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Molecular Mechanical Calculation on Cyclodextrin Inclusion Complexes. I. The Structures of α-Cyclodextrin Complexes Estimated by van der Waals Interaction Energy Calculation

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The geometries of inclusion complexes of α-cyclodextrin (α-CD) with krypton, methanol, 1-propanol, and *p*-nitrophenol were estimated on the basis of the calculation of energies (E_{vdw}) due to the van der Waals interactions between the CD and the guest molecules. The E_{vdw} values were computed by the use of Hill's potential equation. A spatial relationship at which the E_{vdw} value became minimal was in good agreement with that observed by X-ray crystallography for such a guest molecule as 1-propanol or *p*-nitrophenol, which is large in size and less polar. On the other hand, a significantly large deviation was found between the observed and the calculated geometries of the inclusion complex in such polar and/or small guest molecules as methanol and krypton.

Cyclodextrin (CD) is a truncated cone-shaped oligosaccharide composed of six (α-CD), seven (β-CD), or more D-glucose residues attached by α-(1,4) linkages. The CD catalyzes a variety of organic reactions in a stereospecific manner *via* the preceding inclusion of guest molecules within its intramolecular cavity.[1,2] For a comprehensive understanding of the stereospecificity in the binding and catalytic processes of CD, it is essential to define the spatial relationships (geometries) within the inclusion complexes. In this regard, the three-dimensional structures of CD and its inclusion complexes have been investigated by means of X-ray crystallography,[2,3] and NMR[4,5] and CD[6,7] spectrometries. However, these methods are too toilsome to be readily applied to any host-guest molecular system. Instead, Corey-Pauling-Koltum (CPK) molecular models have been widely used to predict the geometries of CD inclusion complexes.[1] The CPK models are constructed on the basis of van der Waals radii of atoms and are a convenient tool for the examination of intermolecular spatial relationships in molecular adducts. However, no one can estimate, with the aid of the models, which of the possible geometric isomers of CD–guest inclusion complexes is actually dominant in the complexation process, owing mainly to the lack of information on interaction energies. In order to estimate the geometry of a CD–guest complex more definitively, it is required to evaluate energy differences between the possible geometric isomers. Molecular mechanical calculation (semiempirical force-field calculation)[8,9] is a method available at hand for this purpose. This method involves the calculation of bond stretching, bond angle strain, torsional, and van der Waals interaction energies. Recently, Tabushi *et al.*[10] have successfully applied this method to α-CD systems to elucidate some aspects of the driving force of inclusion.

The present study deals with a structural analysis of some α-CD–guest inclusion complexes on the basis of the calculation of the van der Waals interaction energy (E_{vdw}) alone, as a first step with the intention of relating the structures, stabilities, and reactivities of CD inclusion complexes to energies estimated by molecular mechanical calculation. The van der Waals interaction, together with hydrophobic interaction, is regarded as a dominant binding force contributing to the association of CD with a guest molecule.[10–14] Since the magnitude of the van der Waals interaction is highly dependent on the interatomic distance, the geometry of a CD–guest complex may be largely governed by this interaction. The disregard of other interactions may inevitably result in some discrepancy between observed and calculated geometries. Even so, it is worthwhile to make clear the scope or limitation of this simplified method. For this purpose, the calculation was carried out on several guest molecules, such as krypton, methanol, 1-propanol, and *p*-nitrophenol, which differ in size and in polarity from one another. The molecular structures of α-CD complexes with these guest molecules have already been determined by the X-ray method.[15–18] The E_{vdw} values were computed for each molecular system at a variety of geometric relationships, and the position at which the E_{vdw} value becomes minimum was searched for by the use of the steepest descent method for nonlinear optimization programming.

Method for Calculation

The energy, E_{vdw}, was calculated by the use of Hill's potential equation (Eq. 1),[19] which was first utilized by Tabushi *et al.*[10] for the calculation of CD inclusion.

$$E_{vdw} = a \sum_{i}\sum_{j} \varepsilon_{ij}\ (r_{ij}/d_{ij})^{6} + b\sum_{i}\sum_{j} \varepsilon_{ij}\ \exp(d_{ij}/cr_{ij}) \qquad (1)$$

In this equation, the subscripts, i and j, denote interacting atoms belonging to α-CD and a guest molecule respectively, d_{ij}, the interatomic distance, r_{ij} and ε_{ij},

TABLE 1. VAN DER WAALS PARAMETERS FOR THE HILL EQUATION

Atom	r/nm	ε/kJ mol^{-1}
H	0.120[a,b,c]	0.176[a,b]
C(sp^2)	0.185[d]	0.084[d]
C(sp^3)	0.170[b,c]	0.448[b]
N	0.155[c]	0.397[e]
O	0.152[c]	0.485[f]
Kr	0.207[a]	1.368[a]

a) Ref. 19. b) N. L. Allinger, M. A. Miller, F. A. Van Catledge, and J. A. Hirsch, *J. Am. Chem. Soc.*, **89**, 4345 (1967). c) A. Bondi, *J. Phys. Chem.*,**68**, 441 (1964). d) N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Am. Chem. Soc.*, **91**, 337 (1969). e) Ref. 8. f) N. L. Allinger, M. A. DaRooge, and R. B. Hermann, *J. Org. Chem.*, **26**, 3626 (1961).

the sum of van der Waals radii (r) and a geometrical mean of energetic parameters (ε) respectively with regard to the interacting atoms of i and j, and a, b, and c, constants equal to -2.25, 8.28×10^5, and -0.0736[19] respectively. The values of r and ε used in the present study are summarized in Table 1. All of the atoms were taken into account in the calculation except hydrogen atoms attached to oxygen atoms of α-CD. Thus, 36 carbon atoms, 30 oxygen atoms, and 42 hydrogen atoms of α-CD were chosen. The structure of a α-CD–guest complex in which E_{vdw} becomes minimum was determined by the steepest descent method with a FACOM M-140F computer at Shimane University.

The Coordinates of Atoms Composing of α-CD. The atomic coordinates of α-CD used in the calculations were determined on the basis of the following three assumptions. (1) Each glucopyranose skeleton of α-CD has the same structure as the "Gl" glucopyranose residue of a α-CD–potassium acetate complex.[20] (2) The α-CD macrocycle retains a regular hexagonal structure with the C_6 element of symmetry, irrespective of the guest molecule. In this connection, the Cartesian coordinates were fixed so that the Z-axis refers to the six-fold axis of rotation, the XY plane to a plane defined by the six O(4) atoms of α-CD, and X-axis to a diagonal through G3O (4) and G6O (4) atoms. (3) The angle of each glucopyranose residue to the Z-axis is determined so as to minimize the conformational energy (E_{conf}) of α-CD. The value of E_{conf} was calculated by the use of semiempirical force-field parameters for the van der Waals and angle bending energies. Since it was assumed that the structure of each glucopyranose residue is unchanged, the conformational energies due to the interactions between atoms belonging to the same residue were excluded from this calculation. The E_{conf} value was minimal at $\phi=12.30°$, where ϕ denotes an angle of a plane defined by C(1), C(3), and C(5) atoms of a glucopyranose residue to the Z-axis. Table 2 shows a part of the atomic coordinates of α-CD obtained, together with a few parameters which represent the aspects of the conformation of the α-CD macrocycle. The ϕ value calculated is slightly larger than that observed.[20] The bond angle (θ) of a glucosidic linkage and the distance (r_{d}) between a pair of diagonal O(4) atoms for the calculated structure are virtually equal to those for the observed one.

TABLE 2. A PART OF α-CD ATOMIC COORDINATES USED FOR THE CALCULATION OF THE VAN DER WAALS INTERACTION ENERGY[a)]

Atom	x/nm	y/nm	z/nm
GlC(1)	0.1759	0.5014	−0.0352
GlC(2)	0.0949	0.5567	0.0819
GlC(3)	−0.0303	0.4702	0.1054
GlC(4)	−0.1126	0.4663	−0.0228
GlC(5)	−0.0250	0.4159	−0.1399
GlC(6)	−0.0983	0.4255	−0.2710
GlO(2)	0.1791	0.5601	0.1990
GlO(3)	−0.1108	0.5274	0.2093
GlO(4)	−0.2145	0.3716	0.0000
GlO(5)	0.0919	0.5001	−0.1505
GlO(6)	−0.0196	0.3752	−0.3787
GlH(1)	0.2638	0.5637	−0.0534
GlH(2)	0.0634	0.6584	0.0581
GlH(3)	−0.0007	0.3688	0.1333
GlH(4)	−0.1545	0.5645	−0.0453
GlH(5)	0.0055	0.3129	−0.1217
GlH(6) A	−0.1229	0.5301	−0.2902
GlH(6) B	−0.1901	0.3671	−0.2643

a) Parameters representing the conformation of the α-CD macrocycle: $\phi=12.30°$ (obsd, $8.7\pm0.5°$), $\theta=119.26°$ (obsd, $119.1\pm0.2°$), and $r_{\mathrm{d}}=0.8581$ nm (obsd, 0.849 ± 0.011 nm).

Geometry of an Organic Guest Molecule. The geometry of an organic guest molecule was determined by calculation using bond lengths taken from the literature[21] and with bond angles which were taken as 109.5° for aliphatic carbon and alcoholic oxygen atoms and 120.0° for aromatic carbon atoms. It was also assumed that a straight-chain alkyl group always retains a zigzag *trans* planar conformation.

Results

The atomic coordinates obtained by the E_{vdw} calculation are compared with those observed in Table 3 to 6. Only the z-coordinates of atoms are given in the tables in order to simplify the representation. The observed atomic coordinates were re-calculated from the X-ray crystallographic data.[15–18] In this calculation, the Cartesian coordinates were transformed so that the observed least-squares plane of six O(4) atoms of α-CD accords with the XY plane and the y-coordinates of a pair of diagonal O(4) atoms become equal to zero.

The X-ray study[15] revealed that, in a α-CD–Kr adduct obtained under Kr pressure of 304 kPa, the Kr is statistically disordered over three positions. Each Kr atom is approximately located on the Z-axis. The

TABLE 3. THE z-VALUES OF Kr IN A α-CD–Kr COMPLEX[a)]

	z/nm		
	Site A	Site B	Site C
Obsd	−0.168	−0.016	−0.073
Calcd	−0.158	−0.076	—

a) Parameters representing the conformation of the α-CD macrocycle observed: $\phi=11.4\pm4.2°$, $\theta=118.2\pm0.5°$, and $r_{\mathrm{d}}=0.845\pm0.008$ nm.

TABLE 4. THE z-VALUES OF THE CONSTITUENT OXYGEN AND CARBON ATOMS OF METHANOL IN A α-CD–METHANOL COMPLEX[a)]

Atom	z/nm		
	Obsd		Calcd
	Site A	Site B	
O	−0.2832	−0.0723	−0.1572
C	−0.2541	0.0577	−0.0150

a) Parameters representing the conformation of the α-CD macrocycle observed: $\phi=12.1\pm4.4°$, $\theta=119.0\pm0.4°$, and $r_{\mathrm{d}}=0.845\pm0.021$ nm.

Table 5. The z-values of the constituent oxygen and carbon atoms of 1-propanol in a α-CD-1-propanol complex[a)]

Atom	z/nm		
	Obsd		Calcd
	Site A	Site B	
O	−0.243	−0.249	−0.252
C(1)	−0.168	−0.168	−0.174
C(2)	−0.019	−0.019	−0.025
C(3)	0.075	0.061	0.059

a) Parameters representing the conformation of the α-CD macrocycle observed: $\phi=11.3\pm4.1°$, $\theta=119.9\pm0.6°$, and $r_d=0.846\pm0.006$ nm.

Table 6. The z-values of the constituent atoms of p-nitrophenol in a α-CD–p-nitrophenol complex[a)]

No.[b)]	Atom	z/nm	
		Obsd	Calcd
1	C	0.2696	0.2714
2	C	0.2042	0.2029
3	C	0.0665	0.0635
4	C	0.0001	−0.0073
5	C	0.0658	0.0612
6	C	0.2002	0.2006
7	O	0.4028	0.4074
8	O	−0.2023	−0.2143
9	O	−0.2051	−0.2163
10	N	−0.1453	−0.1543
11	H	0.2671	0.2580
12	H	0.0291	0.0102
13	H	0.0109	0.0062
14	H	0.2401	0.2539
15	H	0.4449	0.4552

a) Parameters representing the conformation of the α-CD macrocycle observed: $\phi=9.7\pm2.3°$, $\theta=118.5\pm0.4°$, and $r_d=0.846\pm0.027$ nm. b) The number of each atom is refered to Fig. 2.

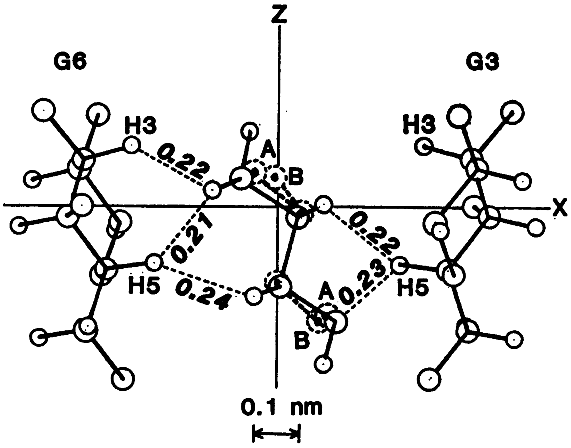

Fig. 1. Geometries calculated (solid lines) and observed (bold dashed lines) for 1-propanol in its α-CD adduct. Letters A and B represent the disordered sites observed for 1-propanol. Interatomic distances are shown in bold italics on fine dashed lines (nm).

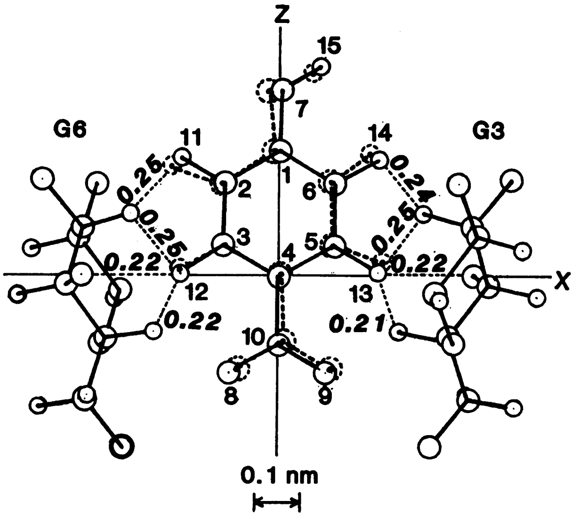

Fig. 2. Geometries calculated (solid lines) and observed (bold dashed lines) for p-nitrophenol in its α-CD adduct. The figures given in roman on the atoms of p-nitrophenol refer to those shown in Table 6. Interatomic distances are shown in bold italics on fine dashed lines (nm).

E_{vdw} calculation for this adduct showed two energy minima at $z=-0.158$ and -0.076 nm. The former is close to the z observed for Kr at site A, whereas the latter deviates considerably from those observed. Fairly large deviations were also found between geometries observed and calculated for a α-CD–methanol complex. The methanol molecule observed is two-fold disordered in sites A and B with equal probability. However, both are located far from the position calculated. In contrast to these cases, the geometries calculated are in good agreement with those observed in the cases of α-CD complexes with 1-propanol and p-nitrophenol. The X-ray study[17)] showed that the hydroxyl and methyl groups of 1-propanol are two-fold disordered in the α-CD cavity, with site A occupied 80%, site B 20%. The average and standard deviations between the atomic coordinates observed and calculated for 4 atoms of oxygen and carbon of 1-propanol are as follows (standard deviations are in parentheses): x, 0.005 (0.022) and 0.012 (0.048) nm, y, 0.001 (0.032) and −0.004 (0.052) nm, and z, 0.010 (0.005) and 0.005 (0.002) nm for site A and B respectively. On the whole, the coordinates observed for site A are in better agreement than those for site B with the calculated coordinates. Corresponding values for the 15 atoms of p-nitrophenol are −0.004 (0.014) nm for x, 0.028 (0.036) nm for y, and 0.003 (0.010) nm for z. Such deviations, as are shown above, are acceptably small, when taking into account the fact that the atomic coordinates of α-CD and the guest molecules used for the calculation are not exactly the same as those observed. The geometric relationships are illustrated for the adducts of 1-propanol and p-nitrophenol in Figs. 1 and 2 respectively. The calculation of atomic distances between the constituent atoms of the α-CD complexes revealed that the hydrogen and oxygen atoms of 1-propanol or the hydrogen atoms of *p*-nitrophenol are in van der Waals contact with some of H(3), H(5), and/or O(4) atoms of α-CD as are shown in the figures.

Discussion

Geometric relationships obtained by the E_{vdw} calculation were in good agreement with those observed by the X-ray method in the cases of α-CD complexes with 1-propanol and *p*-nitrophenol. These guest molecules are large enough in size to give significantly large stabilization energies due to the van der Waals interaction ($-E_{vdw}=57.36$ and 52.26 kJ mol^{-1} for 1-propanol and *p*-nitrophenol adducts respectively). On the other hand, deviations between observed and calculated geometries are appreciably large for the krypton and methanol adducts. These molecules are small in size so that the stabilization energies due to the van der Waals interaction are small ($-E_{vdw}=26.15$ or 26.12 kJ mol^{-1} for the krypton adduct and 29.16 kJ mol^{-1} for the methanol adduct). Thus interactions other than the van der Waals one, such as hydrogen bonding and dipole-dipole and hydrophobic interactions, may considerably influence the geometries of these adducts.

The present method of calculation sometimes provides a criterion to judge which of the possible geometric isomers of a α-CD–guest inclusion complex is actually dominant in the complexation process. Harata[18] showed that *p*-nitrophenol is included in such a specific manner that the nitro group is located within the α-CD cavity, whereas the phenolic hydroxyl group protrudes from the O(2), O(3) side. However, it is geometrically possible that *p*-nitrophenol is situated upside down in the cavity. The stabilization energy due to the van der Waals interaction was calculated to be 52.26 kJ mol^{-1} for the former and 41.17 kJ mol^{-1} for the latter. Thus, it is possible to predict the specific orientation of the guest molecule in the α-CD cavity on the basis of the E_{vdw} calculation alone.

A number of problems still remain to be solved. First, it was assumed in the present study that the conformation of α-CD is unchanged during the complexation process. Actually, it has been found that the macrocyclic conformation of α-CD is affected by the inclusion of a guest molecule. The primary hydroxyl groups of α-CD shows both *gauche-gauche* and *gauche-trans* conformations, although only the latter was taken into account in the present study. On the other hand, the E_{vdw} values obtained may serve to elucidate the role of the van der Waals interaction in the stabilization of any α-CD–guest inclusion complexes. In addition, the method can easily be extended so as to include β- and γ-CD systems. These problems will be dealt with in subsequent work.

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