98[17] on Fujitsu VPP 5000 supercomputer (13GB 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.)) for each complex. 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

The *ab initio* quantum mechanical full optimizations without any constraint were carried out for two kinds of complexation mode for each conformer: combining cone, partial-cone, and 1,3-alternate conformers of host **1** with guest in two different locations (the crown-6-ether (cr) or benzene-rings pocket (bz)) of calix[4]arene-crown ether. To have an insight into the binding of organic ammonium guests, simple alkylamines were chosen as model compounds. The results of *ab initio* HF/6-31G energies for the complexes of partial-cone and 1,3-alternate calix[4]crown-6-ether with alkyl ammonium ions are listed in Tables 1 and 2. Table 1 reports the *ab initio* HF/6-31G absolute and relative energies (in atomic unit) of the different complexes of calix[4]crown-

6-ether with representative linear alkyl ammonium cations. Table 2 reports the results of Table 1 converted as the relative energies of three kinds of complexes in kcal/mol for the sake of readability.

When one sees Table 2, the partial-cone-complex with NH_4^+(cr) and the partial-cone-complex with NH_4^+(bz) in three-benzene-rings pocket are found to be 9.76 kcal/mol and 36.76 kcal/mol less stable than the most stable cone-complex with NH_4^+(cr) in crown-ether ring, respectively. Within partial-cone-complex, the NH_4^+(cr) is much more stable than the complex in benzene-rings pocket by 27 kcal/mol. The trend in relative stability between the positions of ammonium ion in two possible binding locations is similar to that of already reported cone-complex.[12] Other kinds of linear alkyl ammonium complexes all showed similar trend for the relative stabilities in these *ab initio* quantum mechanical calculations. When one compares the relative stabilities of the host in partial cone conformation for the different guests in Table 2, the guest in the crown ether moiety (guest(cr) mode) generally has the higher complexation efficiencies for all kinds of the alkyl ammonium ions than in the three-benzene-rings pocket of the partial cone conformation of host molecule **1**.

Figure 2 shows the final *ab initio* calculated structure of partial cone conformation of **1** complexed in crown-ether moiety with propyl ammonium ion. The calculated structure does not affected significantly with the size of alkyl group in ammonium ion up to the ethyl ammonium guest. However, for the propyl ammonium complex, rigorous optimization changed its conformation to the more stable cone analogue. Therefore, we had to position the propyl ammonium guest at the other side of crown-6-ether moiety as a starting structure. In this case the rest of ionophore structures are relatively unaffected. Figure 3 shows the less stable structure of partial cone conformation of **1** complexed in the three-benzene-rings pocket with propyl ammonium ion. The different position of the crown-6-ether moiety (either vertical or flattened) did not influence the relative stability of the complexes for various alkyl ammonium guests, which might be due to the fact that the alkyl groups of the guest located in upper rim part adopting the outward orientation.

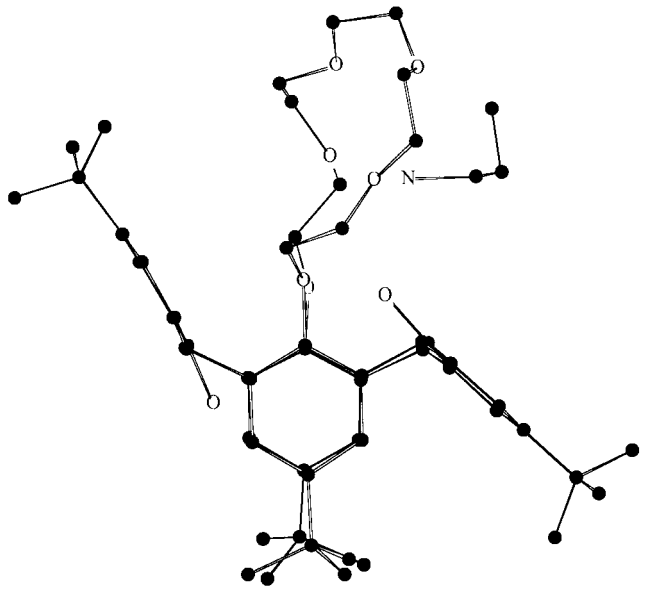

Figure 2. *Ab initio* calculated structure of partial-cone conformation of **1** complexed in crown-ether ring with *n*-propyl ammonium ion.

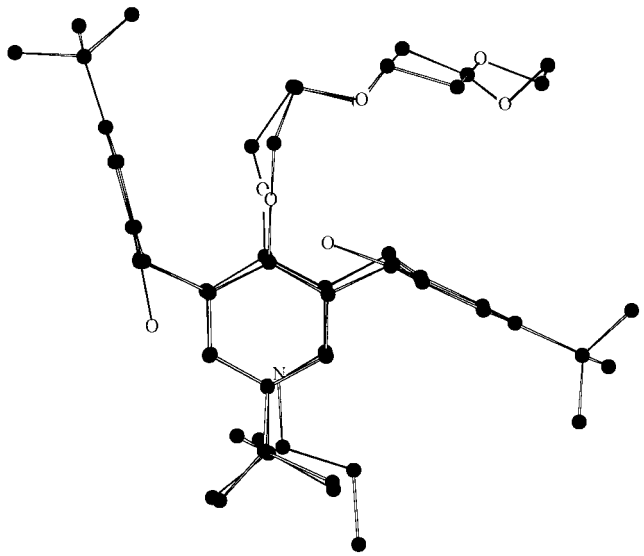

Figure 3. *Ab initio* calculated structure of partial-cone conformation of **1** complexed in the calix[4]arene-cavity consisted of benzene rings with n-propyl ammonium ion.

When one sees Table 2, the 1,3-alternate-complex with NH_4^+(cr) and the 1,3-alternate-complex with NH_4^+(bz) in two-benzene-rings pocket opposite to the crown ether

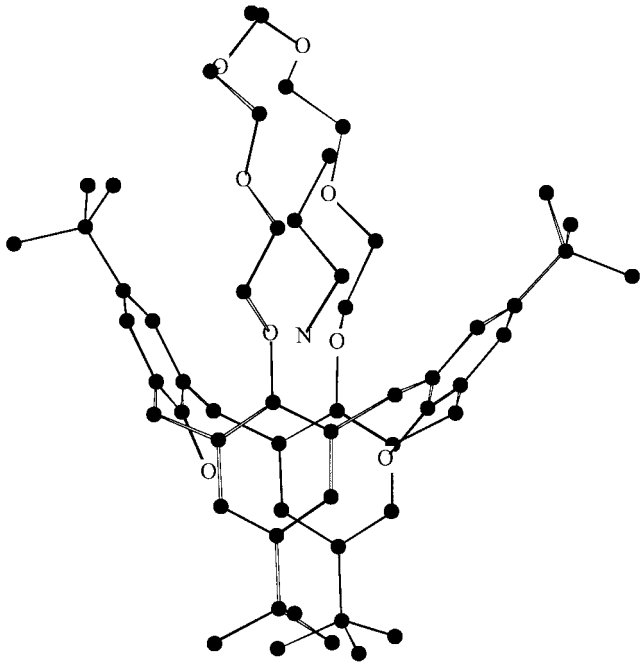

Figure 4. *Ab initio* calculated structure of 1,3-alternate conformation of **1** complexed in crown-ether ring with *n*-propyl ammonium ion.

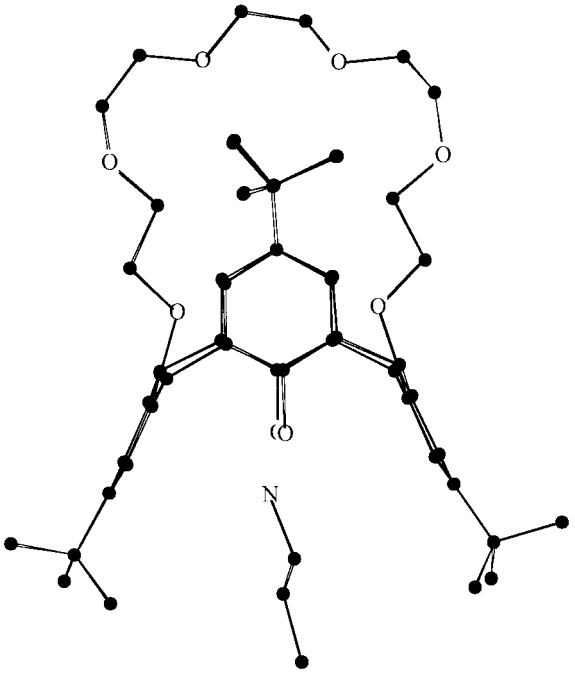

Figure 5. *Ab initio* calculated structure of 1,3-alternate conformation of **1** complexed in calix[4]arene-cavity consisted of benzene rings with n-propyl ammonium ion.

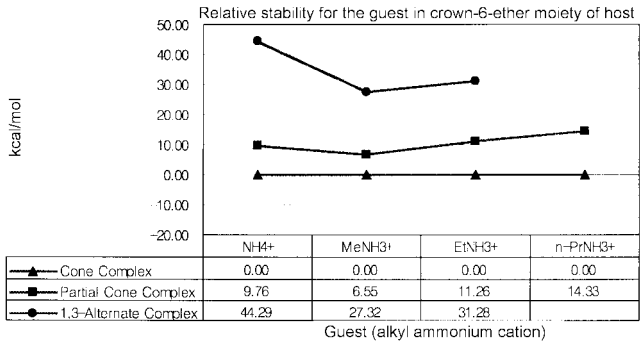

Figure 6. Relative stability (kcal/mol) for the alkyl ammonium guest in crown-6-ether moiety of host **1**.

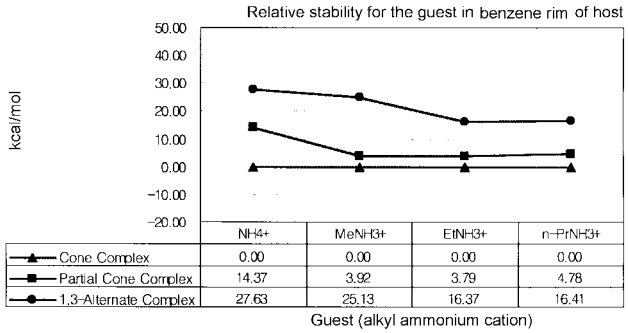

Figure 7. Relative stability (kcal/mol) for the alkyl ammonium guest in benzene rim of host **1**.

moiety are found to be 20.68 kcal/mol and 50.02 kcal/mol less stable than the most stable cone-complex with NH_4^+(cr) in crown-ether ring. The 1,3-alternate-complex with NH_4^+ in crown-ether moiety is more stable than the 1,3-alternate-complex in benzene-rings pocket as other conformers. Figure 4 shows the final *ab initio* structure of 1,3-alternate conformation of **1** complexed in crown-ether moiety with propyl ammonium ion. In this case, one of the *tert*-butyl groups of two alternate rings moves somewhat outward from the crown ether moiety as the size of the alkyl group increases, which results in more flattened conformation of the ionophore. Figure 5 shows the less stable structure of the 1,3-alternate conformation of **1** complexed in the two-benzene-rings pocket opposite to the crown ether moiety with propyl ammonium ion. The substituent effects on the conformation of ionophore are again negligible due to the outward orientation for the alkyl groups of the guest. The stability of the complexes in general decreases in the order of $NH_4^+ > MeNH_3^+ > EtNH_3^+ > PrNH_3^+$, which is in good agreement with the experimental results.[9]

In order to depict the relative energies for the alkyl ammonium guest in crown-6-ether moiety and in benzene rim of host **1**, we converted the data in Table 2 into two different plots of Figures 6 and 7, respectively. Figure 6 shows the relative stability (kcal/mol) for the alkyl ammonium guest in crown-6-ether moiety of host **1**. The *n*-propyl ammonium complex of 1,3-alternate conformer was so unstable that further *ab initio* geometry optimization would convert it to partial cone analogue due to the steric hindrance of *n*-propyl group in the ammonium cation. Therefore, this value (72.60 kcal/mol) is omitted in the plot. As one sees Figure 6, all of the 1,3-alternate complexes are more than 27 kcal/mol unstable compared with the cone analogues. Figure 7 shows the relative stability (kcal/mol) for the alkyl ammonium guest in benzene rim of host **1**. Here, the 1,3-alternate conformers are again most unstable, but the magnitude of differences is much smaller than crown-6-ether pocket complexes, less than 28 kcal/mol compared with the cone analogues. An interesting result in this plot is that the partial cone complexes of the ammonium ion with alkyl group have very much similar stability compared to cone complexes. One of the reasons might be due to smaller but fairly noticeable CH-aromatic π interactions in three benzene rings compared to cone complexes.

In order to complete the previous AM1 semi-empirical quantum mechanical calculation of complexes of calix[4]-crown-6-ether with alkyl ammonium ions,[11] we have also computed the relevant energies of the partial-cone and 1,3-alternate complexes in which the guest cation is in benzene-rings pocket. Here again the stability of the complexes decreases in the order of $NH_4^+ > MeNH_3^+ > EtNH_3^+ > PrNH_3^+$, which is in line with the experimental results.[9] As we have compared the quantum mechanical stabilities of the different partial-cone and 1,3-alternate complexes, the relative energies of AM1 semi-empirical method are in parallel to the trend of *ab initio* HF/6-31G quantum mechanical calculations. Therefore, when one does not have enough computing resources for the *ab initio* calculations, it is possible to utilize the less expensive semi-empirical AM1 quantum mechanical methods to get relative stabilities of different

conformations for the calix[4]crown-6-ether and its related systems.

Conclusion

We have performed *ab initio* HF/6-31G quantum mechanical calculations for the complexation of *p-tert*-butylcalix-[4]crown-6-ether in partial cone and 1,3-alternate conformation with varying alkyl ammonium ions. 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 as in cone-complexes. The *ab initio* 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 in all cases shows the highest complexation efficiency with cone conformation than partial-cone and 1,3-alternate conformational analogues. These *ab initio* HF/6-31G results are in satisfactory agreement with the results of preliminary publication[11] which have used less expensive calculation methods such as AM1 semi-empirical quantum mechanics and also with experimental results.[9]

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