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Atom-atom potential analysis of the complexing characteristics of cyclodextrins (host) with benzene and *p*-dihalobenzenes (guest)

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Intermolecular interaction and modelling calculations on the complexes of α-, β- and γ-cyclodextrins (host) with benzene and *p*-dihalobenzenes (guest) were performed. The complex formation mechanism between the host and guest molecules was evaluated from three-dimensional potential maps generated by the atom-atom potential method, and the molecular packing of the complexed compounds was visualized by a space-fill representation. Stable inclusion complexes only form when both the host and guest molecules experience a significant decrease in the complexing potential. The host and guest molecules have a maximum molecular surface contact at the minimum potential, which depends on both the cavity size and the molecular volumes of the guest molecules. The calculated interaction energies can be correlated to the association constants of complex formation determined from experiment. The molecular dynamics of the guest molecules are also discussed.

INTRODUCTION

α-, β- and γ-cyclodextrins are cyclic oligosaccharides composed of six, seven and eight D-glucopyranose units linked by α(1-4) bonds. The geometries of the α-, β- and γ-cyclodextrins (hosts) give torus-shaped hydrophobic cavities which can fit a wide variety of guest molecules.[1-3] The particular feature of their inclusion behaviour is that the cyclodextrins can form inclusion complexes in solution which are preserved on crystallization. This behaviour differs from that in most other host molecules in which a suitable cavity is only present on crystallization. The non-covalent bonding between the cyclodextrins and the guest molecules elucidates the inclusion complex formation, the catalysis mechanism, and the enzymic modelling.

Crystal and molecular structures, and many other chemico-physical properties of inclusion complexes of the cyclodextrins with different guest molecules have been elucidated by many researchers using X-ray and various physical methods.[4] Theoretical calculations and molecular modelling of some of these inclusion complexes have also been performed.[5-7]

The atom-atom potential (AAP) gives a semi-empirical method to study large molecules and macromolecules. The major interactions considered in an AAP calculation are the non-bonded energy, which includes usually the dispersion and exchange energy terms; an electrostatic term can be also included to give a more flexible form to the equation used in the calculation. The potential energy is computed between identical molecules or non-identical host and guest molecules, so that it may be used to study inclusion compounds. Since zero potential energy is assumed for the guest molecule at infinity, the absolute potential energy is the energy needed to bring the guest molecule from infinity into the cavity of the host molecule. For inclusion complexes, these potential energies are defined as *complexing energies*.

The present work describes and develops the atom-atom potential (AAP) method to study inclusion complexes of the cyclodextrins with benzene and *p*-dihalobenzenes, to predict the host-guest interaction, the mechanism of complex formation, the molecular packing, and the molecular dynamics of the system.

METHODS

The calculations were performed with an AAP programme developed in our laboratory for an IBM compatible personal computer. The programme was derived from Gavezotti's OPEC programme[8] and written in Pascal language for the IBM PC utility. This programme can change the topological positions of one molecule (guest) with respect to another (host)

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Table 1 Parameters of the atom-atom (6-exp) potentials[a]

	A ($kcal\,mol^{-1}\,Å^6$)	B ($kcal\,mol^{-1}$)	C ($Å^{-1}$)
C...C	421	716000	3.68
H...H	29	49000	4.29
O...O	259.4	77700	4.18
F...F	148	42000	4.15
Cl...Cl	2980	4580	2.262
Br...Br	3628	270600	3.28
I...I	8373	372900	3.03

[a] The values of the cross terms are determined by $A_{ij} = (A_{ii}A_{jj})^{1/2}$, $B_{ij} = (B_{ii}B_{jj})^{1/2}$, $C_{ij} = (C_{ii} + C_{jj})/2$.

Table 2 The minimization results and some averaged geometrical data for the α-, β- and γ-cyclodextrins

	α-CD	β-CD	γ-CD
MMX energy (kcal/mol)	35.26	38.00	43.98
Dipole moment (deby)	6.87	6.99	6.98
Iteration	30	50	190
Torsion angle (°)			
C(1)-C(2)-C(3)-C(4)	−56.3	−56.5	−56.3
C(2)-C(3)-C(4)-C(5)	50.3	53.4	55.2
C(3)-C(4)-C(5)-O(5)	−50.7	−54.7	−57.2
C(4)-C(5)-O(5)-C(1)	−63.8	−61.5	−59.4
C(5)-O(5)-C(1)-C(2)	−63.8	−61.5	−59.4
O(5)-C(1)-C(2)-C(3)	61.3	59.0	56.7
O(5)-C(1)-O(4')-C(4')	103.0	105.2	106.2
C(2)-C(1)-O(4')-C(4')	−136.7	−133.2	−131.1
C(1)-O(4')-C(4')-C(3')	134.3	131.9	130.6
C(1)-O(4')-C(4')-C(5')	−106.6	−109.4	−111.0
Distances in macrocycle (Å)			
O(4)...O(4')	4.38	4.46	4.58
O(2)...O(3')	3.25	3.13	3.07
Angles in macrocycle (°)			
O(4)...C(1)-O(4')-C(4')	162	165	166
C(1)-O(4')-C(4')...O(4')	−166	−168	−169
O(4)...O(4')...O(4'')	119.3	127.9	134.4

in the minimization procedure, by using translations and rotations. The atom-atom potential used for the host-guest interaction is a two-centre function[9]

$$E_p = \sum_i^{host} \sum_j^{guest} E_{ij} \qquad (1)$$

where the index i runs over the atoms of the *host* molecules and j over the atoms of the *guest* molecules. E_{ij} has the (*6-exp*) Buckingham expression

$$E_{ij} = -A_{ij}r_{ij}^{-6} + B_{ij}\exp(-C_{ij}r_{ij}) \qquad (2)$$

where r_{ij} are the atom-atom intermolecular distances between the host and guest molecules; A_{ij}, B_{ij} and C_{ij} are empirical parameters depending only on the specific atoms involved in the interaction, they are given by Mirsky[10] and extended by Gavezzotti.[8] Table 1 shows the parameters used in the calculations.

The geometries of the cyclodextrins, and the guest molecules under consideration, were obtained from molecular mechanics. The energy minimization used the MMX force field.[11] Thus, one unit of glucopyranose was first constructed and minimized, and the α-, β- and γ-cyclodextrin structures were generated by rotating this unit under six-, seven- and eight-fold symmetry

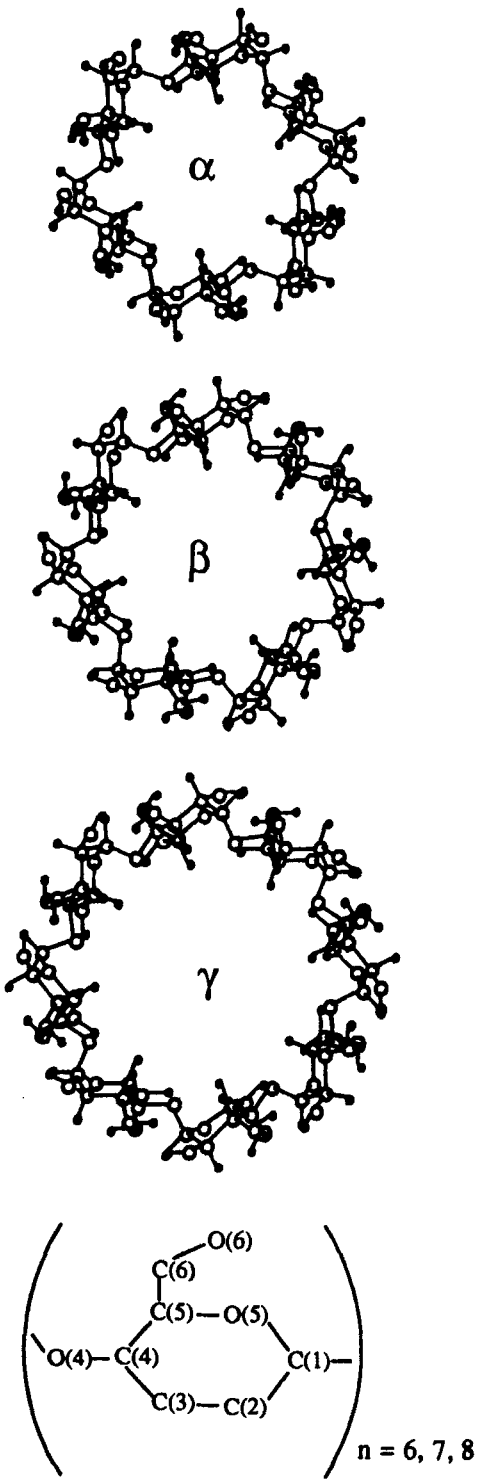

Figure 1 Computer-generated structures for α-, β- and γ-cyclodextrin.

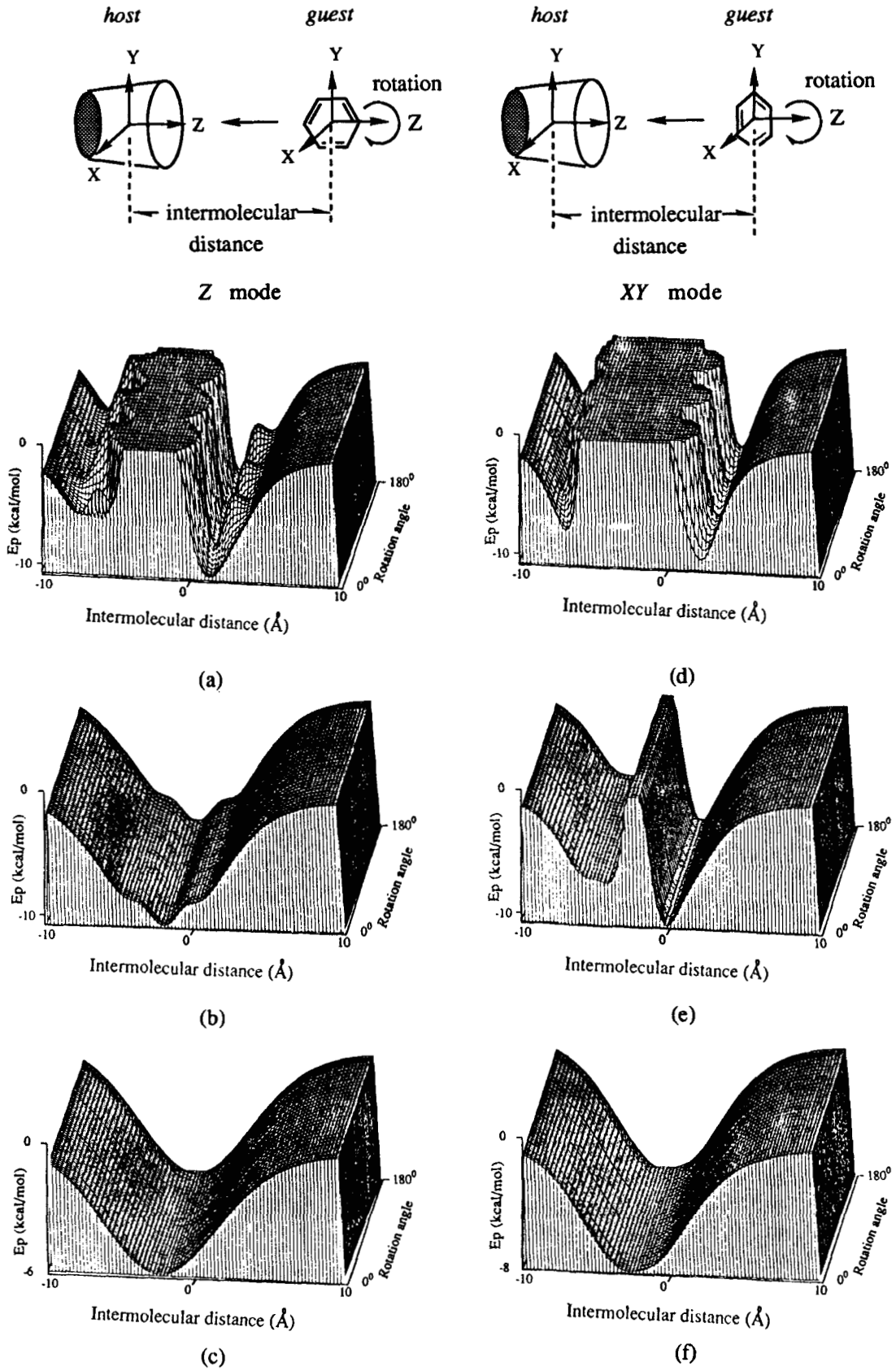

Figure 2 Potential maps for α-, β- and γ-cyclodextrin complexed with benzene. Potentials, Ep, are plotted against the intermolecular distances and rotation angles. (a) α-CD in the *Z* mode; (b) β-CD in the *Z* mode; (c) γ-CD in the *Z* mode; (d) α-CD in the *XY* mode; (e) β-CD in the *XY* mode; (f) γ-CD in the *XY* mode.

and minimized. Selected minimization results and averaged geometrical data obtained for the α-, β- and γ-cyclodextrins are given in Table 2. The geometries of benzene and *p*-dihalobenzenes were obtained using the MMX force field with the π-VESCF routines.[12]

The reduced mass centres of the cyclodextrins and of the guest molecules were chosen as the two origins of the individual coordinates for the atom-atom potential calculations. The atom-atom potential energy was thus related to the intermolecular distances between the cyclodextrins and their guest molecules. The three-dimensional maps of potential were built with potential values computed by systematically moving the guest molecule relative to the host molecules by translation (from −10 to 10 Å, step 0.2 Å) and rotation (from 0 to 180°, step 3°).

RESULTS AND DISCUSSION

Molecular structures of cyclodextrins

α-, β- and γ-cyclodextrin structures were generated using the MMX force field. The initial molecular geometry has six-, seven- and eight-fold symmetry which was little altered in the course of the energy minimization. Table 2 gives the results and some averaged geometrical data; the minimized structures are shown in Fig. 1. The molecular structures obtained for the cyclodextrins agree well with published X-ray diffraction results.[13]

The glucose unit within the α-, β- and γ-cyclodextrins is rigid, because its conformation is only slightly changed from α- to γ-cyclodextrin. The macrocyclic geometry is formed by linking six, seven and eight glucose units to give the α-, β- and γ-cyclodextrin. The shape of the cavities resembles a pail with a hole in the bottom. The O(4)...O(4′) distance and O(4)...O(4′)...O(4″) angle define the diameter of the cavity, while the O(4)...C(1)-O(4′) and C(1)-O(4′)-C(4′)...O(4′) torsion angles define the height of the cavity. The cavity volumes in α-, β- and γ-cyclodextrin are 147, 226 and 368 Å^3.

Molecular complexing mode

A guest molecule can take any molecular orientation in approaching a host cavity of cyclodextrin to form an inclusion complex. Only two modes are considered to contribute significantly to the molecular complexing of the cyclodextrins with the two-fold symmetric guest molecules: (1) the *Z* mode—the cavity axis of the cyclodextrins (*z* axis) and the symmetry axis of the guest molecules coincide; and (2) the *XY* mode—the cavity axis of the cyclodextrins is perpendicular to the benzene ring plane (*xy* plane) of the guest molecules. The inclusion complexes may be formed whenever a guest molecule approaches a host cavity from either the wider or the narrower rim in the two complexing modes. Figure 2 shows the three-dimensional potential maps of the α-, β- and γ-cyclodextrin inclusion complexes with the benzene molecule in the *Z* and *XY* modes.

For the benzene to complex with α-cyclodextrin in the *Z* mode, the benzene molecule is favoured to enter the host cavity through the wider rim because of the much lower potential. The host cavity has a potential wall so that the benzene molecule cannot penetrate completely into the cavity. The cavity shows also sub-minima of potential corresponding to the six-fold symmetry of the α-cyclodextrin molecule.

The larger cavity in the β-cyclodextrin does not show a potential wall so that it is possible for the benzene to enter the host cavity from both rims and to penetrate completely into the cavity. Near the minimum potential, the complex has small sub-minimum, therefore the benzene molecule can fit tightly within the cavity.

A further increase in cavity size in the γ-cyclodextrin

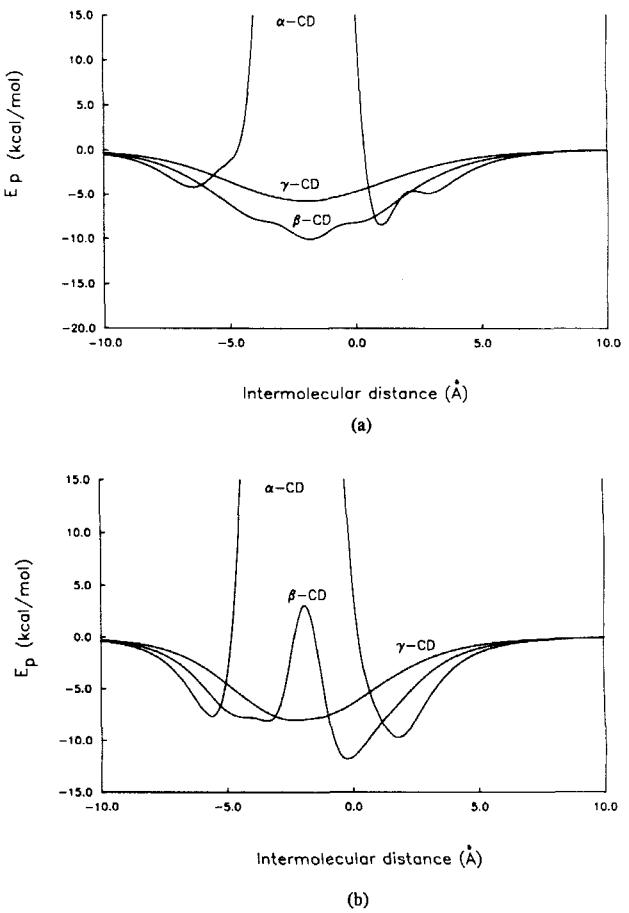

Figure 3 Comparison of the complexing energies for α-, β- and γ-cyclodextrin complexed with benzene, (a) in the *Z* mode; (b) in the *XY* mode.

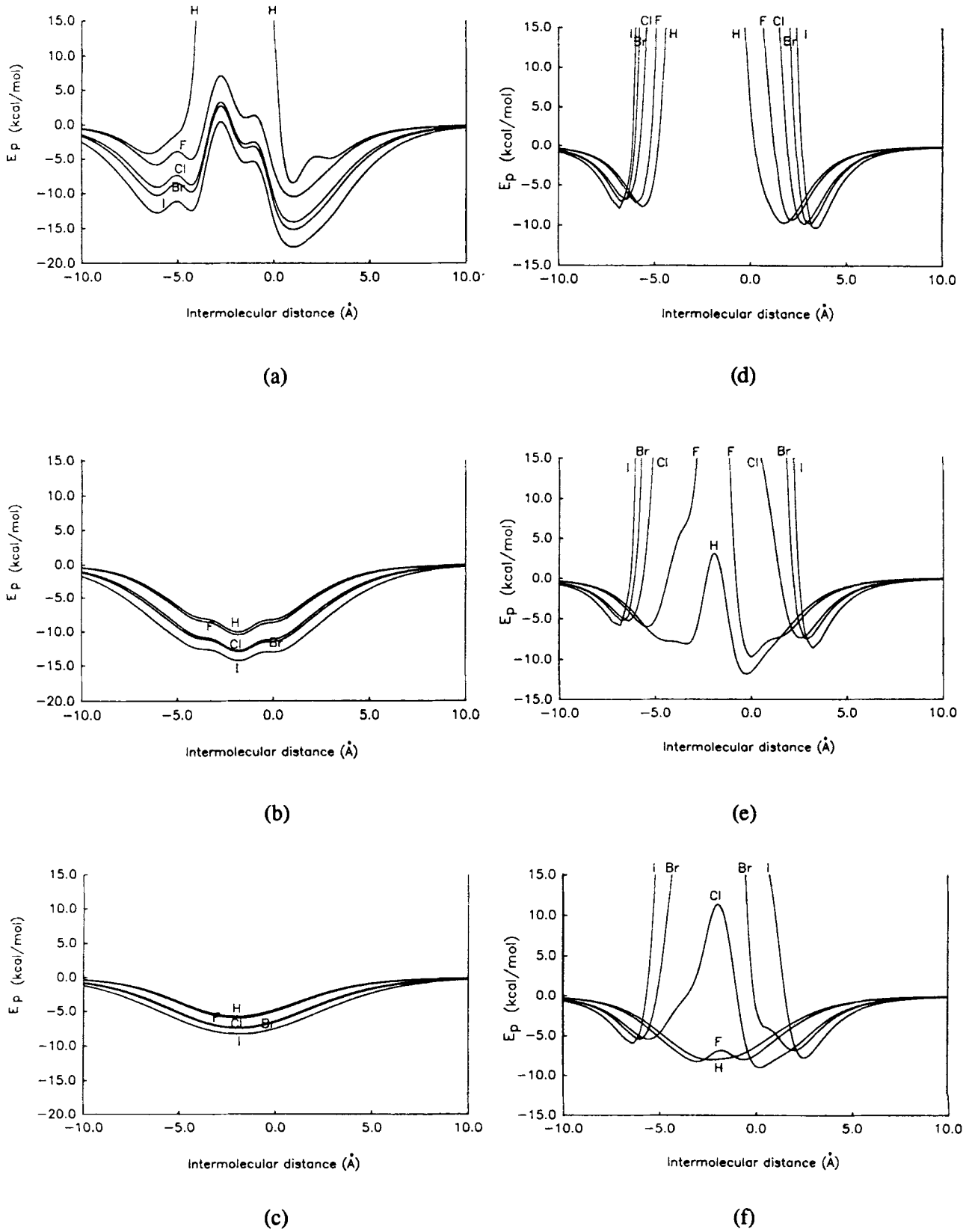

Figure 4 Plots of complexing energies versus intermolecular distance for α-, β- and γ-cyclodextrin complexed with p-$C_6H_4X_2$ guest molecules (X = H, F, Cl, Br, I). (a) α-CD in the Z mode; (b) β-CD in the Z mode; (c) γ-CD in the Z mode; (d) α-CD in the XY mode; (e) β-CD in the XY mode; (f) γ-CD in the XY mode.

allows the benzene molecule to enter the cavity with freedom. The very smooth potential curve at the minimum implies that the benzene molecule may experience significant molecular motion.

Similar results are obtained for the cyclodextrin/benzene complexes in the XY mode. Thus, the cavity of the α-cyclodextrin inclusion complex has a potential wall which is thicker than that in the Z mode, so that the benzene has difficulty in entering the cavity of α-cyclodextrin in the XY mode. For β-cyclodextrin, the situation is changed, the complex has a thinner potential wall, and a stable complex can be formed when the benzene molecule enters the cavity through the wider rim. However, for the largest cavity of γ-cyclodextrin, the benzene molecule can enter the cavity from both sides because of the absence of any potential wall in the cavity, and molecular motion may occur at the minimum potential.

Figure 3 compares the potential curves of the cyclodextrins with benzene in the Z and XY modes.

Complexing stability of the inclusion complex

Hydrogen bonding, van der Waals force and hydrophobic interaction[2] are considered responsible for the host-guest interactions in the cyclodextrin inclusion complexes. These molecular interactions are usually defined as intermediate-range interactions which are difficult to calculate using ab initio methods for large-sized molecules. The problem is that the expressions for the interaction energy are too complicated to compute even using high-speed computers. Therefore, the atom-atom method with analytical functions has been introduced to overcome this problem. Since the empirical parameters in the analytical function are obtained by fitting experiment, usually at room temperature, this semi-empirical method can give reliable results on intermolecular interactions for different inclusion systems.[14-16]

Figure 3 shows that the cyclodextrin inclusion complexes with benzene in the Z and XY modes have minimum potentials in the order of β- > α- > γ-cyclodextrin. The β-cyclodextrin forms the most stable complex because the guest molecule volume is suitably accommodated by the cavity, whereas the cavity of α-cyclodextrin is slightly too small and that of γ-cyclodextrin slightly too big.

The potential energy should change with the molecular volume of the guest molecules. Figure 4 shows the potential energy curves of the cyclodextrin inclusion complexes with the different *p*-dihalobenzenes, plus that of benzene. In the Z mode, the four *p*-dihalobenzene analogues have very similar potential curves to those of the benzene molecule in all three cyclodextrins. Thus, the minimum potential gradually

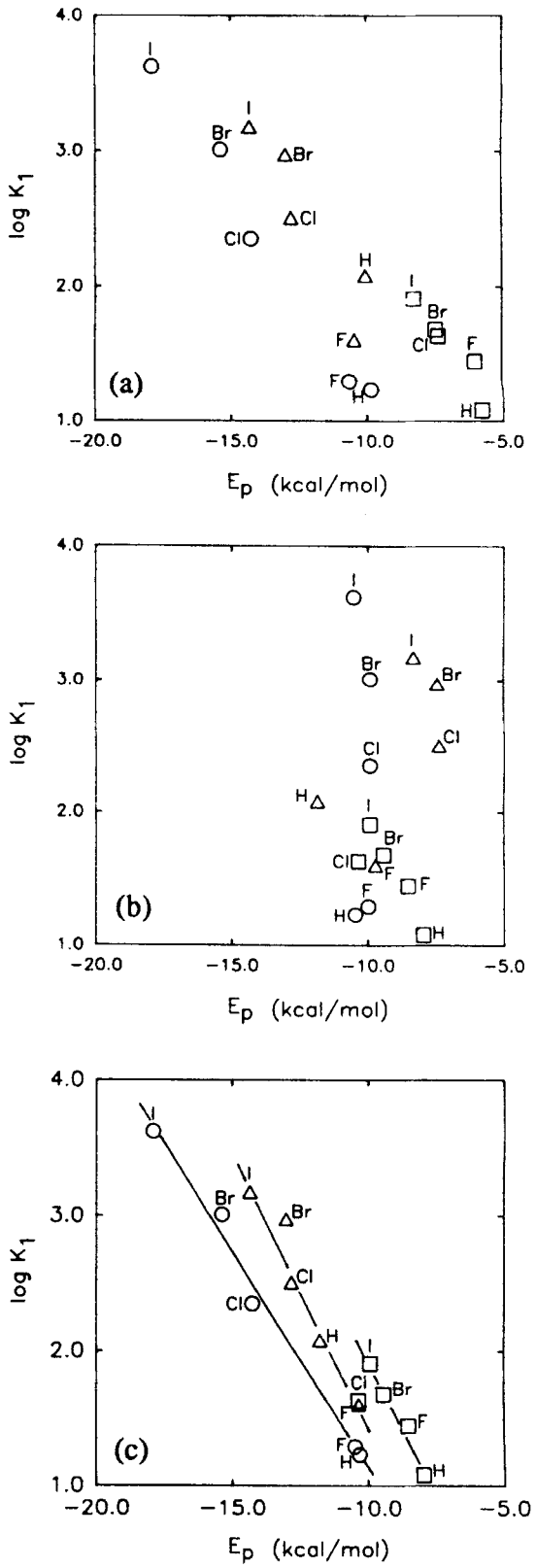

Figure 5 Dependence of the association constant on the complexing energies of α-, β- and γ-cyclodextrin (O α-CD, □ β-CD, Δ γ-CD) complexed with *p*-$C_6H_4X_2$ guest molecules (X = H, F, Cl, Br, I). (a) plots of log K_1 vs. Ep in the Z mode; (b) plots of log K_1 vs. Ep in the XY mode; (c) plots of log K_1 vs. total Ep.

Table 3 The complexing association constants K_1 (M^{-1}) and the potential energies E_p (kcal/mol) with distribution (in parentheses) of the cyclodextrin inclusion complexes

	α-CD				β-CD				γ-CD			
	E_p				E_p				E_p			
Guest	*Z*	*XY*	*total*	K_1[a]	*Z*	*XY*	*total*	K_1[a]	*Z*	*XY*	*total*	K_1[a]
Benzene	−9.859 (0.259)	−10.477 (0.741)	−10.316	17	−10.104 (0.048)	−11.876 (0.952)	−11.791	120	−5.785 (0.023)	−8.016 (0.977)	−7.966	12
p-Diflurobenzene	−10.654 (0.753)	−9.994 (0.247)	−10.491	19.6	−10.515 (0.786)	−9.744 (0.214)	−10.350	40	−6.017 (0.013)	−8.568 (0.987)	−8.534	28
p-Dichlorobenzene	−14.280 (0.999)	−9.927 (0.001)	−14.277	225	−12.835 (1.000)	−7.384 (0.000)	−12.834	320	−7.383 (0.006)	−10.379 (0.994)	−10.360	43
p-Dibromobenzene	−15.390 (1.000)	−9.920 (0.000)	−15.390	1020	−13.031 (1.000)	−7.459 (0.000)	−13.031	940	−7.481 (0.032)	−9.501 (0.968)	−9.436	48
p-Diiodobenzene	−17.917 (1.000)	−10.524 (0.000)	−17.917	4200	−14.359 (1.000)	−8.334 (0.000)	−14.359	1500	−8.290 (0.051)	−10.022 (0.949)	−9.933	81

[a] Values measured by Sanemasa *et al.*[17] and Takuma *et al.*[18]

decreases while the molecular volume of the guest molecules gradually increases from benzene to *p*-diiodobenzene, and the minimum potentials occur at almost the same intermolecular distance from one guest molecule to another. Consequently, for a given host molecule of the cyclodextrins, the complexing models do not depend on the guest molecule volume when the symmetry axes of the guest molecules and the cavity axis coincide. However, an increase in the *para*-substituted group size enables the inclusion complex to undergo a larger host-guest contact of the molecular surfaces which decreases the minimum potential, and the inclusion complex is stabilized.

The situation is quite different when the guest molecules form inclusion complexes with the cyclodextrins in the *XY* mode. Figure 4(d) shows that the potentials of the guest molecules in the cavity of α-cyclodextrin have barely changed at the minimum, but the positions of minima are affected by the guest molecule volume. Thus, as the two *para*-substituted halobenzene groups become larger, the guest molecule moves slightly away from the host cavity because a molecular steric effect.

The same results are also shown in Fig. 4(e)–(f) for the guest molecules in β- and γ-cyclodextrin.

The resulting potential energies of the inclusion complexes can be correlated to the experimental data, the complexing association constants, K_1, measured at room temperature by T. Takuma *et al.*[17,18]

The plots of $\log K_1$ vs. the minimum potentials of the cyclodextrin inclusion complexes in the *Z* and *XY* modes are shown in Fig. 5(a)–(b), and the values are listed in Table 3. The linear relation between $\log K_1$ and E_p is very poor for all three cyclodextrins in each mode. It is clear that in the real inclusion complexing situation the guest molecule can take any molecular orientations to approach the host cavity, so that the complexing potential should be summed over all possible modes

$$E_p(\min) = \sum_i^N n_i E_i(\min) \qquad (3)$$

$E_i(\min)$ is minimal potential energy of *i* mode, n_i is the contribution of *i* mode to the total potential $E_p(\min)$, which may be determined by Boltzmann's expression.

The total number of modes *N* may be large when the complexing modes are obtained by rotating the guest molecule relative to the host molecules with a small angle; since most of them have the same potential profiles, the summation in equation (3) may become trivial. In fact, only distinct complexing modes contribute to E_p, and similar modes are considered to have the same complexing energy. For the inclusion complexes under consideration, only two modes e.g. the *Z* and *XY* modes contribute the total potential energy. Table 3 gives the contribution of the *Z* and *XY* modes and the total potential energy for the α-, β- and γ-cyclodextrin inclusion complexes. It can be seen from Fig. 5(c) that a much better linear relationship holds for these inclusion complexes using equation (3) except for *p*-dibromobenzene in the α- and β-cyclodextrin and *p*-dichlorobenzene in the γ-cyclodextrin.

M. Sakurai *et al.*[19] suggested that dipole-dipole interaction is a major factor in stabilizing the inclusion complex of the cyclodextrins. This idea is unlikely because the dipole moments of α-, β- and γ-cyclodextrin are nearly the same (Table 2) whereas the association constants and complexing potential energies are significantly changed for a given guest molecule in going from α- to γ-cyclodextrin. The van der Waals force plays the major role in the formation of the inclusion complexes. Consequently, the guest

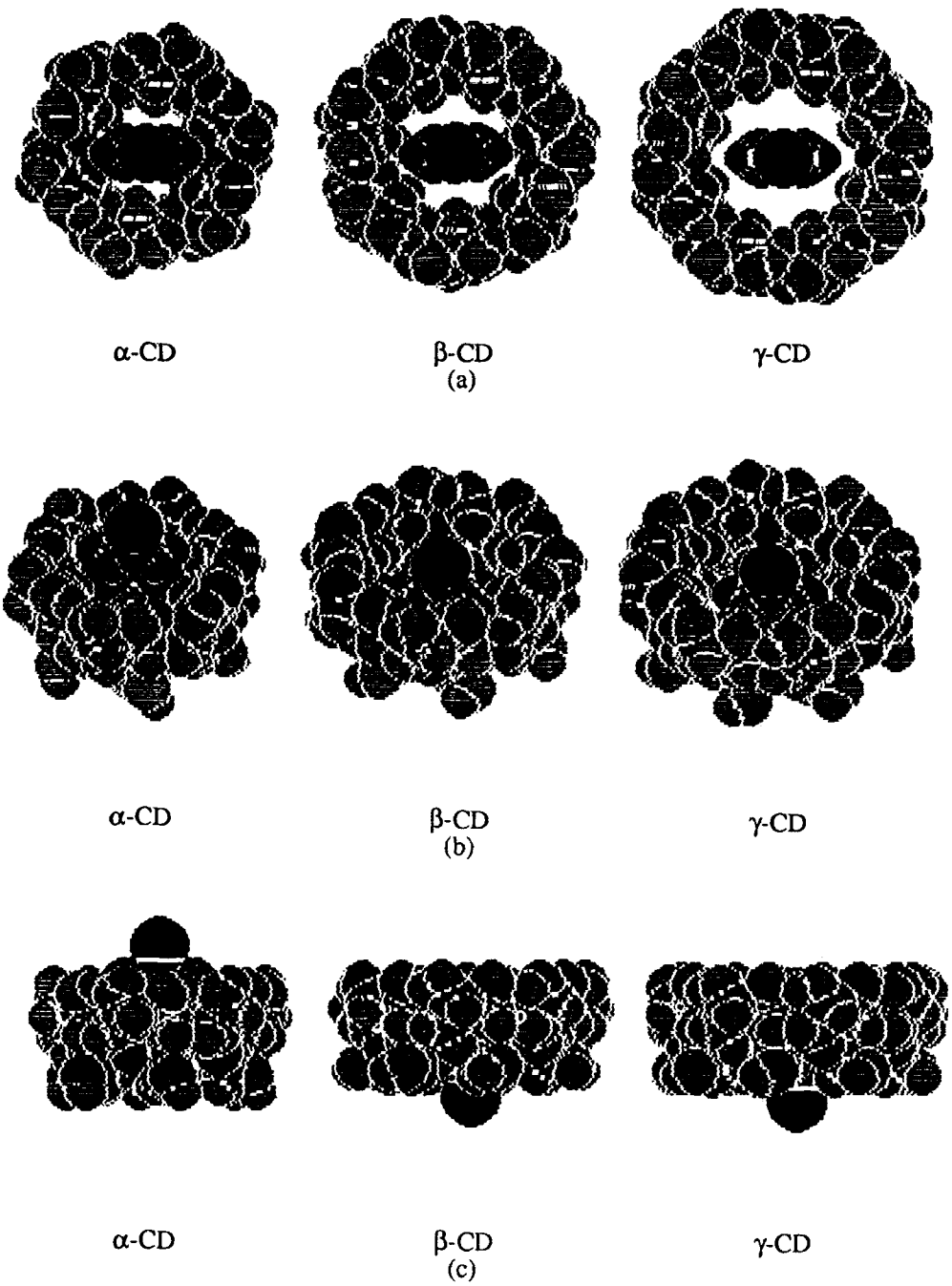

Figure 6 Computer-generated CPK models of the calculated minimum energy packing for *p*-dichlorobenzene in the cavities of α-, β- and γ-cyclodextrin. The *p*-dichlorobenzene unit is shown in solid and the cyclodextrins in shaded. (a) view of the *z* axis in the *Z* mode; b) view of rotating the complex around the *x* axis by 45° in the *Z* mode; (c) view of the *y* axis in the *Z* mode.

molecule tends to enter the host cavity in such a way as to have maximum host-guest molecular contact which increases the net complex stabilization. The host-guest interactions can be thus described by the *close-packing principle.*[9]

Molecular packing of inclusion complex

The molecular packing of the inclusion complexes can be determined by three-dimensional potential maps. The inclusion complex at the minimum potential in the *Z* and *XY* modes are visualized in the space-fill representation using van der Waals radii. Figure 6 shows an example of molecular packing pictures of *p*-dichlorobenzene in α-, β- and γ-cyclodextrin complexes.

In the *Z* mode, the guest molecule has maximum host-guest contact with the cavity of β-cyclodextrin. Whereas the cavity of α-cyclodextrin is relatively smaller so that the guest molecule is only partially

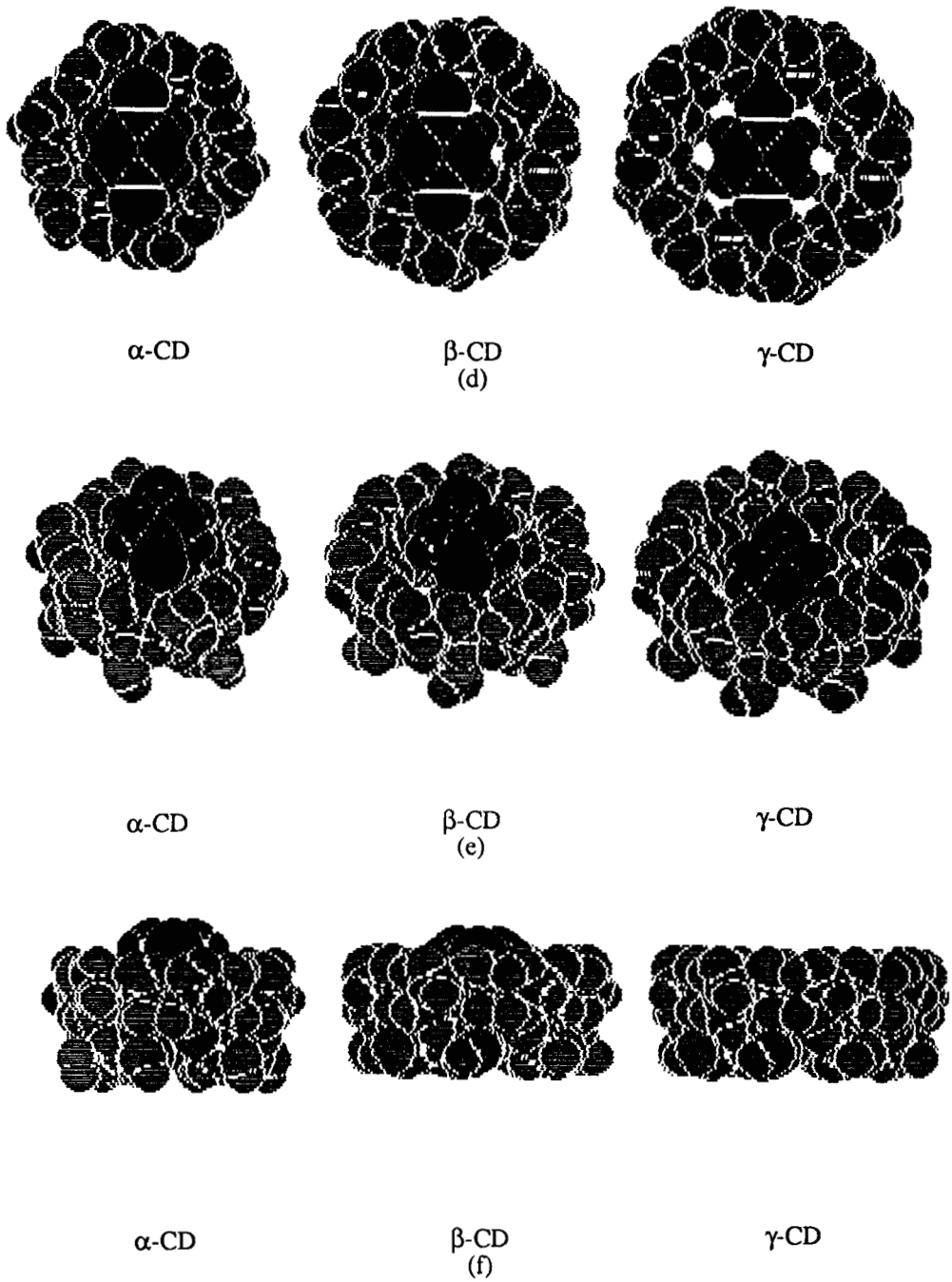

Figure 6 *continued.* (d) view of the z axis in the XY mode; (e) view of rotating the complex around the x axis by 45° in the XY mode; (f) view of the y axis in the XY mode.

accommodated in the cavity, the cavity of γ-cyclodextrin is too big to hold the guest molecule tightly because the guest molecules may pass right through the cavity.

For complexing in the XY mode, the guest molecule cannot be accommodated in the cavities of α- and β-cyclodextrin because of the steric effect of the two substituted chlorine atoms. Thus, the guest molecule can be only stacked on the wider rim of the host cavities. However, the cavity of γ-cyclodextrin is big enough to hold the guest molecule in the XY mode in a stable condition.

It is clear that the molecular models depend on both the volumes of the host cavity and the guest molecule. The stable inclusion complexes can only form when a low potential energy is obtained by high host-guest interaction.

Molecular motion in the cavity

When guest molecules are undergoing molecular motion in the host cavities, i.e. translation, rotation, vibration and libration, their atomic coordinates are changed relative to the atomic coordinates of the host cavity, and the atom-atom potential method can evaluate the guest molecule motion in the cavities of the cyclodextrins.

Translation. Figure 4 shows that the guest molecules under consideration have no significant translation in the cavity of α-cyclodextrin in the *Z* mode because they are constrained within the minimum by the steep potential. As the host cavity becomes bigger, an increase in molecular translation motion is observed. These guest molecules may escape from the large host cavity of γ-cyclodextrin, and this is why the guest molecules benzene and *p*-dihalobenzenes form less stable inclusion complexes with γ-cyclodextrin.[17,18]

Rotation. Figures 7–9 show the potential energy curves for the guest molecules rotating around the *X*, *Y* and *Z* axes of the moment of inertia in the cavities of α-, β- and γ-cyclodextrin. For α-cyclodextrin which has the smallest cavity, only rotation around the *Z*-axis (*C*-*X* bond) is significant because rotation is along the axis containing the halogen atoms. The potential barriers to rotation are 1.2 kcal/mol for all the guest molecules, which seem small enough for these molecules to rotate in the cavity. The rotations around the *X* and *Y* axes give dramatically increased barrier energies with the guest molecule volume, and the molecular motions are usually restricted to the librational mode. Thus, the benzene can freely rotate about the *X* axis but has hindered rotation around the *Y* axis with a barrier of about 11.5 kcal/mol. The potential energy curves increase rapidly and become more steep when the guest molecule size volume increases from *p*-difluorobenzene to *p*-diiodobenzene.

For the intermediate volume of cavity in β-cyclodextrin, there are no potential barriers to rotation around the *Z* axis, so that all guest molecules can rotate freely. The potential energy curves are also modified for the rotations around the *X* and *Y* axes. Thus, not only the benzene but the slightly bigger molecule of *p*-difluorobenzene can also rotate freely in the cavity; even the biggest guest molecule, *p*-diiodobenzene, has an increased degree of librational motion because of its more open potential energy curves.

For the largest cavity in γ-cyclodextrin, there are no energy barriers for any guest molecule rotating around the *X*, *Y* and *Z* axes, so that the guest molecules have complete freedom of rotation.

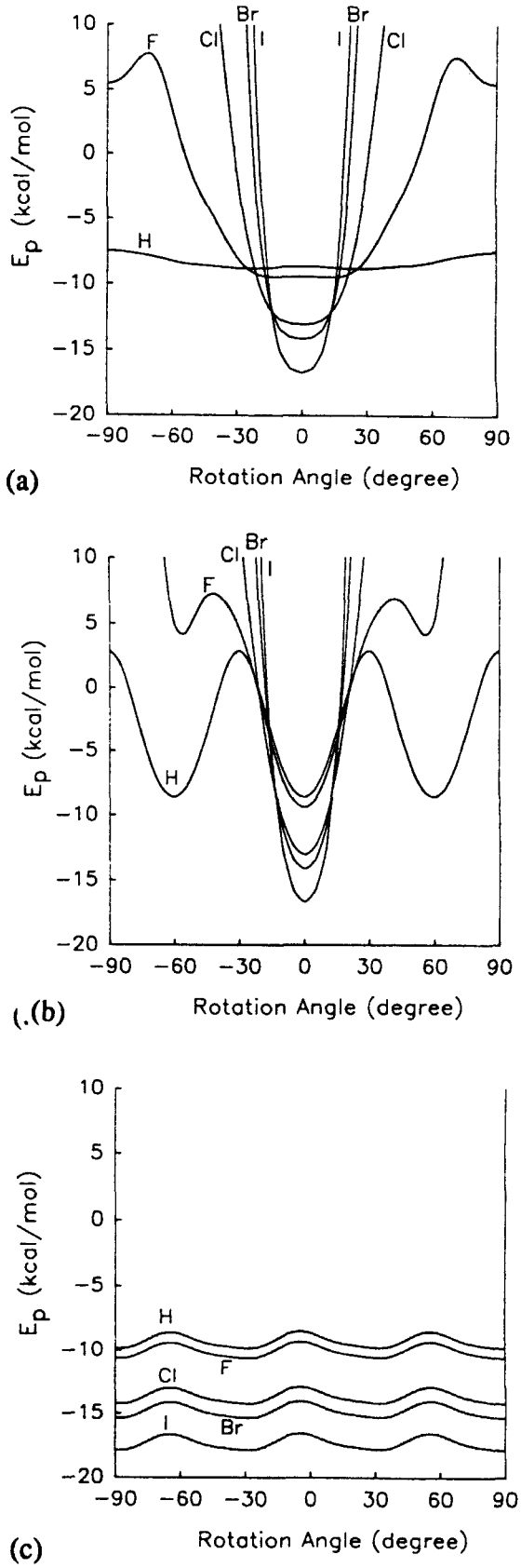

Figure 7 Plots of the complexing energies of α-cyclodextrin complexed with p-$C_6H_4X_2$ guest molecules (X = H, F, Cl, Br, I) versus the angle of rotation around (a) the *x* axis; (b) the *y* axis; (c) the *z* axis.

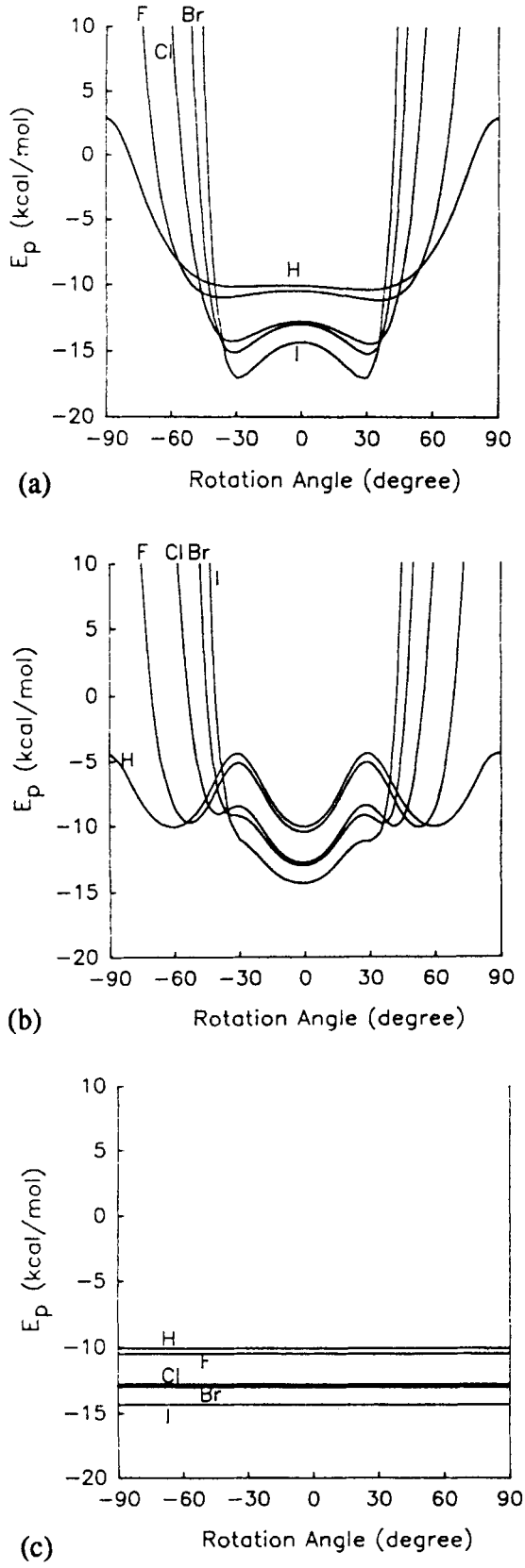

Figure 8 Plots of the complexing energies of β-cyclodextrin complexed with p-$C_6H_4X_2$ guest molecules (X = H, F, Cl, Br, I) versus the angle of rotation around (a) the x axis; (b) the y axis; (c) the z axis.

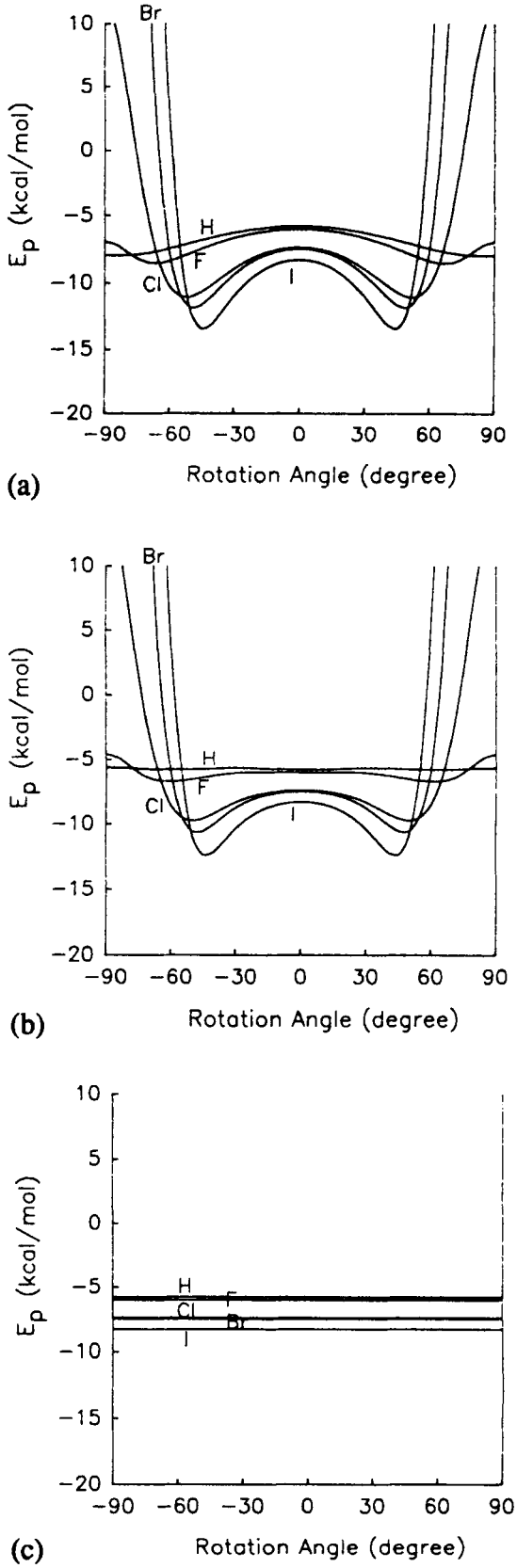

Figure 9 Plots of the complexing energies of γ-cyclodextrin complexed with p-$C_6H_4X_2$ guest molecules (X = H, F, Cl, Br, I) versus the angle of rotation around (a) the x axis; (b) the y axis; (c) the z axis.

CONCLUSION

The atom-atom potential calculations give a reliable semi-empirical method to investigate intermolecular interactions for inclusion complexes of the cyclodextrins at small cost in time and computer. Van der Waals forces are the major factor responsible in stabilizing the inclusion complexes. A minimum potential is achieved when the complexes have a large host-guest contact surface area, which depends on both the volumes of the cavities and the guest molecules. The resulting energies agree well with the experimental data for association constants. The molecular motions of the guest molecules increase with the host cavity volumes.

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