# Analysis of the α-Cyclodextrins including *p*-Nitrophenol as a Guest Molecule with DFT Calculations.

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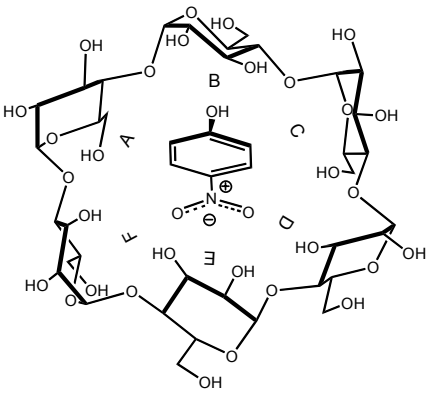
**Abstract**: Structure optimizations of the inclusion complex that was composed of α-cyclodextrin with *p*-nitrophenol were performed by density functional theory (DFT) with several calculation conditions. These calculation conditions were evaluated by comparing the optimized structures with X-ray crystallographically determined structure and the interactions between α-cyclodextrin and *p*-nitrophenol were discussed using the donor-accepter interactions that derived from natural bond orbital (NBO) analysis.

## Introduction

Cyclodextrins are macrocyclic oligosugers most commonly composed of 6-8 glucosidic units. Cyclodextrins and their derivatives have large cavity at the center and work as host molecules by accepting small molecules (called guests) forming inclusion complexes [1-3]. Although, the details of the interactions between the host and the guest molecules are important in the study of the inclusion complexes, the methods to obtain the direct information are limited. In solution state, the important direct information can be obtained by the several measurement techniques of 2D nuclear magnetic resonance (NMR) spectroscopy [1, 4]. In solid state, X-ray single crystallographic analyses are also good method and it gives significant results [1, 5]. Both of these methods are useful, but is nevertheless 2D NMR cannot completely distinguish the complex signals, and the results of crystallographic analyses are not necessarily the same as in the solution state. Commonly, *ab initio* and density functional theory (DFT) calculations are useful in this type of situation; however, the calculations of the inclusion complexes are one of the difficult things and most of previous studies were used semi-empirical calculations or molecular mechanics [1]. One of the reasons is because QM/MM [6], which combine a quantum mechanical (QM) method with a molecular mechanics (MM) method, and ONIOM [7], which can combine any number of molecular orbital method, as well as molecular mechanics methods, used for the calculation of the large molecules is not applicable. In the both of QM/MM and ONIOM, the basic methodology is that to divide a large molecule into an important part and the part which are not so. As for the inclusion complexes, the whole internal circumference of host molecule interacts with a guest molecule; therefore we cannot divide the complexes into parts. It is insufficient for the reason of cannot but use a small basis set, some useful information are expected by the recent DFT calculation method. In this paper, we report the theoretical analysis of the interaction between host and guest molecules with DFT calculations. The calculations were performed to the inclusion complex **1** that was composed of α-cyclodextrin and *p*-nitrophenol without to divide into parts.




**1**

Figure 1: The inclusion complex composed of α–cyclodextrin and *p*-nitrophenol with glucose ring labels A to F.

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## Computational Methods

All geometry optimizations and population analyses were carried out with density functional theory (DFT)[8] at Becke's three parameters (B3) exchange functional along with the Lee-Yang-Parr (LYP) non-local correlation functional (B3LYP) level [9, 10] or Truhalar group's hybrid meta-GGA functional (MPW1B95) [11]. Split valence basis set 3-21G [12] or 3-21+G** with extra polarization [13] and diffuse [14] functions were used in all calculations. The stationary points of **1b-d** were confirmed as energy minima. The calculations of **1e** and **1f** in the presence of water by IEF-PCM method [15] were not converged completely under the usual criteria for determining when a geometry has converged, because of **1e** and **1f** were shown vary flat potential energy surface around the minimum. These calculations were terminated when the forces are smaller than the cutoff value over several cycles even the displacement was larger than cutoff value. Atomic Natural population analysis (NPA) and inter atomic donor-acceptor interactions were derived from natural bond orbital (NBO) analysis [16]. The DFT and the NBO calculations were performed using the Gaussian03 program package [17].

## Results and Discussions

Crystallographically determined structure [17] **1a** provided initial geometries for the optimization of **1** and one of the optimized structure **1b** that was obtained by B3LYP level calculation with 3-21G basis set was shown in Figure 2.

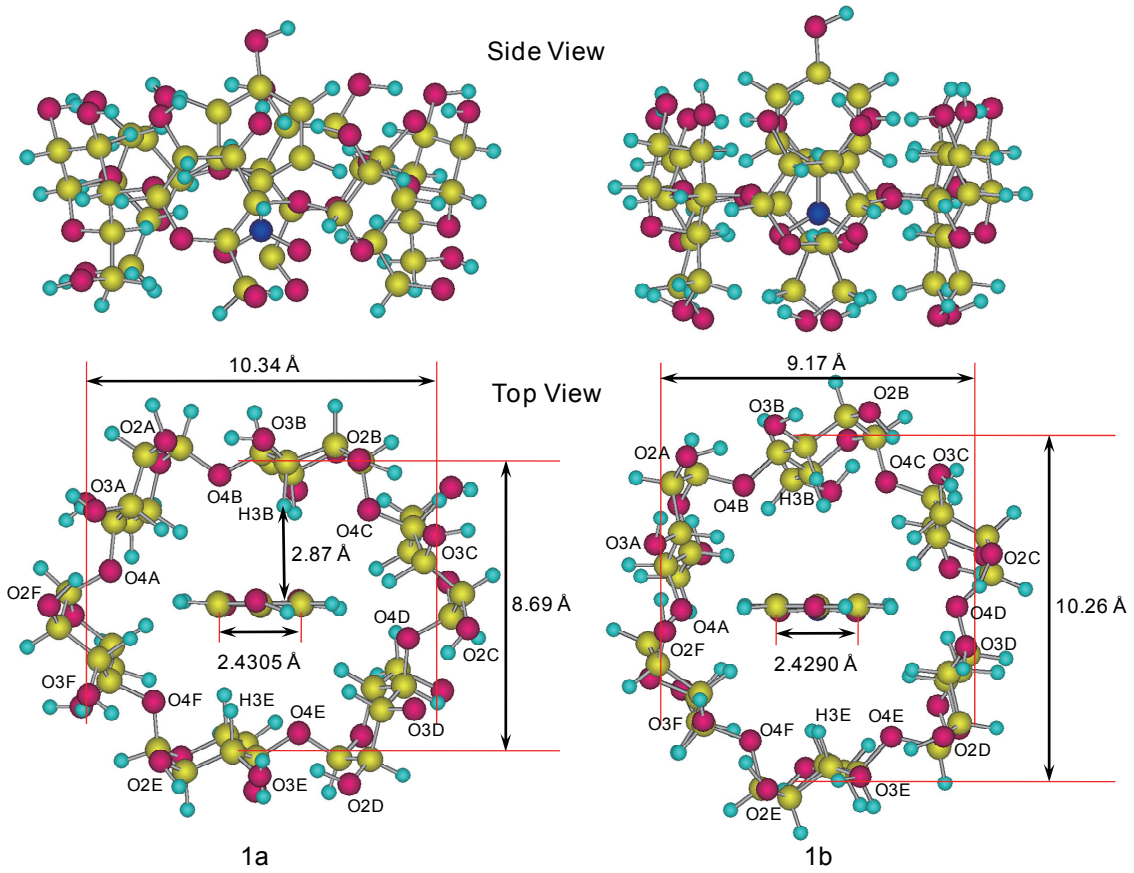


Figure 2: Crystallographically determined structure (**1a**) and the optimized structure by B3LYP/3-21G (**1b**). As for the colored ball, yellow, red, blue, and aqua express carbon, oxygen, nitrogen, and hydrogen, each.

It is clear from the shape of **1a** and **1b**, the cyclodextrin rings of **1a** was transformed along the shape of the guest molecule. The shape can be considered to be an oval, the major and the minor axises were 10.34 Å and 8.69 Å, respectively. On the other hand, the major axis of **1a** became the minor axis with **1b** and the distances of the lengthwise and crosswise directions of **1b** in the figure 2 were 9.17 Å and 10.26 Å each. In case of **1b**, seeing from the top, the guest molecule was lapped over on a straight line to link the O4A to O4D, but moved in **1a**. The location of *p*-nitrophenol in α-cyclodextrin was illustrated in Figure 3 and the cup like structure showed the shape of the host. The anomeric oxygen atoms O4A and O4D were close to the guest hydrogen atoms H2' and H2, respectively. This previous result suggested that the interactions between O4A-H2' and O4D-H2 were overestimated in this calculation conditions. It seemed that the hydrogen atoms H3B and H3E of **1a** were located closer to the aromatic ring plane of *p*-nitrophenol and the distances between the plane and H3B or H3E were 2.87 Å and 3.14 Å each (Table 1). Meanwhile in **1b**, these hydrogens were more than 3.6 Å away from the aromatic ring plane and the facts showed that some interactions cannot evaluated in this calculation.

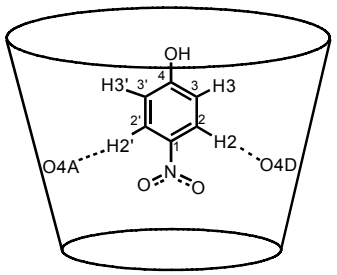


Figure 3: The interactions between O4A-H2' and O4D-H2.

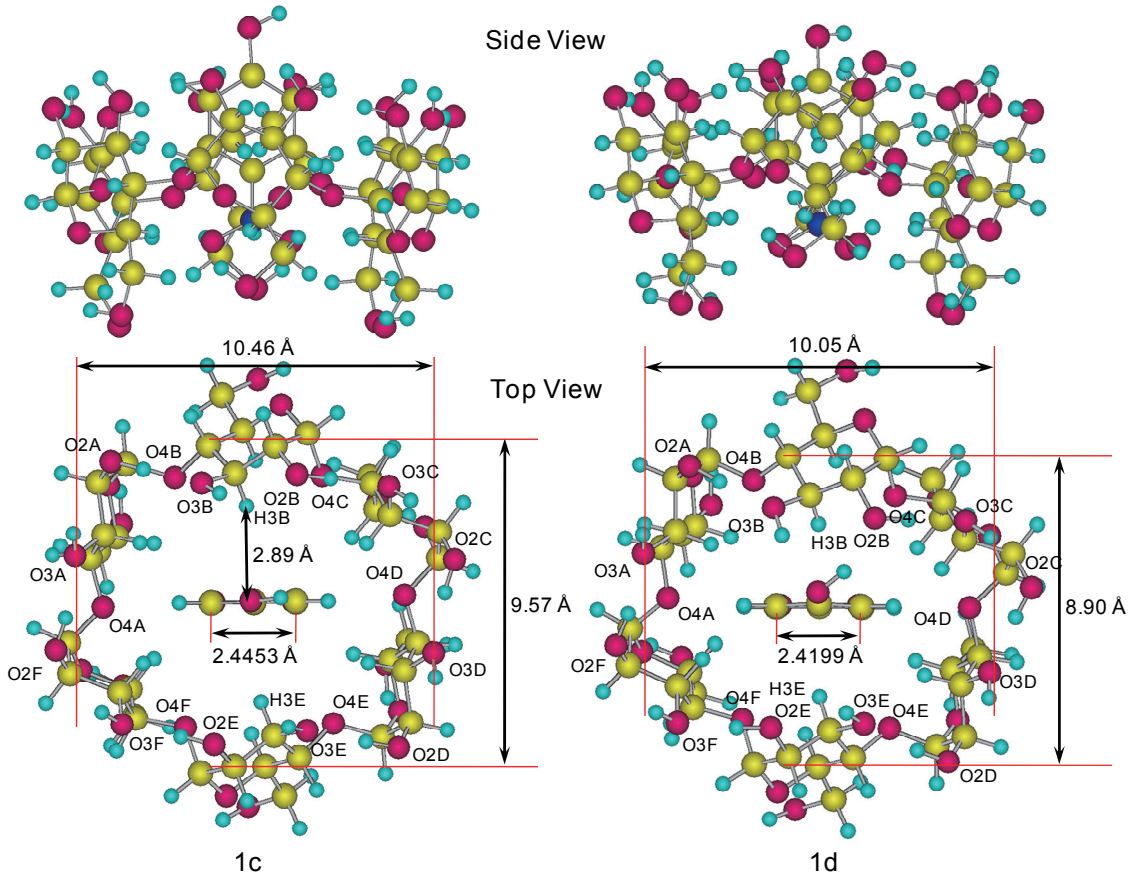


Figure 4: The optimized structures by B3LYP/3-21+G** (**1c**) and MPW1B95/3-21+G** (**1d**). As for the colored ball, yellow, red, blue, and aqua express carbon, oxygen, nitrogen, and hydrogen, each.

Table 1: The structural data of **1a-f**.[a]

| | O4A···H2' | H2···O4D | Distance from H3B to aromatic ring plane | Distance from H3E to aromatic ring plane |
|---|---|---|---|---|
| **1a** | 2.316 | 2.228 | 2.87 | 3.14 |
| **1b** | 2.078 | 2.138 | 3.70 | 3.66 |
| **1c** | 2.304 | 2.351 | 2.89 | 2.92 |
| **1d** | 2.176 | 2.203 | 2.36 | 2.57 |
| **1e** | 2.338 | 2.347 | 3.19 | 3.21 |
| **1f** | 2.364 | 2.345 | 2.85 | 2.73 |

[a] Inter atomic distances and distances from hydrogen to aromatic ring plane are shown in Å.

The 3-21G basis set was too small to calculation that including weak interactions between host and guest molecules and then the 3-21+G** basis set was used as an enough large one. Furthermore, it can be pointed out that the B3LYP functional is not enough to calculate the molecule including weak interactions as the general tendency. The MBW1B95 functional is a one of hybrid meta-GGA functional and the functional is improved the calculation including hydrogen bond and weak interactions. The optimized structures by B3LYP level with 3-21+G** (**1c**) and MBW1B95 level with 3-21+G** (**1d**) were shown in Figure 4 and seemed the interaction between *p*-nitrophenol and glucose ring B or E were estimated than **1b**. Comparing the structure of **1c** and **1d** with **1b**, the distances of O4A···H2' and H2···O4D of **1c** and **1d** were larger than that of **1b** and the distances of H3B···aromatic ring plane and H3E···aromatic ring plane of **1c** and **1d** were smaller than that of **1b**. By this transform, the shapes of **1c** and **1d** were closer to **1a** than **1b**. However, the glucose rings B and E were bent toward *p*-nitrophenol. Especially, the ring B of **1d** was close to *p*-nitrophenol by the hydrogen bond between O2B and phenolic hydroxyl group.

This inconvenience was resolved with the calculation including solvent effect. The optimizations were performed in the presence of water ($\varepsilon = 78.39$) using IEF-PCM method and the shapes by B3LYP level with 3-21+G** (**1e**) and MPW1B95 level with 3-21+G** (**1f**) were shown in Figure 5. Among the all structures obtained in this study, the shape of **1f** was nearest to **1a**.

One of the remaining problems is the hydrogen bond between secondary hydroxyl groups. It has great influences to the shape of the complex **1** was that the strength of hydrogen bond of inter-glucose rings, such as O2A-H···O3B etc. The C2-OH group of one glucopyranoside unit can form a hydrogen bond with the C3-OH group of the adjacent glucopyranose unit. In the cyclodextrin, a complete secondary belt is formed by these hydrogen bonds; therefore the estimation of the strength of hydrogen bond affects the size of secondary hydroxyl groups' side. To the analysis of the strength, the distances between oxygen atoms of secondary hydroxyl groups were shown in Table 2. Normally, it is reasonable to compare the distances between oxygen and hydrogen atoms; however the positions of hydrogen atoms determined by X-ray crystallographic analysis were not enough reliability. The overestimation of the strength of hydrogen bond was obvious from the results that the most of the calculated inter-oxygen atoms' distances (**1b-f**) were smaller than that of X-ray crystallographic analysis (**1a**).

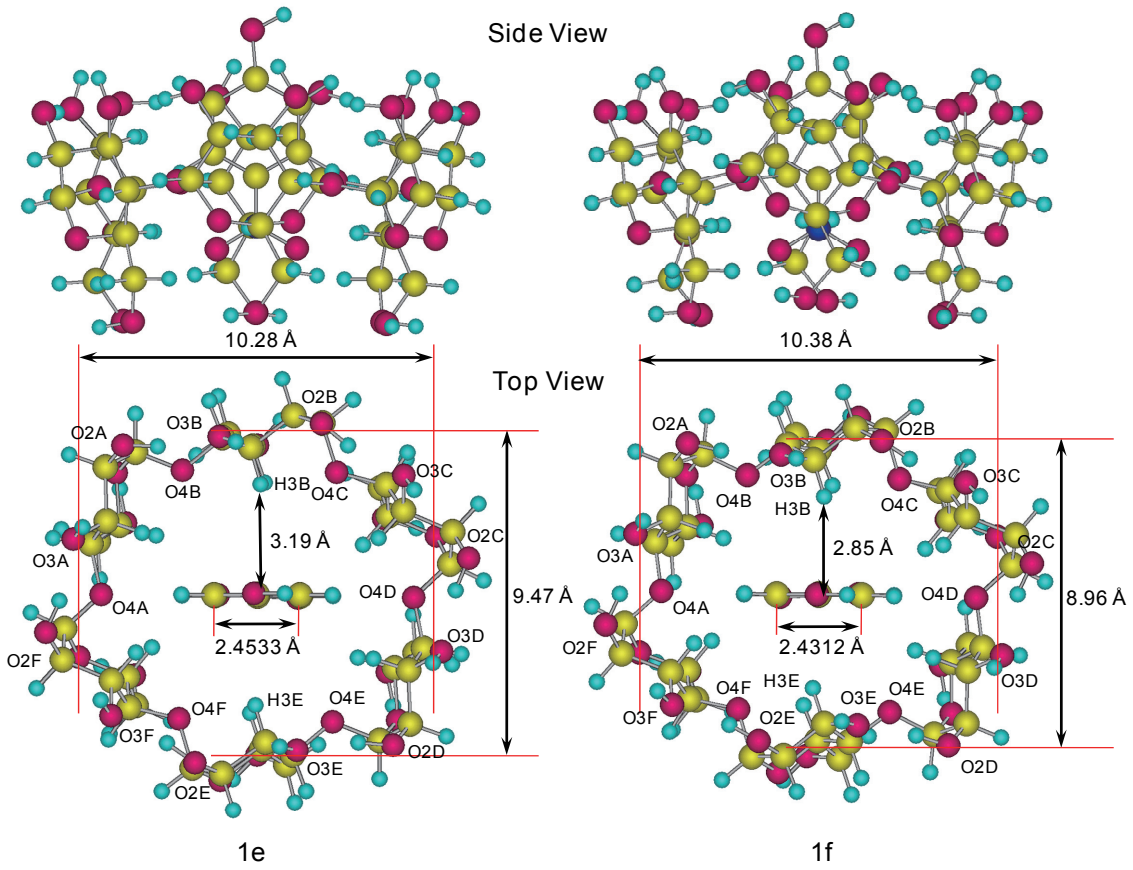


Figure 5: The structures by B3LYP/3-21+G** (**1e**) and MPW1B95/3-21+G** (**1f**) with solvent effect. As for the colored ball, yellow, red, blue, and aqua express carbon, oxygen, nitrogen, and hydrogen, each.

Table 2: The distances (Å) of oxygen atoms of inter-glucose rings

| | O2F···O3A | O2A···O3B | O2B···O3C | O2C···O3D | O2D···O3E | O2E···O3F |
|---|---|---|---|---|---|---|
| **1a** | 3.068 | 2.862 | 3.135 | 2.846 | 2.650 | 2.859 |
| **1b** | 2.725 | 2.771 | 2.793 | 2.882 | 2.724 | 2.763 |
| **1c** | 2.803 | 2.722 | 2.756 | 2.795 | 2.723 | 2.755 |
| **1d** | 2.768 | 2.690 | 2.732 | 2.706 | 2.667 | 2.706 |
| **1e** | 2.740 | 2.711 | 2.724 | 2.757 | 2.691 | 2.728 |
| **1f** | 2.787 | 2.748 | 2.781 | 2.777 | 2.755 | 2.765 |

As the detail interactions between host and guest molecules, the donor-accepter interactions of **1f** were analyzed using NBO program. The obtained stabilization energies by the electron donation were 9.11 and 21.01 kcal/mol from the host to the guest and from the guest to the host, respectively. The principal interactions of 9.11 kcal/mol were 1.95 and 2.11 kcal/mol stabilization energies from the lone pair on O4A and O4D to σ*-H2'-C2' and σ*-H2-C2, respectively (Table 3). The details of the 21.01 kcal/mol were also shown in Table 4. The vacant σ*-H3-C3 and σ*-H5-C5 orbitals on each glucopyranoside unit expanded to inside and these orbitals worked as main electron accepters from *p*-nitrophenol. The

electrons at π-orbitals and σ-H-C orbitals of aromatic ring were donated to mainly the σ*-H3-C3 and σ*-H5-C5 orbitals on glucopyranoside units A, C, D, and F. The orbitals σ*-H5A-C5A, σ*-H5C-C5C, σ*-H5D-C5D, and σ*-H5F-C5F were accepted additional electron donations from lone pairs at oxygen atoms of $NO_2$ group, therefore the large stabilization energies were obtained.

Table 3: The stabilization energies from the host to the guest

| Donor | Accepter | Stabilization energy [kcal/mol] |
|---|---|---|
| O4A | σ*-H2'-C2' | 1.95 |
| O4D | σ*-H2-C2 | 2.11 |
| σ-C5A-H5A | Mainly σ*-H2'-C2' | 0.48 |
| σ-C5C-H5C | Mainly σ*-H2-C2 | 0.45 |
| σ-C5D-H5D | Mainly σ*-H2-C2 | 0.39 |
| σ-C5F-H5F | Mainly σ*-H2'-C2' | 0.49 |
| Total of the other small interactions | | 3.24 |
| Total | | 9.11 |

Table 4: The stabilization energies from the guest to the host

| Donor | Accepter | Stabilization energy [kcal/mol] |
|---|---|---|
| Mainly σ-H-C, π-C-C, and lone pairs of $NO_2$ group | σ*-H3A-C3A | 1.22 |
| | σ*-H5A-C5A | 2.18 |
| | σ*-H3B-C3B | 0.58 |
| | σ*-H5B-C5B | 0.08 |
| | σ*-H3C-C3C | 0.45 |
| | σ*-H5C-C5C | 3.35 |
| | σ*-H3D-C3D | 1.38 |
| | σ*-H5D-C5D | 3.40 |
| | σ*-H3E-C3E | 0.00 |
| | σ*-H5E-C5E | 0.06 |
| | σ*-H3F-C3F | 0.96 |
| | σ*-H5F-C5F | 2.90 |
| Total of the other small interactions | | 4.55 |
| Total | | 21.01 |

## Conclusion

The structure optimizations of the large inclusion complex composed of α-cyclodextrin with *p*-nitrophenol were carried out by density functional theory and the result of the calculation using recently reported new functional MBW1B95 level with 3-21+G** basis set showed basically good correspondence to the X-ray crystallographically determined structure. Using the obtained structure, the detail analyses between donor and accepter orbitals were performed. The stabilization energies were obtained mainly by the electron donation from the guest molecule to the vacant σ*-H3-C3 and σ*-H5-C5 orbitals, and additionally by the electron donation from the lone pairs on anomeric O4s, σ-H3-C3, and σ-H5-C5 orbitals to the guest molecule.

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