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Conformational studies of *p-t*-butylcalix(4)arene and its toluene complex

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Theoretical investigation of the conformations of *p-t*-butylcalix(4)arene and its toluene complex were carried out. The hydrogen bonding potential function suitable for the cyclic hydrogen bonds of calix(4)arene was obtained by least-squares fitting to the ab initio MO calculation results. It was found that the calix(4)arene has an enough flexibility for the complexation with molecules a little larger than the pore composed of the *t*-butyl groups; the complex formation does not need any activation energy. During the complex formation, the conformational changes of the calix(4)arene are small. Contribution of the dispersion interaction to the complexation energy is predominant. The cyclic hydrogen bond may not induce the allosteric effect at the binding site.

Key words: *p-t*-Butylcalix(4)arene — Conformation — Complex — Inclusion — MO

1. Introduction

Calixarenes [1] are macrocyclic compounds essentially made of the phenolic residues linked by methylene groups (-CH_2-). Calixarenes, having an enforced hydrophobic cavity, are attractive model compounds for studies related to the specific interactions between host and guest molecules [2-5]. In particular, the "cone-shaped" calixarenes have strong complexing ability because the definite sized and shaped cavity offers strong nonbonding hydrophobic interactions with the guest molecules, and they have a property which selectively takes appropriate guest molecules into their cavities. Thus, they may be used as a simple model which might contain some features of enzyme specificity and biological receptors.

Among the calixarenes, *p*-*t*-butylcalix(4)arene (simply calix(4)arene) is able to form inclusion complexes with some small molecules, such as chloroform, benzene, and toluene, with great affinity [1]. The toluene complex of the calix(4)arene has been well elucidated by X-ray diffraction analysis [6]. It has a C_2 symmetry and the crystal structure was classified as $P4/m$ space group, $a = b = 12.756$ (2) Å, $c = 13.793$ (3) Å, $Z = 2$. In the case of the calix(4)arene, the intramolecular cyclic hydrogen bonds and the methylene groups ($-CH_2-$) connecting the phenolic residues may cause the four *t*-butyl groups to align in a circle. Therefore these *t*-butyl groups may provide a binding specificity, especially for molecules with a finite size. Many spectroscopic (particularly "nmr") and synthetic studies on calixarenes have been carried out [1, 6–17]. Although many theoretical investigations of crown ethers and spherands, belonging to the same class of "macrocylic compound" as calixarenes, have been performed [18–22], there has been only a simple energy calculation of *p*-octylcalix(4)arene [12].

The purpose of this work is to construct the intra- and intermolecular potential functions which are suitable for the conformational studies of calix(4)arene and its toluene complex respectively. Conformational studies were then carried using these potential functions. From the results of the conformational studies, the origin of the driving force forming the strong complex will be investigated, and it was examined whether the allosteric effect is induced by the intramolecular hydrogen bonds at the binding site formed with the four *t*-butyl groups.

2. Method

2.1. Model compounds

In this study the geometry of the free calix(4)arene is constrained in a cone of C_4 symmetry (model I in Fig. 1), although many conformations ("cone", "partial cone", "1,2-alternate", and "1,3-alternate") are possible [13]; this is because the Gibbs free energy for the inversion of the *t*-butyl group from C_4 calix(4)arene

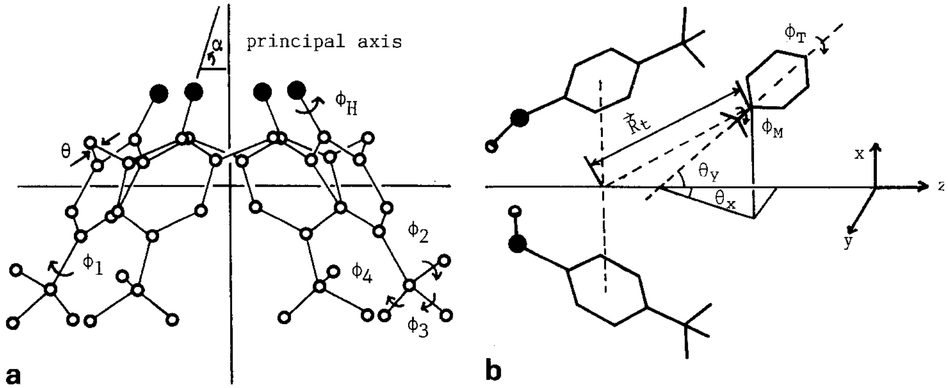

Fig. 1. Models and geometrical parameters used in this study. **a** Model I; **b** model II; hydrogen (◒), carbon (○), oxygen (●)

was reported as 15.84 kcal/mole [9]. If the phenyl rings and all the C–C bonds are assumed to be rigid, the bond angles (θ) of the -CH$_2$- group and the distance (dcc) between the center of the phenyl ring and the principal C_4 axis are not independent geometrical parameters. Denoting the inclination of the phenyl ring with respect to the plane perpendicular to the C_4 axis by α, the geometrical parameters dcc and θ can be described as follows:

$$\mathrm{dcc} = 2.5262 + 1.4585 \cos\alpha \tag{1}$$

$$\theta = \cos^{-1}(-0.8660\cos\alpha + 0.250\sin\alpha) \tag{2}$$

Then, the conformation of model I can be described by six geometrical parameters. As shown in Fig. 1, the parameters are the inclination (α), the dihedral angle (ϕ_H) of the hydroxyl group, the dihedral angle (ϕ_1) of the *t*-butyl group, and the dihedral angles (ϕ_2, ϕ_3, and ϕ_4) of three -CH$_3$ groups in the *t*-butyl group.

For the energetic investigation of the complex formation with toluene (model II), seven additional geometrical parameters were introduced as described in Fig. 1. The geometrical origin of both models is defined as the intersection point of the principal axis with the square plane connecting the four centers of phenyl rings, although the center of mass point may be better for representing the geometrical changes. The additional parameters are as follows: the dihedral angle (ϕ_M) of the methyl group with respect to the phenyl ring of toluene, and the angles θ_x, θ_y, and ϕ_T, which represent the orientation of the toluene relative to the coordinate system. The position of toluene with respect to the origin is described by the vector ($\boldsymbol{R}_t(T_x, T_y, T_z)$) from the origin to the alpha ring carbon in toluene. T_z and θ_y (or θ_x) are defined as the inclusion distance ($d = T_z$) and the inclusion angle of toluene into the cavity respectively.

The minimum energy conformations for model I and model II were calculated using the optimization program (VA10A) [23], and the potential energy functions are described below. Also, *ab initio* STO-3G MO calculations were performed (Table 1) with the parts of model I as shown in Fig. 2; It uses the two geometrical parameters α and ϕ_H. Using these results, the potential function for the cyclic hydrogen bond of the present system was described as a function of α and ϕ_H.

2.2. *Potential energy functions*

The following total energy (E^t) description may be suitable for the calculation of the stabilities and the minimum-energy conformations of our model systems.

$$E^t = \sum_{i=1}^{N}\left(E_i^{\mathrm{pol}} + \sum_{j>i=1}^{N}\left(E_{ij}^{\mathrm{el}} + E_{ij}^{d-r}\right)\right) + \sum_{k=1}^{4} E_k^{bd} + \sum_{l=1}^{4} E_l^{hb} \tag{3}$$

where E_{ij}^{el}, E_i^{pol}, E_{ij}^{d-r}, E_k^{bd}, and E_l^{hb} are the electrostatic energy of *i* and *j* atomic pair, the polarization energy of *i*th atom, the dispersion-repulsion energy of the *i*, *j* atomic pair, the energy of *k*th C–CH$_2$–C angle bending, and the energy of *l*th hydrogen bonding pair, respectively.

Table 1. The energies (STO-3G) of the model used for the functional representation of the hydrogen bond

α	ϕ_H	$-(E+4.021\times10^5)$	ΔE
47	10	69.612	6.994
	20	70.376	6.230
	30	69.775	6.851
52	10	70.661	5.945
	20	71.795	4.881
	30	71.650	4.956
	40	68.601	8.005
55	25	70.060	6.546
	35	68.927	7.679
57	10	75.105	1.501
	20	76.418	0.188
	30	76.606	0.000
	35	75.851	0.755
	40	74.347	2.259
	45	72.060	4.546
	50	69.078	7.528
	55	65.590	11.016
59	25	64.541	12.065
	30	64.372	12.234
	35	63.650	12.956
62	30	58.207	18.399
	40	56.370	20.236

E and ΔE are in kcal/mole, α and ϕ_H are in deg

2.2.1. Electrostatic energy. The electrostatic energy was calculated with the following formula:

$$E_{ij}^{\mathrm{el}} = q_i q_j / \varepsilon r_{ij}, \tag{4}$$

where q_i and q_j are the net atomic charges of atoms i and j, r_{ij} is the interatomic distance between atoms i and j, and the dielectric constant ε assumed to be unity. In this study, the net atomic charge was calculated as follows:

$$\sum_{i=1}^{13} q_i^{\mathrm{MO}} + \sum_{j=1}^{13} q_j^{EE} = 0 \tag{5}$$

where q_i^{MO} is the net atomic charge of ith atom in the HO-C_6H_2-CH_2 unit obtained from the MO calculations, and q_j^{EE} is the net atomic charge of jth atom in the $(CH_3)_3C$- group, which is calculated from the electronegativity equalization [24]. The hydrogen bonding pairs are not included in the calculation of E_{ij}^{el} and E_{ij}^{d-r}.

2.2.2. Dispersion repulsion energy. The dispersion and repulsion energy was calculated according to a Kitaigorodskii type potential function [25]:

$$E_{ij}^{d-r} = k_i k_j [-A/Z^6 + (1 - q_i/N_i^{\mathrm{val}})(1 - q_j/N_j^{\mathrm{val}}) C \cdot \exp(-\alpha \cdot Z)], \tag{6}$$

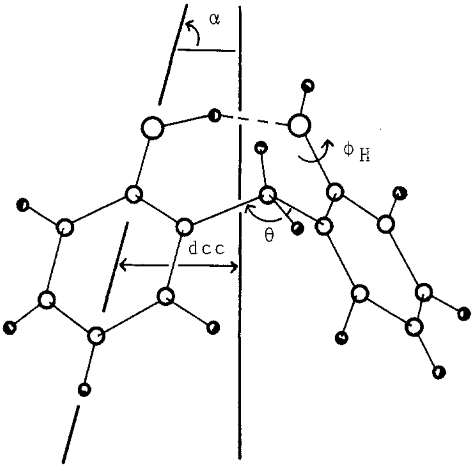

Fig. 2. The model used for the MO calculation

where

$$Z = r_{ij}/r_{ij}^0 \tag{6a}$$

$$r_{ij}^0 = ((2r_i^w)(2r_j^w))^{1/2}. \tag{6b}$$

r_i^w and r_j^w are the van der Waals radii of the atoms *i* and *j*, respectively [26]. The factors $(1 - q_i/N_i^{\mathrm{val}})$ represent the influence of the atomic electron population on the repulsion energy; N^{val} is the number of valence electrons of the neutral atom. The multiplicative factors k_i and k_j allow for the variation of the minimum value of the potential E_{ij}^{d-r} according to the nature of the interacting atoms ($k_H = k_C = 1$, $k_O = 1.36$). The parameters A, C, and α are 0.214 kcal/mole, 47 000 kcal/mole, and 12.35 respectively [27].

2.2.3. Polarization energy. The polarization energy in the electric field was obtained as a sum of atomic polarization energies:

$$E_i^{\mathrm{pol}} = -1/2\alpha_i\left(\sum_{j\neq i}^{N} \varepsilon_{ij}\right)^2, \tag{7}$$

where α_i and ε_{ij} represent the polarizability of *i*th atom, and the electric field at *i*th atomic position created by *j*th atom, respectively.

2.2.4. Bending energy. For the bending energy of the C-CH$_2$-C angle connecting the phenyl rings, a harmonic potential functions was used:

$$E_k^{bd} = 1/2K_\theta(\theta - \theta_0)^2, \tag{8}$$

where the bond angle force constant K_θ is 82.08 kcal/mole/deg.^{2}, θ_0 is 109.5° [28], and θ was calculated from Eq. (2).

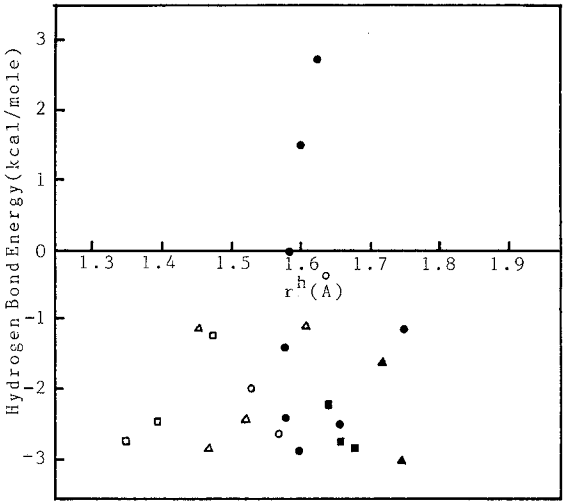

Fig. 3. The plot of hydrogen bond energies as a function of the bond length (r^h) at several αs: 47° (□), 52°(△), 55° (○), 57° (●), 59° (■), 62° (▲)

2.2.5. Hydrogen bond energy. Although many hydrogen bonding potential functions have been proposed, it is not obvious which are suitable for the description of hydrogen bonding in the calixarene system. Most of the potential functions give abnormally large hydrogen bond energies. Therefore, using the MO calculation results mentioned above, a new hydrogen bonding potential function capable of explaining the cyclic hydrogen bond of the calixarene was developed.

The hydrogen bond energy (E_l^{hb}) was defined as follows:

$$E_l^{hb} = E_{\mathrm{MO}}^{t} - E_{\mathrm{MO}}^{rs} - (E^{\mathrm{el}} + E^{\mathrm{pol}} + E^{d-r} + E^{bd}), \tag{9}$$

where the energies in parenthesis were described above, and E_{MO}^{t} and E_{MO}^{rs} are the total and the reference state energies obtained from the MO calculations on the model in Fig. 2.

The hydrogen bond energies are plotted against r^h at several α in Fig. 3. Since the hydrogen bond is strongly affected by the bond angle, the hydrogen bond energies in Fig. 3 cannot be represented as a simple function of r^h. In the present work, E_l^{hb} of the system was described as a function of r^h and α (or ϕ_H and α) only. A reduced hydrogen bond distance (r_{red}^h) was introduced as a function of r^h and α as follows (upper diagram in Fig. 4):

$$r_{\mathrm{red}}^h = r^h + 0.0261(57.0 - \alpha). \tag{10}$$

The r_{red}^h contains information about both the distance and the angle of the hydrogen bond.

In Fig. 4, the hydrogen bond energies are plotted against the r_{red}^h, and it can be seen that most of the point (hydrogen bond energies) are located on one curve. As shown in Fig. 4, the hydrogen bonding potential energy (E_l^{hb}) cannot be

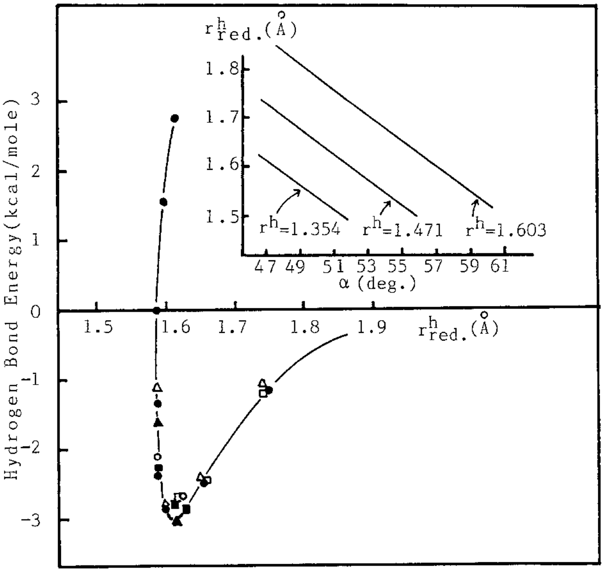

Fig. 4. The hydrogen bond energy as a function of the reduced hydrogen bond length ($r^h_{\rm red}$). Upper diagram is the plot of $r^h_{\rm red}$ as a function of α and r^h

described by a one-to-one function of the r^h_{red}, because the hydrogen atom in the hydroxyl group can locate two point equidistant from its acceptor oxygen. Therefore, a switching function(S) was introduced as follows:

$$E_l^{hb}(\Delta r) = S \cdot D_e(\exp(-2\alpha_1 \Delta r) - 2\exp(-\alpha_2 \Delta r)), \tag{11}$$

where

$$\Delta r = r^h_{\rm red} - r_e.$$

The potential parameters D_e, r_e, α_1, and α_2 were determined by a least-squares fit to Fig. 4, which resulted in the values 2.936 kcal/mole, 1.612 Å, 14.797 Å^{-1}, and 12.444 Å^{-1} respectively. The switching function S is 1 for $\phi_H < 45°$ and -1 for $\phi_H \geq 45°$.

3. Results and discussion

3.1. Conformational study of p-t-butylcalix(4)arene

The stabilization energy (E^{st}) relative to the reference state and the energies contributed to the E^{st} are depicted in Fig. 5 as a function of α; the minimum energy is obtained at each α. The stabilization energy is defined as

$$E^{st} = E^t - E^{rs} \tag{12}$$

where E^t is the total energy of model I calculated from Eq. (3), and the reference state energy (E^{rs}) is defined as

$$E^{rs} = 4\left(E^m - \sum_i \sum_{j>i} E(i,j)\right), \tag{12a}$$

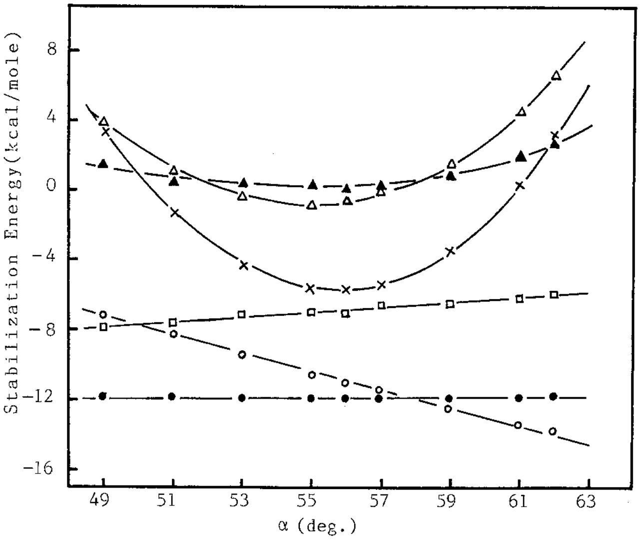

Fig. 5. Each potential energy terms contribution to the stabilization energy is plotted against α: Electrostatic (○), polarization (□, +25), dispersion (△, −50), bending (▲), hydrogen bonds (●), stabilization energy (×)

where E^m is the energy of the repeating unit, $C(CH_3)_3C_6H_2CH_2OH$, and $E(i, j)$ is the interaction energy between atomic group i and j in the same repeating unit. These atomic groups are -OH, $-CH_2$, $-C_6H_2$, and $-C(CH_3)_3$.

As shown in Fig. 5, both the C-CH_2-C bending and the dispersion energies have their minimum values near the $\alpha = 55°$, and the electrostatic and polarization energies contribute to the E^{st} in opposite ways. The hydrogen bond energy remains nearly constant, about 3 kcal per bond pair, although the dihedral angle of the -OH group (ϕ_H) varies from 24° to 34° as α is changed from 47° to 66°.

The minimum energy configurations (ϕ_H, r^h) of the cyclic hydrogen bonds are listed in Table 2 for several α. Since the linear hydrogen bond is energetically favorable, as the interatomic distance r^h increases the hydrogen bond angle (θ^h) also increases in order to form a strong hydrogen bond; therefore the reduced hydrogen bond distance does not change much, as shown in Table 2. Since the calix(4)arene can form a strong hydrogen bond over a wide range of α (from 47° to 66°), the conformation of the calix(4)arene and the activity of the binding site formed with four $-C(CH_3)_3$ are not influenced much by the hydrogen bonding near the equilibrium geometry. The vibrational frequency of O–H stretching of the calix(4)arene was reported to appear at low frequency ($3160\,cm^{-1}$) [1]. This provides strong evidence of intramolecular hydrogen bonds.

The stabilization energy of the model I has its minimum of −5.75 kcal/mol at $\alpha = 55.6°$. The other geometrical parameters ϕ_H, ϕ_1, ϕ_2, ϕ_3, and ϕ_4 are obtained as 26°, −30°, 76°, −60°, and 44° respectively. The conformation of model I is influenced largely by the repulsion between the oxygen atoms in the -OH groups,

Table 2. The hydrogen bond energies calculated at various α

α	r^h	θ^h	ϕ_H	r^h_{red}	E^{hb}
41	1.261	149.68	21.05	1.679	−8.08
43	1.295	151.87	22.45	1.661	−10.02
45	1.332	154.00	23.78	1.645	−11.14
47	1.375	155.33	24.37	1.635	−11.70
49	1.420	156.04	24.53	1.625	−11.91
51	1.468	156.90	24.94	1.624	−12.00
53	1.517	157.65	25.36	1.621	−12.00
55	1.566	158.56	25.99	1.619	−11.98
57	1.618	159.47	26.71	1.618	−11.96
59	1.669	160.84	27.84	1.616	−11.93
61	1.720	162.54	29.30	1.615	−11.89
64	1.797	166.04	32.38	1.614	−11.85
66	1.852	167.93	34.39	1.617	−11.93

E^{hb} in kcal/mole; θ^h is the hydrogen bond angle (O-H···O)

$E^{d-r}_{\text{O}\cdots\text{O}}$ is 2 kcal/mole per O···O pair at $\alpha = 56°$, and between the benzene ring carbons connected to the -CH$_2$- group, $E^{d-r}_{\text{C}\cdots\text{C}}$ is 7.53 kcal/mole per C···C pair at $\alpha = 56°$. Since the repulsive energies are sensitive to α and the first derivatives of these energies with respect to α have different signs, the α value is determined mainly by these two repulsions. The dihedral angles ϕ_1, ϕ_2, ϕ_3, and ϕ_4 maintain the values obtained for $\alpha = 55.6°$ (i.e. −30°, 76°, −60°, and 44°, respectively) as α changes from 49° to 62°. The stabilization energy is described with parabolic function of α as

$$E^{st}(\alpha) = 0.15(\alpha - 55.6)^2 - 5.75 \tag{13}$$

and the force constant for the angle α change, $(\partial^2 E^{st}/\partial\alpha^2)_{\alpha=55.6}$, was obtained as 0.30 kcal/mole/deg. Since the opening of the pore formed by the four *t*-butyl groups (binding site) does not need much energy, only 0.15 kcal/mole/deg. at the equilibrium ($\alpha = 55.6°$) this binding site has enough flexibility for complex formation with molecules having a diameter a little larger than the pore.

3.2. *Inclusion of toluene to p-t-butylcalix*(4)*arene*

The inclusion energy (E^{in}) between calix(4)arene and toluene is defined as follows:

$$E^{in} = E(\text{model I, toluene}) - (E(\text{model I}) + E(\text{toluene})). \tag{14}$$

Even though the *X*-ray diffraction study has revealed that the inclusion complex has a head-to-tail conformation, with the methyl group of a toluene being captured by the cavity, several other inclusion angles are also considered in this study. The total energy and the optimized geometrical parameters of the minimum energy conformations are obtained at several inclusion angles and are listed in Table 3. In Fig. 6, the complex formation energies (E^{in}) are plotted along the inclusion distance. In the wide range of inclusion angles, the inclusion energy

Table 3. Total energies and optimized geometrical parameters for inclusion angles

θ_y	d	α	E^t
1	2.95	55.20	−22.45
30	3.03	54.79	−22.27
45	3.33	54.44	−20.86
90	5.55	55.83	−14.59
180	4.73	55.21	−20.59

E^t is in kcal/mole, d in Å, and θ_y, α in deg.

E^{in} is about 20 kcal/mole, as shown in Fig. 6. At the same time, the tail-to-tail inclusion also forms a stable complex. Therefore in solution, both head-to-tail and tail-to-tail complexes may exist, although in the crystal only the head-to-tail complex is found; however with $\theta_y = 90°$, the inclusion is impossible. The most stable complex was obtained with $\theta_y = 0°$.

Figure 7 shows the inclusion energy plotted against the inclusion distance (d) with $\theta_y = 0°$. The most stable complex was obtained at $\alpha = 55.20°$, $T_z = 2.90$ Å, $\phi_H = 26°$, $\phi_1 = -30°$, $\phi_2 = 76°$, $\phi_3 = -60°$, $\phi_4 = 44°$, $\phi_M = 60°$, $\theta_x = 0°$, $\theta_y = 0°$, $\theta_T = 45°$, and $T_x = T_y = 0.0$ Å. At this conformation, for $T_z = 2.90$ Å, the methyl group of the toluene is completely encapsulated in the cavity, but the phenyl ring of the toluene is exposed from the cavity; the inclusion energy was calculated as −22.45 kcal/mole. Changes in the hydrogen bond energy and E(toluene) with respect to d are negligibly small. Since the dispersion interaction is predominant and the other long range interaction energies (polarization and electrostatic) are

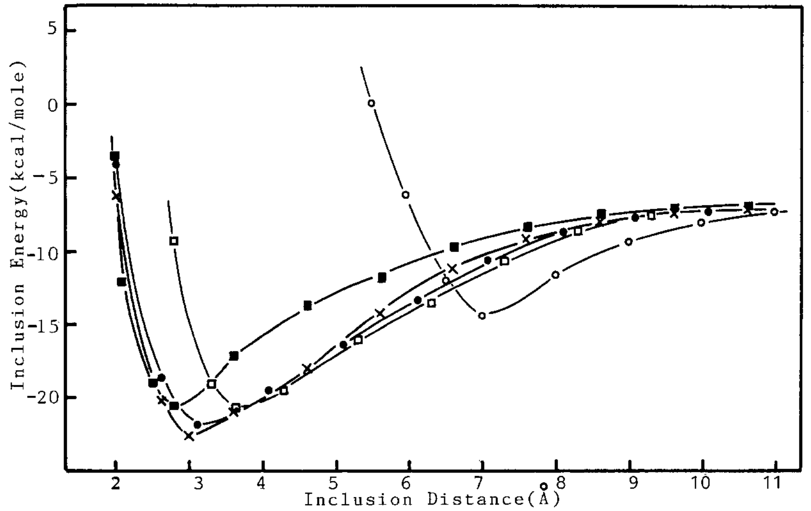

Fig. 6. The total energy is plotted against the inclusion distance at several inclusion angles: $\theta_y = 0°$ (×), 30° (●), 45° (□), 90° (○), 180° (■)

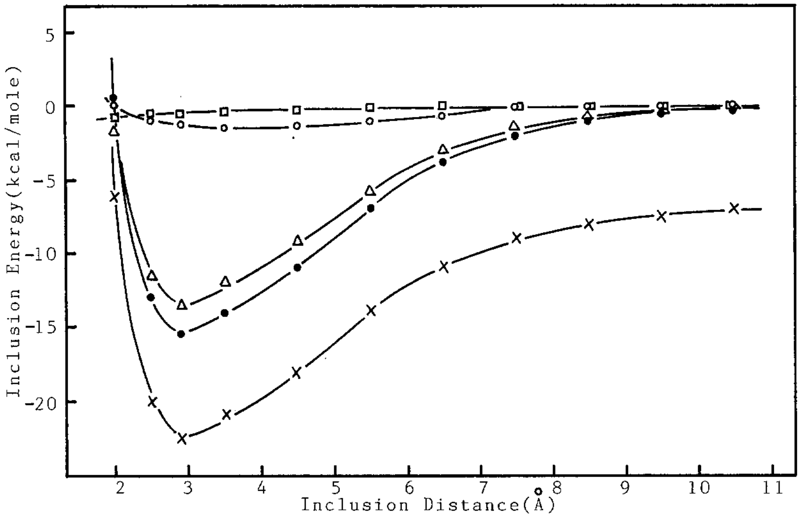

Fig. 7. Each potential terms contributions to the inclusion energy is plotted against the inclusion ($\theta_y = 0°$): Electrostatic (○), polarization (□), dispersion (△), inclusion (●), total energy (×)

relatively small, the inclusion procedure may be controlled mainly by the dispersion interaction: inclusion is mainly determined by collisions between active sites. The inclusion energy may be described with a quadratic function of d near the optimized inclusion distance,

$$E^{in}(d) = 4.02(d - 2.90)^2 - 22.45, \tag{15}$$

and hence the force constant for the changes in inclusion distance near the equilibrium position, $(\partial^2 E^t / \partial d^2)_{d=2.90}$, was found to be 8.04 kcal/mole/Å^2.

It was reported that the decapturing conditions of guest molecules are severe, such as heating for a long time at high temperature and low pressure [1], and so a high activation energy barrier might be expected for the decapturation of the toluene. As shown in Fig. 7, the decapturation of the toluene does need a large activation energy; however there is not energy barrier for the inclusion of the toluene even though the calix(4)arene undergoes a strain of 1.35 kcal/mole as α changes ±3° from the equilibrium position. This strain in the calix(4)arene is relatively small compared with the favourable dispersion interaction of calix(4)arene with the toluene.

The energy needed for the rotation of toluene in complex was obtained at several fixed inclusion distances(d) Fig. 8. Since the highest rotational barrier is only 0.6 kcal/mole, and it appears only at the optimum position, the toluene molecule can rotate almost freely during and after the inclusion.

4. Conclusions

In this work, the theoretical treatment of conformational studies of *p*-*t*-butylcalix(4)arene and its toluene complex were presented. In particular, the potential

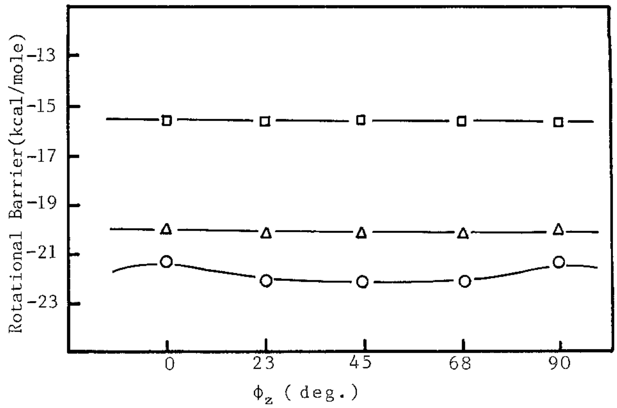

Fig. 8. The rotational energy of the toluene molecule during the complex formation is plotted against ϕ_z at several inclusion distances: 5 Å (□), 3.5 Å (△), 2.90 Å (○)

energy function suitable for the hydrogen bonding in the calix(4)arene was obtained from the MO calculations energies. As previously mentioned, during the complex formation the hydrogen bond energy does not change much near the equilibrium geometry, and therefore this hydrogen bond does not induce any significant allosteric effect at the binding site. The lowest energy structure of the model compound is in good agreement with the X-ray diffraction results. The optimized geometrical parameter of the complex α (55.20°) differs 2° from those of the X-ray diffraction analysis, but this difference may be compensated for by a crystal packing effect, since all the models used in this calculation are in free molecular states. Also, it is shown that the binding site of the calix(4)arene has an enough flexibility for complex formation with toluene, and the complex formation does not need any activation energy. Since most of the inclusion energy is contributed by the dispersion interaction, the long range interaction energies are relatively small, and the fraction of effective collision for the inclusion may depend strongly on θ_y, T_x, and T_z.

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