Approach to the Aspects of Driving Force of Inclusion by α-Cyclodextrin

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Abstract: A comprehensive model of the inclusion process of α-cyclodextrin is presented herein. van der Waals interaction energy, Allinger's conformation energy, solvation energy of apolar solute in water, hydrogen bond energy of water molecules in the cavity of α-cyclodextrin hexahydrate, and all other possible energies were taken into account for the calculation of free-energy change by complexing an apolar guest molecule by α-cyclodextrin. Motional freedoms of all of the particles relevant to the inclusion process were taken into consideration. The calculated values of the net stabilization free energy of α-cyclodextrin complexes with benzene, methyl orange, and p-iodoaniline were 4.50, 6.20, and 8.99 kcal mol^{-1}, respectively, which were in good agreement with the observed values. The largest value of 10.09 kcal mol^{-1} was obtained as the van der Waals stabilization energy of the α-cyclodextrin-p-iodoaniline complex which was most easily understood as a result of large atomic polarizability of iodine atom and/or better fit of the iodide substrate to α-cyclodextrin's cavity than the other substrates. The value of the solvation energy ($-\Delta H^g_{cluster}$) ranges from 4.1 to 7.1 kcal mol^{-1}, depending upon the size of the apolar moiety of the guest molecule, or the number of water molecules in the first layer of water clusters. The increase in entropy which accompanies breaking of the water clusters around the apolar guest has been found to be a nonnegligible term which contributes to the net stabilization of the inclusion complex. A true aspect that α-cyclodextrin in the complex has a larger conformation energy by ca. 4 kcal mol^{-1} than that in the hexahydrate is also pointed out. Therefore, a speculation presented early by others that the strain relief is the main driving force of the formation of the inclusion complexes of α-cyclodextrin is to be corrected based on the present results.

Cyclodextrin (cycloamylose), which is well known to form inclusion complexes with a variety of organic molecules, has attracted widespread interests in structural chemistry,[1] pharmacological applications,[2] and especially as a model for studies of enzyme–substrate interaction.[3] The quasi-enzyme behavior that cyclodextrin exhibits in substrate binding suggests that the interaction is specific between cyclodextrin and some guest molecules. Hydrogen bonding,[4] van der Waals interaction,[5] and/or hydrophobic interaction[6] had been the forces proposed for the interaction, but still a great deal of uncertainties remain to be clarified as to the nature of binding force, the nature of structured water around (or in proximity to) the inclusion complex in water, molecular dynamics of inclusion, and so on.

It is a fairly reasonable hypothesis that the molecular structure of α-cyclodextrin in water closely resembles that of α-cyclodextrin hexahydrate in the crystalline state,[1b,d] although these are not necessarily the same in details. α-Cyclodextrin holds two water molecules in the cavity hydrogen bonded to each other and to two glucopyranose rings which are more normal to the axis of the α-cyclodextrin torus than the other glucopyranose rings. Strain energy associated with the anomalous rings of the hexahydrate was intuitively attributed by Manor and Saenger to the driving force of the formation of inclusion complexes with organic molecules,[1b,7] since no such anomaly was seen in the latter complexes. Among the forces proposed for the interaction between the host (cyclodextrin) and the guest (organic molecule), hydrophobic binding seems to have the most solid basis given by experiments. For instance, an expansion of the hydrophobic region of cyclodextrin by "capping" its cavity had been found to enhance the substrate binding.[3f,8] The importance of hydrogen bonding in the inclusion complex is very questionable, since no drastic drop of the substrate binding was observed for a modified cyclodextrin which is incapable of hydrogen bonding.[9] The first theoretical approach to the aspects of driving force of inclusion by cyclodextrin was reported by Harata with partial success in the estimation of the binding force.[10] His approach, however, clarified that point charge and dipole model are not fruitful bases for evaluation of polar bonding in the inclusion process. It is evident, therefore, that the bonding nature of inclusion

complexes of cyclodextrin is a current subject of controversy on which more light must be shed.

The authors now present here thus far the most comprehensive model of the inclusion process of α-cyclodextrin. The hypothesis of a thermodynamic process of the inclusion together with tools of semiempirical potential functions of van der Waals[11] and Allinger's conformation energy[12] has been found to give successful results in the evaluation of complex stabilization. Additionally, the present theoretical and quantitative analyses of the inclusion phenomenon have led us to the conclusions that (1) van der Waals interaction between the host and the guest is critical in the stabilization of the complex, (2) the stabilization is largely compensated for by the term of water clusters, (3) the conformational change is unfavorable to the inclusion complex. This is the first case where cyclodextrin's conformation energy is taken quantitatively into consideration for studies of inclusion complexes.

Thermodynamic Picture of the Inclusion Process. The phenomenon of inclusion is a composite process which is understood by thermodynamics. In Figure 1 is schematically shown the thermodynamic process of inclusion proposed by the authors. Then the net stabilization of the inclusion complex can be evaluated as the sum of the free-energy changes of the four processes. For this purpose, the following assignments of thermodynamic quantities and assumptions were made.

(1) α-Cyclodextrin in water includes two water molecules hydrogen bonded to each other and to cyclodextrin, in the same manner as α-cyclodextrin hexahydrate does.[1b,d] These water molecules have neither translational nor rotational freedoms. Release of the two water molecules from the cavity is the first hypothetical process for the inclusion. The process accompanies losses of van der Waals interaction (H^w_{vdw}) and hydrogen bonding ($-2\Delta H_{H\text{-bond}}$), gains of motional freedoms of two water molecules as to translation ($2S^w_{trans}$) and three-dimensional rotation ($2S^w_{rot(3\text{-}D)}$), and a change in conformation energy of α-cyclodextrin. Vibrational freedoms both of water molecules and the guest molecule were assumed constant.

(2) The second step is the transformation of the extruded gaseous water molecules into a liquid phase. As the enthalpy change ($-\Delta H^w_{vap}$) and entropy change ($\Delta S^w_{gas\rightarrow liq}$) for the condensation of water at 25 °C, reliable values of 10.46 kcal
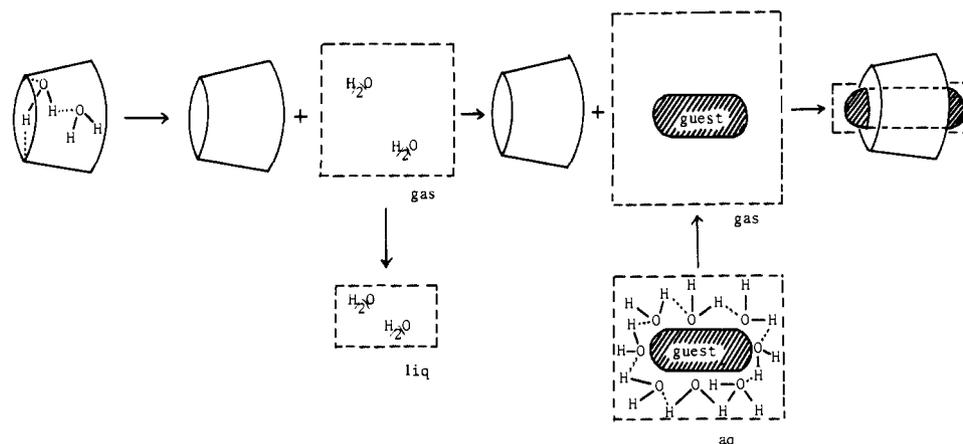
Figure 1. Schematic representation of the thermodynamic process of inclusion of an organic guest molecule by α-cyclodextrin in water solution.

Table I. Calculated Values of Enthalpy Change[a]

Guest	$H^c_{vdw} - H^w_{vdw}$	$H^c_{conf} - H^w_{conf}$	$-\Delta H^g_{cluster}$	$-2\Delta H^w_{vap}$	$-2H_{H\text{-}bond}$	$\Delta H_{inclusion}$
Benzene	−3.75	+4.38	+4.10	−20.92[b]	+12.2	−3.99
p-Iodoaniline	−10.09	+4.38	+7.08	−20.92[b]	+12.2	−7.35
Methyl orange	−8.35	+3.83	+6.71	−20.92[b]	+12.2	−6.53

[a] kcal mol^{-1}, 25 °C. [b] A value of 10.46 kcal/mol as the vaporization enthalpy of water was derived from the following experimental values: the heat of vaporization of water at 100 °C = 9.716 71 kcal/mol;[14] the work bringing 1 mol of water from 25 °C to 100 °C = 1.349 kcal/mol;[15] the work bringing a mole of gaseous water from 100 °C to 25 °C = −0.604 kcal/mol.[16]

Table II. The Calculated Values of Entropy Changes[a]

Guest	$S^g_{rot(1\text{-}D)} - S^g_{rot(3\text{-}D)} - S^g_{trans}$	$-\Delta S^g_{clust}$	$-2(-S^w_{rot(3\text{-}D)} - S^w_{trans} + 2\Delta S^w_{gas\text{-}liq}$[b]	$\Delta S_{inclusion}$
Benzene	−52.0	+20.1	+33.6	+1.7
p-Iodoaniline	−62.9	+34.8	+33.6	+5.5
Methyl orange	−67.6	+32.9	+33.6	−1.1

[a] cal deg^{-1} mol^{-1}, 25 °C. [b] Reference 15.

mol^{-1} (derived from the reported value, see footnotes in Tables I and II) and 16.80 cal deg^{-1} mol^{-1} (reported) were adopted, respectively.

(3) An apolar solute (guest molecule) is transferred from water to the ideal gaseous state leaving a structured cavity behind. The cavity then collapses with redistribution of the water molecules. According to the theory of Némethy and Scheraga,[6] icelike structured water (water clusters) forms a cavity which fits an apolar solute with van der Waals contact. They had shown that the work requisite to break the water cluster is proportional to the number of hydrogen bonds or the number of water molecules in the first layer of water clusters. Application of their theory to the present study, i.e., counting the number of water molecules in the water cluster of the guest molecule (see Calculation Method) using a space-filling model, gives us the estimated value of the free-energy change for the present step. Such an estimated value is sufficiently reliable in magnitude at the present stage, since the calculation procedure taken by Némethy and Scheraga was a reconciliation of their theory with experimental data observed for typical apolar solutes like methane or benzene.

(4) Binding of the guest molecule, the last hypothetical step of inclusion, accompanies van der Waals stabilization (H^g_{vdw}) and a change in conformational energy of cyclodextrin. A freedom of one-dimensional rotation was allowed for the inclusion complex between the aromatic guest molecule and cyclodextrin (Figure 2).
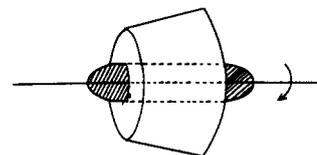
Figure 2. The schematic representation of the rotational freedom allowed for the guest molecule in the binding state.

The enthalpy change ($\Delta H_{inclusion}$) and entropy change ($\Delta S_{inclusion}$) relevant to the inclusion of organic molecule by α-cyclodextrin in aqueous solution now can be calculated using eq 1 and 2, respectively, where superscripts, c, w, and g correspond to inclusion complex, water molecule, and guest molecule, respectively.

$$\Delta H_{inclusion} = (H^c_{vdw} - H^w_{vdw}) + (H^c_{conf} - H^w_{conf}) - \Delta H^g_{cluster} - 2\Delta H^w_{vap} - 2H_{H\text{-}bond} \quad (1)$$

$$\Delta S_{inclusion} = (S^g_{rot(1\text{-}D)} - S^g_{rot(3\text{-}D)} - S^g_{trans}) - 2(-S^w_{rot(3\text{-}D)} - S^w_{trans}) + 2\Delta S^w_{gas\to liq} - \Delta S^g_{cluster} \quad (2)$$

Calculation Method. Evaluations of $\Delta H_{cluster}$ and $\Delta S_{cluster}$ were carried out as follows. A guest molecule, in general, in its binding state was assumed to preserve a portion of water cluster, since as was shown for α-cyclodextrin-methyl orange complex by crystallographic x-ray studies, the size of the hydrophobic cavity of α-cyclodextrin is by no means deep enough to include a whole of a guest molecule longer than ca. 7 Å. This strongly indicates that, for instance, the 20 water molecules in the cluster around benzene must be too much to be evaluated as the number of "frozen" water molecules to be liberated into the bulk water from the cluster when benzene is included by α-cyclodextrin. Eleven is the estimated difference in number of water molecules of the cluster between uncomplexed and complexed state of benzene. Both the nature and the size of a guest molecule are the critical factors which control the number (Figure 3). In these estimations atomic coordinates of complexes were taken from reported x-ray studies and counting the number of water molecules in the first layer of the
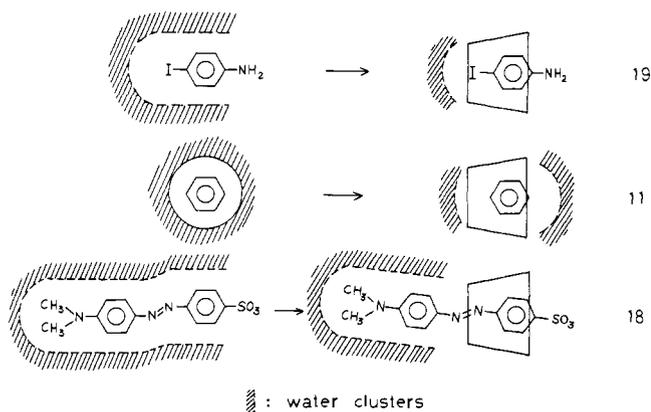
Figure 3. Estimated difference in number of water molecules in the first layer of the water cluster.

cluster was carried out using a space-filling model. Some such anomalies were seen in reported atomic coordinates taken from x-ray results that makes abnormally long C–O, C–C, or C–H bond lengths.[1j,k] Since these anomalies seem to be associated with errors for difference Fourier synthesis, these atomic coordinates were corrected so that the strains of the corresponding bonds are minimized.[13] Corrected coordinates were used for the following calculations too.

van der Waals interaction energy was calculated using Hill's potential (eq 3), where r is the interatomic distance, r^* is the sum of van der Waals radii of the interacting two atoms, and ϵ is a parameter which is defined individually for each pair of the interacting two atoms.[11]

$$E_{vdw} = -2.25\epsilon(r^*/r)^6 + 8.28$$
$$\times 10^5 \, \epsilon \exp(-r/0.0736r^*) \quad (3)$$

Allinger's method[12] was used for the calculation of conformational energy (H_{conf}), which is composed of bond stretching, bond angle strain, torsional, and nonbonded interaction energies. All of the atoms were taken into account in the calculation of van der Waals and conformational energies except atoms whose bond freely rotates. Thus 36 carbon atoms, 24 oxygen atoms, and 30 hydrogen atoms of α-cyclodextrin were chosen. Nonbonded interaction was calculated only for sets of two atoms whose interatomic distance is less than 4 Å.

One-dimensional rotational, three-dimensional rotational, and translational entropies are given by eq 4, 5, and 6, respectively, where N_A is Avogadro's number, k is the Boltzmann constant, h is the Planck constant, M is the molecular weight, T is the absolute temperature, P is the pressure in atomic units, I is the moment of inertia, and σ is the symmetry number.

$$S_{rot(1-D)} = N_a k \left\{ \frac{1}{2} + \frac{1}{2} \ln \frac{8\pi^2 I k T}{h^2} - \ln \sigma_1 \right\} \quad (4)$$

$$S_{rot(3-D)} = N_A k \left\{ \frac{3}{2} + \frac{1}{2} \ln \frac{(8\pi^2 k T)^3 I_1 I_2 I_3}{h^6} - \ln \sigma_3 \right\} \quad (5)$$

$$S_{trans} = N_A k \left\{ \frac{3}{2} \ln \frac{2\pi}{h^2 N_A 10^3} + \frac{5}{2} \ln k + \frac{5}{2} \right.$$
$$\left. - \ln (1.01325 \times 10^5) + \frac{3}{2} \ln M + \frac{5}{2} \ln T - \ln P \right\} \quad (6)$$

Calculations were aided by a digital computer FACOM 230-75 at the Computation Center of Kyushu University.

Results and Discussion

In order to show the applicability of the proposed representation to a general case of inclusion process, the authors

Table III. The Calculated Free-Energy Change in Inclusion Complex Formation[a]

Guest	$\Delta H_{inclusion}$	$-T\Delta S_{inclusion}$	$\Delta G_{inclusion}$	
			Calcd	Obsd
Benzene	−3.99	−0.51	−4.50	
p-Iodoaniline	−7.35	−1.64	−8.99	−5.9
Methyl orange	−6.53	+0.33	−6.20	−5.1

[a] kcal mol^{-1}, 25 °C.

adopted three guest molecules with considerably different size and structure, i.e., benzene, p-iodoaniline, and methyl orange; for the latter two the atomic coordinates of inclusion complexes had been determined by x-ray studies.[1j,k] The calculated thermodynamic parameters are grouped in several terms (Table I and II), in order to provide easy access to quantitative analyses of molecular aspects of inclusion complexes. The calculated net stabilizations of the complexes are shown in Table III.

The first thing to note in the results in Table I is that the value of $\Delta H_{inclusion}$ is largely dependent on the van der Waals stabilization of the complex and the water cluster. The markedly great van der Waals stabilization of the p-iodoaniline-α-cyclodextrin complex ($\Delta H^c_{vdw} = -10.09$ kcal mol^{-1}) is most easily rationalized as a result of the large atomic polarizability of iodine and/or better fit of the α-cyclodextrin-substrate complex than the others.

The larger the van der Waals stabilization is, the more the extent of the collapse of water cluster is accompanied by the inclusion process. Thus a change in extent of the compensation of these two major terms reflects the increase in net stabilization of the complex in the enthalpy term in a series of benzene, methyl orange, and p-iodoaniline. The stabilization of the gaseous water molecules in cyclodextrin's cavity ($H^w_{vdw} + 2H_{H-bond} = -16$ kcal/mol) is less than the enthalpy change for the condensation of these gaseous water molecules into the liquid phase ($2\Delta H^w_{vap} = -20.92$ kcal/mol). This supports a naming of "high-energy water" given by Saenger et al.[7] to the included water molecules of cyclodextrin hexahydrate. The freeze of motional freedoms of the guest molecule (-50 to -60 cal deg^{-1} mol^{-1}) is to a large extent compensated for by entropy increases from other origins, especially from loss of the water cluster around the guest molecule in the bulk medium. It has been approved, therefore, that breaking the water clusters is one of the most important factors which are favorable to the formation of the inclusion complexes. This means that "hand-counting" the number of hydrogen bonds or the number of the water molecules in the water clusters is an unsatisfactory aspect of the theory of Némethy and Scheraga, despite the wealth of theoretical details and its satisfactory coincidence with experimental data. For extensive development of the present approach and applications to a variety of significant biological interactions, non- or semiempirical theory to evaluate the number of water molecules in the water clusters should be exploited on the one hand, and much more accurate experimental data should be accumulated on the other. As to specificity in the substrate binding by cyclodextrin, a general rule may be presented based on our results. Since the compensation of ΔH_{vdw} with $\Delta H_{cluster}$ leaves yet some net stabilization of the complex in the enthalpy term as clarified above, specificity in the complex formation is to be observed for a substrate which has the best host–guest fit (van der Waals stabilization) among guest molecules with a *similar* structure. In fact, this is usually seen in the specificity of the substrate binding by cyclodextrin that many authors so far reported.

Two orthogonal glucopyranose rings of α-cyclodextrin hexahydrate had been assumed to bear strain energy and release it upon complexing a guest molecule. Manor and Saenger

speculated that the strain relief with a concomitant expulsion of "high-energy" water molecules from the cavity is the major driving force of inclusion of organic molecules.[7] However, an opposite conclusion is for the first time drawn from the results of the present calculations. The change in conformation energy from the hydrate to an inclusion complex was found to be of a magnitude of ca. 4 kcal mol^{-1} (Table I), being unexpectedly large with a *positive* sign. The calculation results have shown that each of the strain energies of the C-O-C bond (α-1,4 linkage) between any pair of glucopyranose rings of α-cyclodextrin hexahydrate is not so large, despite a less symmetrical conformation of the torus and the presence of two orthogonal pyranose rings. It is concluded, therefore, that the conformation energy accumulated on the complex is attributable to the ellipsoidal conformation of cyclodextrin torus.

In conclusion, it has been shown that van der Waals interaction, conformation energy, and water clusters are the most important terms which govern the inclusion process as far as specificity in the substrate binding by cyclodextrin is concerned. The present concept of the inclusion phenomenon and calculation procedures has been shown to be tools fruitful enough to be extended to significant and sophisticated problems of host-guest complexes such as active-site directed binding of substrates (or inhibitors) to enzymes or antigen-antibody interactions.

References and Notes

(1) (a) W. Saenger and R. K. McMullan, *Acta Crystallogr., Sect. B*, **30**, 2019 (1974); (b) P. C. Manor and W. Saenger, *Nature (London)*, **237**, 392 (1972); (c) W. Saenger and M. Noltemeyer, *Angew. Chem.*, **86**, 594 (1974); (d) P. C. Manor and W. Saenger, *J. Am. Chem. Soc.*, **96**, 3630 (1974); (e) R. K. McMullan, W. Saenger, J. Fayos, and D. Mootz, *Carbohydr. Res.*, **31**, 211 (1973); (f) B. Hingerty and W. Saenger, *J. Am. Chem. Soc.*, **98**, 3357 (1975); (g) *Nature (London)*, **225**, 396 (1970); (h) M. Noltmeyer and W. Saenger, *ibid.*, **259**, 629 (1976); (i) K. Harata and H. Uedaira, *ibid.*, **253**, 190 (1975); (j) K. Harata, *Bull. Chem. Soc. Jpn*, **48**, 2409 (1975); (k) *ibid.*, **49**, 1493 (1976); (l) *ibid.*, **49**, 2066 (1976); (m) A. Hybl, R. E. Rurdle, and D. E. Williams, *J. Am. Chem. Soc.*, **87**, 2779 (1965); (n) K. Flohr, R. M. Paton, and E. T. Kaiser, *ibid.*, **97**, 1209 (1975); (o) J. Martinie, J. Michon, and A. Rassatt, *ibid.*, **97**, 1818 (1975).

(2) (a) T. Nishibori, Y. Matsuoka, and T. Matsumoto, *Ouyou Yakuri*, **8**, 797 (1974); (b) N. Taira and S. Satoh, *Life Sci.*, **15**, 987 (1974); (c) K. Ikeda, K. Uekama, and M. Otagiri, *Chem. Pharm. Bull.*, **23**, 201 (1975); (d) Y. Hamada, N. Nambu, and T. Nagai, *ibid.*, **23**, 1205 (1975).

(3) (a) F. Cramer and G. Mackensen, *Chem. Ber.*, **103**, 2138 (1970); (b) M. L. Bender, R. L. Van Etten, G. A. Clowes, and J. F. Sebastian, *J. Am. Chem. Soc.*, **88**, 2318 (1966); (c) R. Breslow and L. E. Overman, *ibid.*, **92**, 1075 (1970); (d) D. E. Tutt and M. A. Schwartz, *ibid.*, **93**, 767 (1971); (e) H. J. Brass and M. L. Bender, *ibid.*, **95**, 5391 (1973); (f) R. Breslow and J. Emert, *ibid.*, **97**, 670 (1975); (g) F. Cramer, W. Saenger, and H.-ch. Spatz, *ibid.*, **89**, 14 (1967); (h) R. Bergern, Y. Machida, and K. Bloch, *J. Biol. Chem.*, **250**, 1223 (1975); (i) F. Cramer and W. Kampe, *J. Am. Chem. Soc.*, **87**, 1115 (1965); (j) N. Hennrich and F. Cramer, *ibid.*, **87**, 1121 (1965); (k) F. Cramer and D.-C. G. Mackensen, *Angew. Chem.*, **78**, 641 (1966); (l) T. S. Staub and M. L. Bender, *J. Am. Chem. Soc.*, **94**, 8875 (1972); (m) T. S. Straub and M. L. Bender, *ibid.*, **94**, 888 (1972); (n) D. L. Vander Jagt, F. L. Killian, and M. L. Bender, *ibid.*, **92**, 1016 (1970).

(4) F. Cramer and W. Kample, *J. Am. Chem. Soc.*, **87**, 1115 (1965).

(5) F. Cramer, *Angew. Chem.*, **73**, 49 (1967).

(6) G. Némethy and H. A. Scheraga, *J. Chem. Phys.*, **36**, 3401 (1962).

(7) W. Saenger, M. Noltemeyer, P. C. Manor, B. Hingerty, and B. Klar, *Bioorg. Chem.*, **5**, 187 (1976).

(8) I. Tabushi, K. Shimokawa, N. Shimidzu, H. Shirakata, and K. Fujita, *J. Am. Chem. Soc.*, **98**, 7855 (1976).

(9) R. J. Bergeron and M. P. Meeley, *Bioorg. Chem.*, **5**, 197 (1976).

(10) K. Harata, *Bull. Chem. Soc. Jpn*, **49**, 2066 (1976).

(11) (a) T. L. Hill, *J. Chem. Phys.*, **16**, 399 (1948). (b) Parameter ϵ is a geometrical mean of the following values for each of the two interacting atoms (cf. ref 11c).

	H	C_{sp}^3	N	O	I	S	C_{sp}^2
kcal/mol	0.042	0.107	0.095	0.116	0.623	0.314	0.020
Ref	11a	11f	11d	11c	11c	11c	11e

(c) E. L. Elliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Wiley, New York, N.Y., 1965, pp 449–453; (d) N. L. Allinger, M. A. DaRooge, and R. B. Hermann, *J. Org. Chem.*, **26**, 3626 (1961); (e) N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Am. Chem. Soc.*, **91**, 337 (1969); (f) N. L. Allinger and W. Szkrybalo, *J. Org. Chem.*, **27**, 4601 (1962).

(12) (a) N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tyminski, and F. A. Van Catledge, *J. Am. Chem. Soc.*, **90**, 1199 (1968); (b) N. L. Allinger, M. A. Miller, F. A. Van Catledge, and J. A. Hirsch, *ibid.*, **89**, 4345 (1967); (c) N. L. Allinger and D. Y. Chung, *ibid.*, **98**, 6798 (1976).

(13) The effect of a change in coordinates of a given atom is easily obtained by the concomitant change in the conformation energy (the sum of bond stretching energy, angle strain, torsional strain, and nonbonded interaction). One of the simplest solutions to the correction of several of those anomalous coordinates seen in the original x-ray results is to minimize the conformation energy of a system of atoms for which those corrections seem to be necessary.

For the correction of anomalous coordinates of a given atom in a glucopyranose skeleton, we chose one or two more adjacent atoms (depending upon the extent of their anomalies), which is directly bound to the atom in question, and the conformation energy relevant to these atoms was minimized. Other anomalies were seen in the coordinates of atoms whose bond freely rotates (e.g., oxygen atom in the C-OH bond). For these, the correction was simply done by minimizing the corresponding stretching energy. The changes in Cartesian coordinates are continued until the energy no longer decreases using a method of steepest descent: K. B. Wiberg, *J. Am. Chem. Soc.*, **87**, 1070 (1965).

The corrected coordinates are designated by the following corrected bond lengths in angstroms: *p*-iodoaniline complex; C(4)–C(5), 1.522; C(11)–O(44), 1.423; C(15)–O(46), 1.416; C(17)–O(48), 1.421; C(23)–O(52), 1.416; C(27)–O(54), 1.416. Methyl orange complex, C(5)–C(6), 1.511; C(8)–C(9), 1.511; C(15)–C(16), 1.511; C(17)–C(18), 1.508; C(1)–O(22), 1.416; C(3)–O(20), 1.416; C(5)–O(22), 1.414; C(10)–O(25), 1.416; C(14)–O(27), 1.416; C(16)–O(29), 1.413; C(17)–O(30), 1.427; C(10)–H(39), 1.094; C(11)–H(40), 1.094, where the number of the atom is the same as that employed in ref 1j and 1k.

The coordinates corrections were satisfactorily done, since the corrected bond lengths are in good agreement with the reported bond lengths of α-D-glucose that were determined from x-ray and neutron diffraction studies: C–O, 1.4226 ± 0.0139; C–C, 1.5191 ± 0.0081; C–H, 1.0989 ± 0.0053 Å [E. Hough, S. Neidle, D. Rogers, and P. G. H. Troughton, *Acta Crystallogr., Sect. B*, **29**, 365 (1973); G. M. Brown and H. A. Levy, *Science*, **147**, 1038 (1965)]. The sum of the longitudinal deformation energies of all of the bonds whose lengths were corrected was 0.065 kcal/mol for *p*-iodoaniline complex or 0.051 kcal/mol for methyl orange complex, respectively, which again strongly supports the accuracy of our corrections.

The van der Waals interaction energy ($H^c_{vdw} - H^w_{vdw}$, cf. Table I) did not change a little upon the coordinates corrections. If one still uses the original x-ray coordinates, the bond stretching energy of α-cyclodextrin (vide infra) is so large that the complex formation is no longer allowed ($\Delta H_{inclusion}$ = +1.84 kcal/mol for *p*-iodoaniline complex and +40.46 kcal/mol for methyl orange complex).

Conformation Energy of α-cyclodextrin Inclusion Complex[a]

Guest		Stretching	Bond angle strain	Torsion	Non-bonded	Total
Hexahydrate	X[b]	8.85	22.62	16.21	−27.34	20.34
p-Iodo-	X[b]	17.68	24.86	18.54	−27.17	33.91
aniline	C[c]	8.00	24.50	18.60	−26.39	24.72
Methyl	X[b]	38.06	32.16	22.28	−21.34	71.16
orange	C[c]	3.98	27.11	18.85	−25.77	24.17

[a] kcal/mol. [b] Based on the x-ray coordinates (ref 1j,k). [c] Based on the corrected coordinates.

(14) N. S. Osborne and H. F. Stimson, *J. Res. Natl. Bur. Stand.*, **23**, 197 (1939).

(15) N. E. Dorsey, "Properties of Ordinary Water-Substance", *ACS Monogr.*, **No. 81** (1940).

(16) H. M. Spencer, *J. Am. Chem. Soc.*, **67**, 1859 (1945).