A Molecular Orbital Study of Cyclodextrin Inclusion Complexes. I. The Calculation of the Dipole Moments of α-Cyclodextrin-Aromatic Guest Complexes

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The dipole moments of α-cyclodextrin(α-CD)-aromatic guest systems have been calculated by means of the CNDO/2 molecular orbital (MO) method in order to investigate the role of electrostatic interaction in the stabilization of the inclusion complexes. It is found that α-CD has a remarkably large dipole moment which amounts to 13.5 D and is directed from its secondary hydroxyl side (the wider rim) towards the primary hydroxyl side (the narrower rim). The dipole moments of the guests, benzene derivatives, run antiparallel to that of α-CD in the complexed state. The MO total energy of the α-CD-guest supermolecular complexes shows that these antiparallel-orientations are energitically more favorable than the reversed one. It is concluded that the electrostatic interaction, mainly dipole-dipole interaction, between the α-CD and the guest molecules plays an essential role in determining the guest orientation. On the basis of these results, it is deduced that during complexation the CD molecule undergoes appreciable amount of conformational change, suggesting that the "induced-fit" mechanism is operating when the guest molecule is admitted into the host cavity.

Cyclodextrin (cycloamylose, CD) is a cyclic oligosaccharide composed of at least six α-1,4-linked D-glucose residues. CD has an intramolecular cavity and forms inclusion complexes with a variety of guest molecules. Much attention has been paid to this property of CD, since CD catalyzes various organic reactions via the formation of host-guest complexes in a way similar to that of enzymes. The mechanism of complex formation must be elucidated for a better understanding of the catalytic behavior of CD. A variety of physicochemical models for CD-guest interactions has been proposed.[1-4] Usually, the driving forces for complexation are attributed to the following interactions: van der Waals interaction,[5-9] hydrogen bonding,[10,11] hydrophobic interaction,[12] release of high-energy cavity water,[13,14] release of macrocyclic ring strain,[15,16] and effects of solvent-surface tension.[17] In spite of much effort, there is no general agreement as to the main force stabilizing the inclusion complexes at present.

From the standpoint of intermolecular interaction theory,[18] long-range types of interaction, especially electrostatic interaction, should be primarily important for stabilizing such non-covalent types of molecular complexes. However, there have been no explicit studies on electrostatic properties of CD, e.g., its dipole moment or electronic distribution. Recently, the importance of the dipole-dipole interaction between CD and guest molecules has been pointed out on the basis of NMR measurements of α-CD-aromatic guest complexes.[19,20] Therefore it is of mechanistic interest to study more extensively and directly the CD-guest inclusion phenomena. Quantum-chemical approaches may be suitable for this purpose. We have already confirmed that the CNDO calculation provides valuable information on the geometry of CD-guest complexes.[21,22]

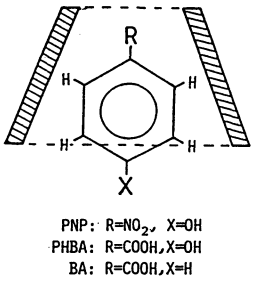
In this paper we calculate the dipole moments of α-CD (composed of six glucose units) and some guest molecules in their complexed states using the CNDO/2 molecular orbital (MO) method. Here *p*-nitrophenol (PNP), *p*-hydroxybenzoic acid (PHBA), benzoic acid (BA), and water are selected as guest molecules because the α-CD inclusion complexes with them have been extensively studied in both solution and crystal.[19-26] On the basis of the calculated results, we discuss the role of dipole-dipole interaction, the leading term of electrostatic interaction, in stabilizing the inclusion complexes. It is suggested that α-CD has a large dipole moment and the dipole-dipole interaction plays a key role in determining the guest-orientation in each complex. Finally, the mechanism of the inclusion process is discussed. The preliminary results have been already reported.[27]

Methods

The dipole moments of the host and guest molecules were calculated using the CNDO/2 method.[28] Each molecular geometry was derived from the X-ray data for the corresponding inclusion complexes: α-CD-water,[25] α-CD-PNP,[26] and α-CD-PHBA.[26] Figure 1 schematically shows the geometries of α-CD-PNP and α-CD-PHBA complexes determined by the X-ray method. The dipole moments of the host α-CD and guest molecules were calculated separately. The three geometries of α-CD derived from these X-ray data are different from each other. The standard geometrical values by Pople and Beveridge[28] were used for BA molecule because of the lack of the crystalline data by X-ray diffraction.

For the α-CD-PNP complex, the dipole moments of the six glucose residues constructing the α-CD molecule were also estimated separately. Here, the C1 and C4 positions of each glucose residue were terminated by the substitution of hydroxyl groups and the geometry of the residual part remains to be identical with that of the X-ray data.

The MO total energies of the α-CD-PNP and -PHBA supermolecuar complexes were obtained for two modes of



PNP: R=NO_2, X=OH
PHBA: R=COOH, X=OH
BA: R=COOH, X=H

Fig. 1. Schematic representation of the inclusion complex between α-CD and some benzene derivatives. The α-CD has a bucket-like cavity; the diameter on the wider-rim side is 8.8 Å and that on the narrower-rim side is 5.6 Å. Due to the bulkiness of the substituents, the orientational freedom of the guest molecule in the cavity is restrained. Usually, two modes of orientations are descriminated according to which substituent is inserted into the cavity. Here the experimentally determined-orientation is shown for each α-CD–guest complex.

guest-orientations (see Fig. 1): i) the nitro or carboxyl group is included in the α-CD cavity, and ii) the phenolic hydroxyl group is in the α-CD cavity. The former corresponds to the X-ray structure. The geometry of the latter was determined on the assumption that the position of the benzene ring relative to the CD-cavity is kept constant against the inversion of the guest-orientation.

Results and Discussion

Dipole Moment of Host and Guest Molecules. The values of dipole moments for the host molecules are shown in Table 1, together with those for the guest molecules. It is apparent that the host α-CD in all the complexes has a remarkably large dipole moment. The direction of the α-CD dipole moment in each complex runs from the side of the secondary hydroxyl groups to the side of the primary hydroxyl groups of α-CD, although it is not exactly parallel to the apparent cavity axis of α-CD.

It has been confirmed that for a variety of small molecules the values of dipole moments based on the CNDO/2 method are in fairly good agreement with the observed data.[1] However, the dipole momens of the α-CDs are too large in comparison with those of ordinary standard molecules. Thus in order to support the above finding, we again attempted to calculate the dipole moment of the α-CDs by means of the MM2 molecular mechanics method.[29] In this method molecular dipole moments are estimated as the sum of bond dipoles, and the accuracy of the computation would not appreciably depend on the size of molecules. As a result the dipole moment of α-CD in the α-CD–PNP complex is evaluated to be 12.4 D,[30] which is sufficiently close to the CNDO-value (13.5 D).

Moreover, the dipole moments of the glucose residues constructing α-CD were calculated in order to investigate the origin of the large dipole moment of α-CD. For the α-CD–PNP complex, the respective glucose units have diverse values of the dipole moments from 1.8 to 5.1 D, as shown in Table 2. According to the X-ray data for this complex,[26] there are some conformational diffrences among these six residues, which should be responsible for the diversity of the dipole moments. Here we could not find explicit correlations between structural parameters and the magnitudes of dipole moments obtained. The dipole moment averaged over all the residues amounts to 3.4 D. The sum of the contributions from all the residues is not less than the apparent dipole moment of the parent molecule. Therefore it is reasonable that the α-CD molecule has the large dipole moment as shown in Table 1.[31]

Table 1. The Dipole Moments of the Host α-CD and the Guests in Their Inclusion Complexes

Guest	Magnitude/D		Direction[a]/degree			
	host	guest	θ	ϕ	ψ	ω
PNP	13.5	5.0	31	19	22	152
PHBA	10.7	2.3	32	41	9	116
BA[b]	—	1.5	—	44	—	—
$(H_2O)_2$	9.5	1.1	80	—	—	138

a) The definitions of θ, ϕ, and ψ are given in Fig. 2. ω indicates the angle between the dipole moment vectors of the host and the guest. Its value was derived from θ, ϕ, and ψ. b) X-Ray data are unavailable.

Table 2. The Dipole Moments of Glucose Residues of α-CD

Glucose No.[a]	Dipole moment/D
1	1.8
2	5.1
3	4.4
4	4.1
5	2.3
6	2.6

a) Each No. of glucose units corresponds to that found in Ref. 13.

The angle ω between the two dipole moment vectors of the host and the guest was derived from the three tilting angles θ, ϕ, and ψ described in Fig. 2. The results (the last column of Table 1) show that in the complexed state the dipole moment of the guest is nearly antiparallel to that of the hosts. The guest orientations in these complexes are schematically shown in Fig. 1. It has been found that the orientations of the guests in aqueous solution[8,15,16] are the same as those in the crystalline state for the α-CD–PNP and the α-CD–PHBA complexes.

For the α-CD–BA complex, it is difficult to estimate the angle ω, since its crystalline structure has not been published. It has been found that the carboxyl-side of BA is located in the α-CD cavity in solution,[17] as also shown in Fig. 1. The calculated dipole moment of BA runs from the carboxyl group to its para position. As in the previous cases, the two dipole moments of the

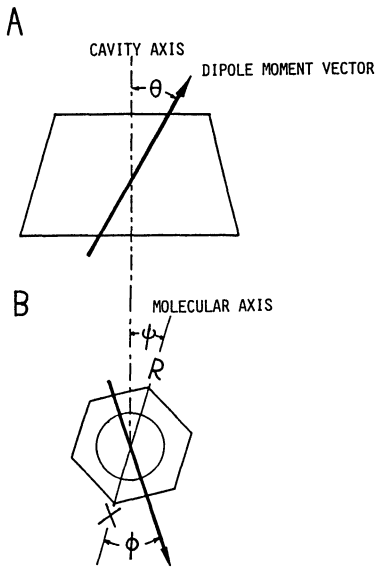


Fig. 2. Definition of the direction in the dipole moment vectors of α-CD and the guest molecules. **A.** The dipole moment of α-CD runs from the wider-rim side to the narrower-rim one. Its direction is defined as the tilting angle θ against the cavity (pseudo-six fold) axis. The angle θ varies dramatically and depends on the type of guest molecule included with concomitant variations in the magnitude of dipole moment. This suggests the conformational change in the macrocyclic ring. **B.** The direction in the dipole moment of the guest molecule is defined as the tilting angle ϕ against its molecular axis. In the crystalline state, the axis is tilted by $\psi°$ against the cavity axis. The angle ψ is estimated from the X-ray data for each complex. Thus, the angle ω between the dipole moment vectors of α-CD and the guest can be derived from θ, ϕ, and ψ. In the complexed state, the dipole moment of the guest is nearly antiparallel to that of the host. The numerical values for the angles defined here are summarized in Table 1.

host and the guest again run antiparallel each other.

Therefore, the antiparallel relationship between the host- and guest-dipole moments holds for all the α-CD complexes studied here, which suggests that electrostatic interaction, chiefly dipole-dipole interaction, is a main contributor stabilizing their complex and thus determines the guest-orientation.

Total Energy of the α-CD-PNP Complex. The MO total energies of the α-CD-guest supermolecular complexes are summarized in Table 3. The total energy of the α-CD-PNP complex with experimentally determined geometry, in which the nitrophenyl group is included in the cavity, is 45 kJ mol^{-1} lower than the sum of the host's and guest's total energies, while that of the complex with the reversed guest-orientation, namely, in the case that the hydroxyphenyl group is in the cavity, is 96 kJ mol^{-1} higher than the sum. Thus, the former orientation is 141 kJ mol^{-1} more stable than the latter. That is, the complex state, in which the nitrophenyl group is included in the cavity, is more stable than the isolated state of

Table 3. The Energy Difference of α-CD-PNP and α-CD-PHBA Complexes for Two Modes of the Guest Orientation

	Energy difference[a]/kJ mol^{-1}	
	PNP	PHBA
Complex[b]	−45	−31
Complex[c]	96	−13

a) Energy difference is calculated from the equation, $E=E_{complex}-E_{host}-E_{guest}$, where $E_{complex}$, E_{host}, and E_{guest} are the total energies for the complex, the host, and the guest, respectively. b) The nitrophenyl and carboxylphenyl groups are located in the α-CD cavity for α-CD-PNP and α-CD-PHBA complexes, respectively. c) The hydroxylphenyl group is located in the cavity.

the two partners, and than the complex state for the reversed guest-orientation. Similarly, in the case of the CD-PHBA complex the experimentally-determined orientation is again more stable. These results imply that the guest-orientations are determined by the electronic interactions, including electrostatic interactions, between the host and the guest molecules.

According to the X-ray data for these complexes, the nitro or carboxyl group is located in the vicinity of the primary hydroxyl groups of CD, but is not hydrogen-bonded with them. Thus, in both cases hydrogen bonding is a less important factor for stabilizing the complexes. However, the polar groups of the guests participate in other hydrogen-bonding networks. The phenolic hydroxyl group protrudes from the CD-cavity, and forms the hydrogen bond with the oxygen atom of the neighboring CD in crystal. Similarly, this group could be hydrogen-bonded with solvent molecules in solution. The effects of such hydrogen bonds, formed with molecules other than the host, on the stabilization of the complexes may be nonnegligible. However, they are not main factors determining the guest-orientation, because for the reversed guest-orientation similar hydrogen-bonding networks in which the newly protruded groups participate are also possible.

On the basis of molecular mechanics calculation, Tabushi et al.[8] have shown that van der Waals interaction is a major contributor for stabilizing α-CD-aromatic guest complexes, and supported the idea that the specificity of substrate binding by CD is mainly related to the extent of host-guest fitting. Mastui[7] has determined the geometry of the some α-CD-guest complexes using Hill's potential,[32] which is an emprical equation evaluating van der Waals interaction. Accoding to his results for the α-CD-PNP complex, the stabilization energy due to van der Waals interaction is 52.26 kJ mol^{-1} for experimentaly determined guest-orientation, and 41.17 kJ mol^{-1} for the reverse guest-orientation. The former is comparable to the stabilization energy estimated from the MO total energy (Table 3). As shown in Table 3, the interaction energy based on the CNDO calculations dramatically

changes depending on the guest-orientation. The energy-difference (141 kJ mol^{-1}) between the two orientations is fairly large compared with that from Mastui's data (11 kJ mol^{-1}).[1] In other words, the van der Waals (dispersion) interactions are less important for determining the guest-orientation than the electronic interaction.

The Formation-Mechanism of α-CD Inclusion Complexes with Aromatic Guests. When two water molecules are included in the α-CD cavity (α-CD-water complex), the dipole moment vector of α-CD considerably deviates from the cavity axis; the θ value in Fig. 2 A is 80°. This finding reflects the fact that the macrocyclic ring of α-CD including two water molecules is highly distorted, as is indicated by Manor and Saenger.[25] On the other hand, in both the α-CD-PNP and α-CD-PHBA complexes, the macrocyclic ring shows a slightly distorted hexagon,[26] corresponding to the smaller tilting angle (θ=30°) of the dipole moment vector.

It is apparent from Table 1 that the values of dipole moment of α-CD in the α-CD-PNP and α-CD-PHBA complexes are larger than that for the α-CD-water complex. Namely, when α-CD accommodates the aromatic guest instead of the two water molecules, its dipole moment becomes larger. Here it is convenient to introduce the induced dipole moment defined as the difference in the dipole moments (magnitudes) between in the α-CD-water and in the α-CD-aromatic guest complexes. The induced dipole moments are evaluated to be 4.0 and 1.2 D for α-CD for the inclusion of PNP and PHBA, respectively. The larger the dipole moment of the guest is, the larger is the induced dipole moment of the α-CD. As described above, the guest-dependence of dipole moment should be related to the conformational changes of the host molecule. Therefore, this finding suggests that on complexation the α-CD molecule undergoes the appreciable extent of conformational changes to strengthen the dipole-dipole interaction with the guest molecules.

If a guest molecule approaches a CD cavity in solution so that its dipole moment would run antiparallel to that of the CD after complexation, the dipole-dipole interaction should produce an energy barrier for complexation and makes it rather difficult to penetrate the guest into the α-CD cavity. This difficulty could be partially removed if the α-CD molecule changes its conformation depending on its relative position to the guest molecules. As described above, the skeleton of α-CD is flexible enough to respond to the perturbation from guest molecules. Thus during the release of included waters and the subsequent inclusion of the guest, the macrocyclic ring of α-CD may take another conformation[34] giving a smaller dipole moment. It is then possible that the conformational change causes the energy barrier to be lower, and thus a guest molecule penetrates into the α-CD cavity more easily. After complexation, α-CD again changes its conformation so that it would make its dipole moment larger to form a more stable complex. The flexibility of the CD macrocycle in aqueous solution has been confirmed by the measurements of ^{13}C spin-lattice relaxation time.[35,36]

More extensive study on the electronic structure of α-CD is required to confirm the above model about the complexation process. At present stage other factors driving the complexation should not be excluded. A thermodynamic study[37] on CD-apolar guest complexation has shown the importance of hydrophobic interaction (apolar binding), which originates from the breakdown of the structural water molecules around an apolar guest. According to this report, a favorable entropy change due to hydrophobic interaction is largely responsible when a guest molecule approaches a CD-cavity from their isolated state. On the other hand, after inclusion of the guest the complex can be stabilized by other factors providing favorable enthalpy change. It is, therefore, natural to say that owing to the hydrophobicity of the aromatic ring PNP is driven into the α-CD cavity with the aid of the hydrophobic interaction. Once the guest is trapped into the α-CD cavity, the complex is predominantly stabilized in terms of the dipole-dipole interaction as is described above.

In conclusion, α-CD has a remarkably large dipole moment so that the host-guest electrostatic interaction can determine a guest orientation in the complexed state. The dipole moment of α-CD varies depending on the type of guest molecule, which reflects the conformational change of the macrocyclic ring of α-CD. On the basis of these results, we conclude that the "induced-fit" mechanism effectively operates on α-CD-guest complex formation and the conformational change of α-CD is caused by the dipole-dipole interaction between the host and the guest molecules. The CD molecule serves a highly electrically anisotropic medium to the guest molecules. The term like a "hydrophobic pocket" is insufficient to describe the character of CD-cavity. We are currently investigating whether these results are applicable to other types of guest molecules like aliphatic compounds.

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31) The feature of the electronic distribution in α-CD can be seen from its electrostatic potential maps. Recently we have found that the side of the secondary hydroxyl groups of the CD has positive potentials, while the side of the primary hydroxyl groups does negative ones. Therefore, a very large separation of charges is caused along the CD-cavity axis, resulting in the large dipole moment. This preliminary result has been already accepted for publication (M. Sakurai et al., *Chem. Lett.*, **1988**, 895).
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