

## A MOLECULAR ORBITAL STUDY OF CYCLODEXTRIN (CYCLOMALTO-OLIGOSACCHARIDE) INCLUSION COMPLEXES. III, DIPOLE MOMENTS OF CYCLODEXTRINS IN VARIOUS TYPES OF INCLUSION COMPLEX

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### ABSTRACT

Large values (10–20 D) of the dipole moments were calculated for cyclomalto-hexaose, -heptaose, and -octaose ( $\alpha$ CD,  $\beta$ CD, and  $\gamma$ CD) and also two types of methylated CD by means of the CNDO/2 MO method, using the X-ray structures of various inclusion complexes. The relative strengths of the dipole moments were  $\alpha$ CD <  $\beta$ CD <  $\gamma$ CD and TM- $\alpha$ CD <  $\alpha$ CD. These properties are explained in terms of integration of the partial dipole moment attributed to each glucosyl residue and are a typical example of the so-called “macrocyclic effects”. The dipole moment of each CD was directed from the secondary to the primary hydroxyl side. In the inclusion complexes of  $\alpha$ CD with some aromatic guest molecules, the guest-dipole moment is antiparallel to that of the host. The dipole moment of the CD strongly influences the orientation of polar guest molecules, and binding of guest molecules distorts the CD and causes large variations in its dipole moment. The overall electrical field of CDs is expressed significantly within the cavity.

### INTRODUCTION

Cyclomalto-oligosaccharides (cyclodextrins, CDs) can form non-bonded inclusion complexes with a variety of guest molecules<sup>1–7</sup>. Hence, CDs have attracted widespread interest as model compounds for studies of enzyme–substrate reactions and donor–acceptor binding, and have found industrial applications<sup>1–7</sup>. The driving forces for complexation have been attributed variously to van der Waals interactions<sup>8–12</sup>, hydrogen bonding<sup>13</sup>, hydrophobic interactions<sup>10,14</sup>, release of high-energy cavity water<sup>15,16</sup>, release of macrocyclic ring strain<sup>17,18</sup>, and effects of solvent–surface tension<sup>19,20</sup>.

The principal difficulty in identifying the main driving force concerns the in-

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trinsic properties of CDs, particularly their affinities for guest molecules ranging from completely non-polar compounds, including rare gases, to organic anions<sup>1-7</sup>. Hence, it is of interest to investigate the host-guest interactions theoretically in detail. One target of CD chemistry is the molecular design of derivatives with high guest-selectivity and catalytic ability, and the strategy for such applications should be based on an understanding of the structure-function relationships.

The CD cavity contains two rings of C-H groups and a ring of oxygen atoms and, usually, is assumed to be relatively hydrophobic<sup>1-7</sup>. Several spectroscopic properties of guest molecules change dramatically on complexation<sup>15,20,21</sup>, which parallel those in relatively apolar solvents. We have demonstrated that the shifts in the <sup>13</sup>C resonances of some aromatic guests, induced by complexation with  $\alpha$ CD, mainly arise from the lower dielectric nature (hydrophobicity) of the CD cavity<sup>22,23</sup>. However, the hydrophobicity alone cannot account fully for the affinity of CD for polar guests and their ionic forms.

Recent CNDO calculations have also shown that  $\alpha$ CD has a large dipole moment (13 D) when it is complexed with such aromatic guests as *p*-nitrophenol (PNP), *p*-hydroxybenzoic acid (PHBA), and benzoic acid (BA)<sup>24</sup>. In addition, a large electrostatic potential gradient is generated<sup>25</sup> throughout the cavity in the complex with PNP, so that it can act as a polar medium.

We now report on the CNDO-dipole moments of  $\alpha$ CD,  $\beta$ CD, and  $\gamma$ CD, and also of 2,3,6-tri-*O*-methyl- $\alpha$ CD (TM- $\alpha$ CD) and 2,6-di-*O*-methyl- $\beta$ CD (DM- $\beta$ CD). This report deals with host-guest complexes for which the X-ray structures are available.

## CALCULATIONS

The dipole moments of the host and guest molecules were obtained using the CNDO/2 MO method<sup>26</sup> because its relative simplicity allowed rapid calculation for such large molecules as CDs. The host-guest complexes studied are listed in Table I together with the references to the X-ray crystal geometries used in the calculations.

For the  $\alpha$ CD-PNP and  $\alpha$ CD-PHBA complexes, the co-ordinates of hydrogen atoms were determined from published X-ray data<sup>34</sup>. For the other complexes, the co-ordinates were determined using the option of "co-ordinate calculation" involved in the MMP2 program<sup>55</sup> for molecular mechanics calculation. It was assumed that the hydrogen atom of each hydroxyl group was located *trans* to the attached skeleton, namely, C-1-C-2-O-2-H-2, C-2-C-3-O-3-H-3, and C-5-C-6-O-6-H-6. According to the corresponding CPK molecular model, the secondary hydroxyl groups form hydrogen bonds between neighboring glucosyl residues (see Fig. 1), which is consistent with the prediction based on experimental data<sup>1</sup>. On the other hand, the OH bond vectors of the primary hydroxyl groups are approximately parallel to the axis of the cavity (see Fig. 1). The other hydrogen atoms are attached to carbon atoms on the assumption of tetrahedral configuration. The geometrical

TABLE I

CD CRYSTAL DATA USED FOR THE MO CALCULATION AND TOTAL ENERGIES

No.	Single crystal	Total energy <sup>a</sup> (10 <sup>2</sup> a.u.)	Ref. <sup>b</sup>
1	C <sub>36</sub> H <sub>60</sub> O <sub>30</sub> · 6H <sub>2</sub> O	-8.5454	27
2	C <sub>36</sub> H <sub>60</sub> O <sub>30</sub> · 6H <sub>2</sub> O	-8.5529	28
3	C <sub>36</sub> H <sub>60</sub> O <sub>30</sub> · 7.57H <sub>2</sub> O	-8.5738	29
4	C <sub>36</sub> H <sub>60</sub> O <sub>30</sub> · I <sub>2</sub> · 4H <sub>2</sub> O	-8.5652	30
5	2C <sub>36</sub> H <sub>60</sub> O <sub>30</sub> · LiI <sub>3</sub> · I <sub>2</sub> · 8H <sub>2</sub> O	-8.5698	31
6	2C <sub>36</sub> H <sub>60</sub> O <sub>30</sub> · Cd <sub>0.5</sub> · I <sub>3</sub> · 27H <sub>2</sub> O	-8.5659	31
7	C <sub>36</sub> H <sub>60</sub> O <sub>30</sub> · C <sub>3</sub> H <sub>8</sub> O · 4.8H <sub>2</sub> O	-8.5702	32
8	C <sub>36</sub> H <sub>60</sub> O <sub>30</sub> · C <sub>2</sub> H <sub>6</sub> OS · 2CH <sub>4</sub> O · 2H <sub>2</sub> O	-8.5679	33
9	C <sub>36</sub> H <sub>60</sub> O <sub>30</sub> · C <sub>3</sub> H <sub>7</sub> NO · 5H <sub>2</sub> O	-8.5679	34
10	C <sub>36</sub> H <sub>60</sub> O <sub>30</sub> · (0.48Kr · 0.78H <sub>2</sub> O) · 5H <sub>2</sub> O	-8.5676	35
11	C <sub>36</sub> H <sub>60</sub> O <sub>30</sub> · (0.74Kr · 0.28H <sub>2</sub> O) · 5H <sub>2</sub> O	-8.5581	35
12	C <sub>36</sub> H <sub>60</sub> O <sub>30</sub> · C <sub>6</sub> H <sub>5</sub> IN · 3H <sub>2</sub> O	-8.5676	36
13	C <sub>36</sub> H <sub>60</sub> O <sub>30</sub> · C <sub>6</sub> H <sub>5</sub> IN · 3H <sub>2</sub> O	-8.5692	37
14	C <sub>36</sub> H <sub>60</sub> O <sub>30</sub> · C <sub>6</sub> H <sub>5</sub> NO <sub>3</sub> · 3H <sub>2</sub> O	-8.5530	38
15	C <sub>36</sub> H <sub>60</sub> O <sub>30</sub> · 2C <sub>6</sub> H <sub>5</sub> NO <sub>3</sub> · 6H <sub>2</sub> O	-8.5645	39
16	C <sub>36</sub> H <sub>60</sub> O <sub>30</sub> · C <sub>7</sub> H <sub>6</sub> O <sub>3</sub> · 3H <sub>2</sub> O	-8.5602	38
17	C <sub>36</sub> H <sub>60</sub> O <sub>30</sub> · C <sub>6</sub> H <sub>7</sub> N <sub>2</sub> O <sub>2</sub> · 6H <sub>2</sub> O	-8.5509	40
18	C <sub>36</sub> H <sub>60</sub> O <sub>30</sub> · C <sub>7</sub> H <sub>6</sub> O · 6H <sub>2</sub> O	-8.5704	41
19	C <sub>36</sub> H <sub>60</sub> O <sub>30</sub> · C <sub>8</sub> H <sub>10</sub> O · 4H <sub>2</sub> O	-8.5705	42
20	C <sub>42</sub> H <sub>70</sub> O <sub>35</sub> · 12H <sub>2</sub> O	-9.9974	43
21	C <sub>42</sub> H <sub>70</sub> O <sub>35</sub> · 11H <sub>2</sub> O	-10.0008	44
22	C <sub>42</sub> H <sub>70</sub> O <sub>35</sub> · 11H <sub>2</sub> O	-10.0053	45
23	2C <sub>42</sub> H <sub>70</sub> O <sub>35</sub> · KI <sub>7</sub> · 9H <sub>2</sub> O	-9.9922	46
24	C <sub>42</sub> H <sub>70</sub> O <sub>35</sub> · CH <sub>4</sub> O · 6.5H <sub>2</sub> O	-9.9979	47
25	C <sub>42</sub> H <sub>70</sub> O <sub>35</sub> · 2HI · 8H <sub>2</sub> O	-9.9983	47
26	C <sub>42</sub> H <sub>70</sub> O <sub>35</sub> · C <sub>7</sub> H <sub>8</sub> O · 5H <sub>2</sub> O	-9.9965	48
27	C <sub>48</sub> H <sub>80</sub> O <sub>40</sub> · 13.3H <sub>2</sub> O	-11.4262	49
28	C <sub>54</sub> H <sub>96</sub> O <sub>30</sub> · C <sub>6</sub> H <sub>5</sub> IN · H <sub>2</sub> O	-10.1271	50
29	C <sub>54</sub> H <sub>96</sub> O <sub>30</sub> · C <sub>7</sub> H <sub>6</sub> O	-10.1264	51
30	C <sub>54</sub> H <sub>96</sub> O <sub>30</sub> · C <sub>6</sub> H <sub>5</sub> NO <sub>3</sub> · H <sub>2</sub> O	-10.1145	52
31	C <sub>56</sub> H <sub>98</sub> O <sub>35</sub> · C <sub>6</sub> H <sub>5</sub> NO <sub>3</sub> · 3H <sub>2</sub> O	-11.2113	53
32	C <sub>56</sub> H <sub>98</sub> O <sub>35</sub> · C <sub>6</sub> H <sub>5</sub> IO · 3H <sub>2</sub> O	-11.2028	54

<sup>a</sup>CNDO/2 total (electronic + nuclear) energy of the host moiety. Energies are given in atomic units.<sup>b</sup>Refs. in which the X-ray data of CD-guest complexes are described.

parameters were as follows: OH and CH bond lengths, 0.94 and 1.11 Å, respectively; COH bond angle, 106.9°.

When the experimental geometries were not given for guest molecules in the above references, the standard geometrical parameters<sup>26</sup> for bond length and bond angle were used. Due to the lack of atomic integral parameters, the CNDO-dipole moments were not obtained for such guests as iodine-containing molecules.

It was confirmed that the dipole moments from the CNDO method accorded, within 1.5D, with those based on the MM2 calculation<sup>55</sup>. Thus, the CNDO data can be supported by a completely independent method for calculation of dipole moment. Furthermore, there was no difference in the electron density on each

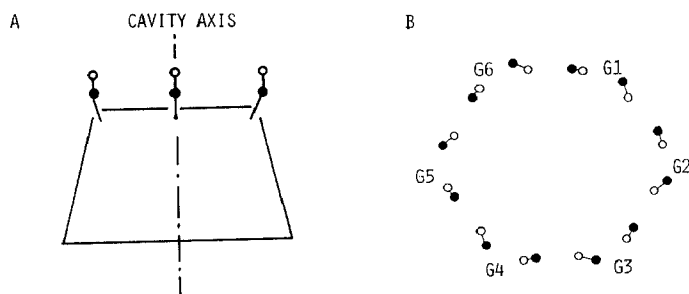


Fig. 1. Assumed orientations of the hydroxyl groups of CD (●, oxygen; ○, hydrogen): A, side view; B, view from the wider-rim side.

atom of the CD molecules on comparison with similar types of atoms of standard molecules. Thus, the geometries used do not cause undesirable distortion of the electronic distribution of the CD molecules.

There remains the possibility that the arbitrary H-addition may result in unrealistic dipole moments for relatively large molecules such as CDs. Spatially large separation of charges could result in a large dipole moment even if the magnitude of the induced charge is small. The dipole moment for the  $\alpha$ CD-2H<sub>2</sub>O complex, calculated using neutron diffraction data<sup>56</sup> in which the co-ordinates of all hydrogen atoms were given, was 2 D larger than the value based on the X-ray structure, which indicates that the method used here does not necessarily overestimate the dipole moments of CDs. There is no theoretical method that can generate systematically minimum energy structures for a wide variety of CD-guest complexes with sufficient accuracy. It may be possible to optimize the position of the hydrogen atoms by keeping the heavy-atom framework fixed in the X-ray structure. However, if such calculations are carried out for CD alone, the physical meanings of the resulting geometries are unclear. Hence, this procedure was abandoned and attention was paid mainly to the dependence of the conformation of the CD macrocycle on its dipole moment.

The average dipole moment of the six units of TM- $\alpha$ CD were calculated. In order to estimate the partial dipole moment per unit, the calculation was applied to analogues in which hydroxyl groups were present at positions 1 and 4.

## RESULTS

Table II summarizes the dipole moments calculated for the host and guest molecules. These values are probably related to the inclusion complexes rather than to the respective isolated molecules, because the geometrical parameters used were based on the X-ray structures of the complexes. There are wide variations in the magnitude and the direction of the host-dipole moments which clearly indicate the occurrence of host-guest interactions in the inclusion complexes. Also, each CD has a dipole moment (10–20 D) which is large in comparison with normal

TABLE II

DIPOLE MOMENTS OF HOST AND GUEST MOLECULES IN THE INCLUSION COMPLEXES

No.	Host	Guest	Dipole moment <sup>a</sup>			
			Host		Guest	
			Magnitude (D)	Direction (°)	Magnitude (D)	Direction (°)
1	$\alpha$ CD	2H <sub>2</sub> O	9.4	79.3	1.1	137.8
2		2H <sub>2</sub> O	7.6	36.3	—	—
3		2.57H <sub>2</sub> O	9.4	71.0	—	—
4		I <sub>2</sub>	19.4	4.4	—	—
5		I <sub>5</sub> <sup>-</sup>	20.5	2.6	—	—
6		I <sub>5</sub> <sup>-</sup>	19.3	0.0	—	—
7		1-Propanol	19.4	3.0	1.3	61.9
8		Methyl sulfoxide	19.2	48.2	—	—
9		<i>N,N</i> -Dimethylformamide	11.1	59.0	1.1	79.5
10		Krypton	19.1	2.3	—	—
11		Krypton	16.8	10.8	—	—
12		<i>p</i> -Iodoaniline	13.0	10.6	—	—
13		<i>p</i> -Iodoaniline	19.7	0.4	—	—
14		<i>p</i> -Nitrophenol <sup>b</sup>	13.5	31.6	5.0	152.0
15		<i>m</i> -Nitrophenol	14.4	0.9	6.2	145.6
16		<i>p</i> -Hydroxybenzoic acid <sup>b</sup>	10.7	31.6	2.3	115.6
17		<i>m</i> -Nitroaniline	18.1	8.8	5.5	155.4
18		Benzaldehyde	18.0	8.0	2.7	39.1
19		1-Phenylethanol	19.4	1.3	1.8	154.8
20	$\beta$ CD	6.5H <sub>2</sub> O	20.6	8.8	—	—
21		6.13H <sub>2</sub> O	14.0	51.5	—	—
22		6.64H <sub>2</sub> O	13.9	43.6	—	—
23		I <sub>7</sub> <sup>-</sup>	20.6	3.9	—	—
24		Methanol	20.4	9.0	—	—
25		I <sup>-</sup>	20.9	7.3	—	—
26	$\gamma$ CD	Benzyl alcohol	20.2	8.7	1.8	73.6
27		5.3H <sub>2</sub> O	23.0	8.0	—	—
28	TM- $\alpha$ CD	<i>p</i> -Iodoaniline	9.3	57.1	—	—
29		Benzaldehyde	5.9	70.0	3.5	92.3
30	DM- $\beta$ CD	<i>p</i> -Nitrophenol	9.5	—	5.0	153.0
31		<i>p</i> -Nitrophenol	7.1	17.5	—	—
32		<i>p</i> -Iodophenol	6.0	26.4	—	—

<sup>a</sup>Direction of dipole moment is defined in Fig. 2. <sup>b</sup>The data for dipole moments are cited from ref. 24.

organic molecules. The intrinsic dipole moment of each host could not be estimated since X-ray data for the completely "empty" state are unavailable. However, the relative values, deduced by comparing the dipole moments in the presence of the same guest molecule, were  $\alpha$ CD <  $\beta$ CD <  $\gamma$ CD and TM- $\alpha$ CD <  $\alpha$ CD.

The sum of the partial dipole moments of the six glucosyl residues in the  $\alpha$ CD-PNP complex is not less than the apparent dipole moment of the parent molecule<sup>24</sup>. This finding implies that the large dipole moments of the  $\alpha$ CD molecules are the sums of the contributions from each glucosyl residue. Thus, the

TABLE III

PARTIAL DIPOLE MOMENTS OF METHYLATED D-GLUCOSYL RESIDUES IN TM- $\alpha$ CD COMPLEXED WITH PNP

		Magnitude (D)	Direction <sup>a</sup> (°)
Glucosyl residue	1	2.6	35.5
	2	3.3	60.9
	3	3.5	87.6
	4	3.6	57.3
	5	1.9	46.4
	6	2.5	29.8
Average		2.9	—

<sup>a</sup>The angle between the dipole moment vector and the cavity axis of TM- $\alpha$ CD.

dipole moments of a series of the CD molecules are expected to become larger as the number of glucosyl residues increases, thereby explaining the first relationship described above.

The average dipole moment of each unit of TM- $\alpha$ CD, complexed with PNP, was evaluated as 2.9 D (Table III), which is smaller than that (3.4 D)<sup>24</sup> for each unit of  $\alpha$ CD. Thus, the dipole moment of the methylated  $\alpha$ CD should be smaller than that of  $\alpha$ CD, thereby explaining the second relationship described above.

In Table II, the direction of the host-dipole moment is expressed as the tilting angle  $\theta$  between the vector of the dipole moment and the axis of the cavity (see Fig. 2). As understood from the definition of  $\theta$ , if this value is sufficiently smaller than 90°, the dipole moment is directed from the secondary to the primary hydroxyl side as found for all of the hosts studied. The value of  $\theta$  should not be zero when the corresponding CD molecule has a structure that is asymmetric around the cavity axis, although, in principle, its value is not necessarily proportional to the extent of distortion of the CD macrocycle. On the other hand, if the value of  $\theta$  is nearly zero, the CD macrocycle is highly symmetrical around the axis. Some variations in  $\theta$ , especially observed in the CD-guest systems, show that the CDs undergo appreciable changes in conformation according to the shape and size of the guests. The relatively tight fitting of guests in  $\alpha$ CD, due to the smaller size of the cavity, facilitates the changes in conformation driven by van der Waals forces. The maximal tilting of the host-dipole moment occurs in the inclusion complexes with water. For the so-called form I complex ( $\alpha$ CD-2H<sub>2</sub>O), one of the six glucosyl residues is tilted as a result of the hydrogen bonding between the primary hydroxyl groups and the guest water molecules, which dramatically lowers the axial symmetry in the macrocycle<sup>27</sup>.

As shown in Fig. 3, the magnitude of the dipole moment tends to decrease with an increase of the tilting angle, although there are some deviations.  $\alpha$ CD has the smallest dipole moment when it is bound to water molecules, which reflects the lower asymmetry in the macrocycle. The co-operative effect of the six glucosyl residues is partially cancelled out by their irregular orientations.

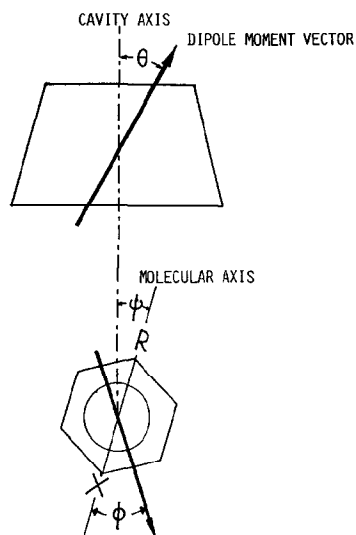


Fig. 2. Direction of the vectors of the dipole moments of CD and the guest molecules. Only the values of  $\omega$  are shown in Table II, which are derived arithmetically from  $\theta$ ,  $\psi$ , and  $\phi$ .

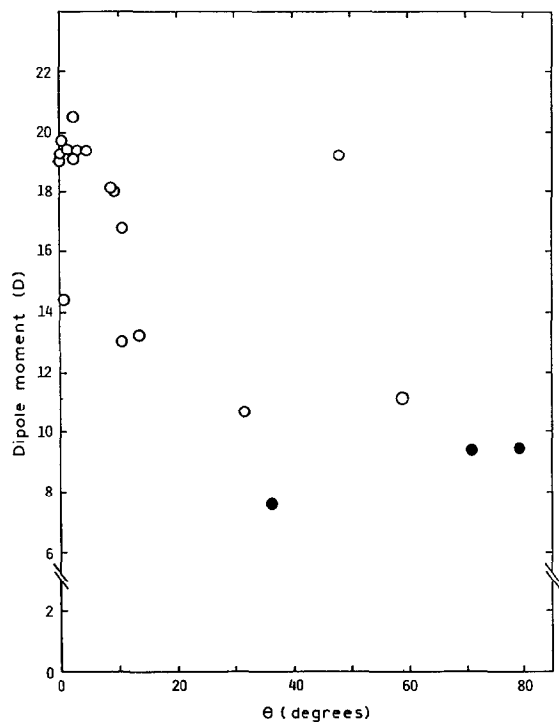


Fig. 3. The plot of the magnitude of the dipole moment of  $\alpha$ -CD against its direction defined as the angle  $\theta$ . The solid circles indicate the points corresponding to the  $\alpha$ -CD-water complexes.

In Table II, the direction of the guest-dipole moment is expressed as the angle  $\omega$  between the vectors of the dipoles of the host and the guest (see Fig. 2). When these vectors are antiparallel, this angle is  $180^\circ$ . As pointed out<sup>24</sup> for some  $\alpha$ CD–aromatic guest complexes, there is orientational specificity in the  $\alpha$ CD–aromatic guest complexes. Thus, the dipole moments of such guests, except benzaldehyde (see below), are approximately antiparallel to that of the host. In the other  $\alpha$ CD–guest complexes, no apparent orientational specificity was found.

## DISCUSSION

Some of the characteristic features of CDs may be deduced from the electrostatic properties represented by their dipole moments. The dipole moments of the CDs are large (10–20 D) and their directions, including those of the methylated CDs, run from the secondary to the primary hydroxyl groups.

The numerical values presented here have not yet been supported because of the lack of experimental data. However, the reliability of the calculation is indicated from the following points. First, the CNDO-dipole moments are consistent with those obtained from the MM2 molecular mechanics calculation to within  $\sim 1$  D. For example, the dipole moments of  $\alpha$ CD complexed with PNP are 12.4 D (MM2) and 13.5 D (CNDO). The large dipole moments of the CDs result from the integrated contributions of each glucosyl residue. Thus, the dipole moments of CDs are typical examples of the so-called “macrocyclic effect”, namely, the co-operation of the constituent units of a macrocyclic molecule. The macrocyclic structure can modify the structure of each of its units so that its physical properties may be unusual compared with those for ordinary molecules.

A change in dipole moment is induced<sup>24</sup> in the host  $\alpha$ CD through the interaction with some aromatic guests; the larger the dipole moment of the guest, the larger is the dipole moment of the host. This tendency, reflected by the inclusion complexes of  $\alpha$ CD with disubstituted benzenes, is also shown by the data now reported.

$\alpha$ CD exhibits a large dipole moment when complexed with krypton (no dipole moment). It is evident from Fig. 3 that geometrical factors, reflected in the tilting angle  $\theta$ , are important in determining the dipole moments of CDs. The degree of distortion of the macrocycle was estimated by measuring the difference between the largest and smallest of the  $R_{22}$  diameters, namely the distances between the three diagonally arranged C-2 carbon atoms on the wider-rim side. The resulting values are 0.51 and 0.88 Å for CD complexed with krypton, where the former is the value for the host having a dipole moment of 19.1 D and the latter for a value of 16.8 D (Table II). The  $R_{22}$  difference in  $\alpha$ CD complexed with PNP is 1.25 Å. These values were obtained using the X-ray data. Clearly, CD has a larger dipole moment when it is less distorted, which reflects the increase in the co-operativity described above.

Apart from the  $\alpha$ CD–water complexes, the dipole moments of CDs are



nearly parallel to the axis of the cavity. This finding predicts the presence of electric fields throughout the cavity, which is inconsistent with the conventional picture that emphasizes the hydrophobic character of the cavity. Certainly, electric fields perpendicular to the axis of the cavity would be averaged out owing to the axial symmetry of the molecule. However, the CD molecules are asymmetric with respect to the average molecular plane, defined as one containing the centre of gravity and perpendicular to the axis of the cavity. Thus, electric fields, generated from the electronic distribution in the molecule, remain to be averaged out along the axis. Consequently, the CD cavity can be regarded as a highly polarized medium, and electrostatic interactions are expected to contribute effectively to stabilizing the inclusion complexes.

Due to the relatively tight contact of a benzene ring within the cavity of  $\alpha$ CD, the orientational freedom of aromatic guest is lowered significantly on complexation. For example, in the complexation of PNP with  $\alpha$ CD, only two modes of orientation are allowed according to which substituent is located in the cavity. Under such constraints, either of these modes occurs preferentially in both solution<sup>21</sup> and solid<sup>38-42</sup> (see Fig. 4). In the  $\alpha$ CD inclusion complexes with aromatic guests, except benzaldehyde, the orientation observed corresponds to the anti-parallel arrangement of the dipoles of the host and guest. This finding suggests that the dipole-dipole interaction of the host and the guest molecules plays a key role in determining the host-guest orientation. For the  $\alpha$ CD-PNP and  $\alpha$ CD-PHBA systems, this possibility has been confirmed already by the CNDO calculation for the host-guest supermolecular complexes<sup>24</sup>.

The  $\alpha$ CD-benzaldehyde complex has an unusual crystalline structure<sup>41</sup>, in that two-thirds of the benzene ring is included in the cavity, whereas the carbonyl group protrudes from the secondary hydroxyl side and is inserted into the cavity of the next host molecule from the primary hydroxyl side. The guest is partially in the inter-host space. Therefore, the observed abnormal value of the angle  $\theta$  does not necessarily reduce the importance of the electrostatic interaction in stabilizing the complex. Rather, the loose contact of the guest with the  $\alpha$ CD cavity, accompanying the large loss of van der Waals attractions, would increase the relative contribution of the electrostatic interactions. Similarly, in  $\alpha$ CD-aliphatics and  $\alpha$ CD-benzyl

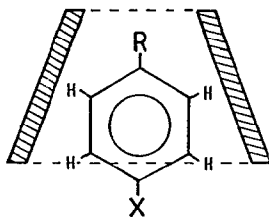


Fig. 4. Schematic representation of the inclusion complex of  $\alpha$ CD with a benzene derivative. The diameters on the wider- and narrower-rims are 8.8 and 5.6 Å, respectively. Due to the bulkiness of the substituents, only two modes of orientation of the guest are possible. When R = NO<sub>2</sub> or X=OH, the figure corresponds to the experimentally determined geometry of the  $\alpha$ CD-PNP complex.

alcohol systems, the guest molecule is expected to fit loosely in the CD cavity. The dipolar approximation used here may be poor for these systems. Explicit energy calculations are required in order to account for the host-guest orientations in these complexes.

CDs have stronger affinities for organic anions than for their unionized forms. For example, the binding constant ( $3700 \text{ mol}^{-1}$ ) of  $\alpha$ CD with *p*-nitrophenolate is considerably larger than that ( $384 \text{ mol}^{-1}$ ) of its un-ionized form<sup>20</sup>. In the inclusion of such an organic anion, stronger coulombic interactions are expected with the internal electric field in the cavity, leading to tighter binding.

It is concluded that the CD cavity can serve as a polar medium for guest molecules.

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