Interactive Force between Cyclodextrin Inclusion Complexes Studied by Atomic Force Microscopy

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Change in the intermolecular interaction between cyclodextrins (CyDs) with guest materials was observed by measuring the adhesion force using atomic force microscopy (AFM) in air. The observed adhesion force with water as the guest material is weaker for α-CyD (composed of 6 glucose) than β-CyD (7 glucose), contrary to the fact that α-CyD is more hydrophilic than β-CyD, indicating that the intrinsic interaction of molecules could be obtained separately from the meniscus force even in air. In addition, the adhesion force depends on the type of guest molecules (H_2O, para-nitrophenol, and triethylendiamine) for α-CyDs, but not for β-CyDs. The observed change was explained well by the change in the dipole moment induced by the structural deformation due to the guest materials.

KEYWORDS: intermolecular interaction, cyclodextrin, atomic force microscopy, adhesion force, inclusion complexes

1. Introduction

Cyclodextrins (CyDs), which are doughnut-shaped oligosaccharides (Fig. 1), have been attracting considerable attention because of their significant potential for applications using their ability to form host-guest compounds. In addition to the well-known development in applications such as molecular delivery,[1] molecular shuttle,[2,3] and indicators for detecting organic compounds,[4] recent success in the formation of film structures of CyD molecules opened up the opportunity for further development of molecular recognition devices such as ion channels and so on.[5,6] CyD molecules consist of glucose units linked in a cyclic form. When the number of linked glucose units is 6 or 7, they are called α- and β-CyD, respectively. Characteristic properties of CyDs change with their size depending on the number of linked glucose units. For example, the diameters of the cavity are 0.45 and 0.7 nm for α- and β-CyDs. Their molecular inclusion selectivity strongly depends on their size.

Recently, structural analysis of self-assembled CyD films two-dimensionally grown on a highly oriented pyrolytic graphite (HOPG) surface was performed on an atomic scale using scanning tunneling microscopy (STM).[7–9] According to the results, the observed molecular structures strongly depend on the type of inclusion compounds present. For example, STM images of the α- and β-CyDs with H_2O molecules show similar channel-like structures with two-fold symmetry, but β-CyD is more densely packed than α-CyD. When para-nitrophenol was chosen as the guest material, α-CyD showed a three-fold symmetric arrangement. Since molecular arrangement depends on the interaction between molecules, the obtained results indicate a clear change in the interaction between CyD molecules depending on the kind of inclusion complexes. In order to deduce and make further use of the potential of this material, analysis of the molecular interaction
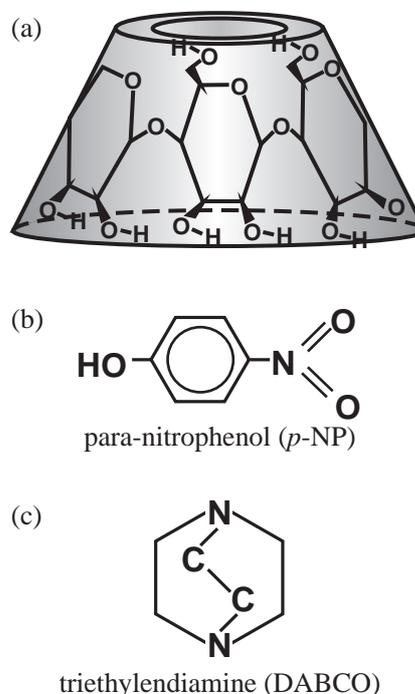
Fig. 1. Schematics of (a) cyclodextrin, (b) para-nitrophenol, and (c) triethylendiamine molecules.

on an atomic scale is very important and urgently needed.

In consideration of this requirement and the experimental results regarding CyD molecules mentioned above, we attempted to estimate the intermolecular interaction between CyD inclusion complexes using atomic force microscopy (AFM) on the self-assembled CyDs. AFM is well known as a promising technique for the measurement of the interaction between two materials on an atomic scale.[10] We succeeded in observing the differences in the molecular interaction depending on the type of inclusion complexes.

2. Experiments

Self-assembled films of CyD molecules were prepared by dropping the aqueous solution of α- or β-CyDs with guest molecules onto a freshly cleaved HOPG substrate.[9] The concentration of the solution was 1 mM. Three types of molecules of different sizes were used as guest molecules; water (H_2O), para-nitrophenol (p-NP), and triethylendiamine (DABCO). When no additional molecule exists in the solution, water is included in CyDs. The schematic structures of p-NP and DABCO molecules are shown in Figs. 1(b) and 1(c), respectively. β-CyD includes all guest molecules, but α-CyD does not in the case of DABCO, because the size of the DABCO molecule is larger than that of the α-CyD cavity.

We focused on the change in the magnitude of adhesion force depending on the guest molecules. The force curve on the freshly cleaved HOPG surface was used as a reference. After all force curve measurements on the CyD thin film surfaces, we measured the force curves on the freshly cleaved HOPG surface again in order to check the tip condition. All experiments were performed in air at room temperature. V-shaped silicon nitride (Si_3N_4) cantilevers (Olympus Co., Japan) with a leg length of $200\,\mu$m and leg width of 20 μm were used in this study. The spring constants of each cantilever were about 0.08 N/m. The force curves were measured within the range from 500 nm to -100 nm of tip-sample distance.

3. Results and Discussion

In order to measure the interaction between CyDs, the interaction between the AFM tip and the CyDs must be stronger. The Si_3N_4 tip surface is covered with an oxide film. CyD molecules have many hydroxyl groups on both sides of the cavity, which are called primary and secondary hydroxyl groups, as shown in Fig. 1(a). Therefore, hydrogen bond interaction is expected to exist between hydroxyl groups of the tip oxide and those of CyD molecules. When CyD molecules are adsorbed on the tip during the force curve measurements on the CyD film, the adhesion force between the tip and the clean HOPG is supposed to change before and after the force curve measurements on the CyD thin film. Figure 2 shows the force distributions measured on freshly cleaved HOPG surface (a) before and (b) after force curve measurements on a CyD thin film surface. After force curve measurements on the CyD thin film surface, the average value of the adhesion force was 3.4 nN, larger compared to that before the measurements, 2.9 nN, as expected.

Then, in order to consider the effect of the meniscus force first, we compared the adhesion force between α- and β-CyD in the case of the guest molecule of water. Since CyD molecules are solable in water, measurements were carried out in air. However, when the adhesion force is measured in air, the influence of the meniscus force caused by the water layer adsorbed on the sample surface is critical for the analysis of the intrinsic interaction between CyD molecules. If the meniscus force is dominant in the measurement, the hydrophilicity of samples is reflected in the adhesion force. Figure 3 shows the force distributions obtained for (a) α- and (b) β-CyDs. The average values of the adhesion forces between α- and β-CyDs were about 6.1 nN and 7.2 nN, respectively.

It is well known that the solubility in water (g/100 ml) of

α- and β-CyD molecules is 14.5 and 1.85, respectively, i.e., α-CyD is more hydrophilic than β-CyD. Therefore, more water is adsorbed on the α-CyDs compared to the β-CyDs. The value of the adhesion force is expected to be larger for α-CyD than β-CyD. However, the measured values of the adhesion
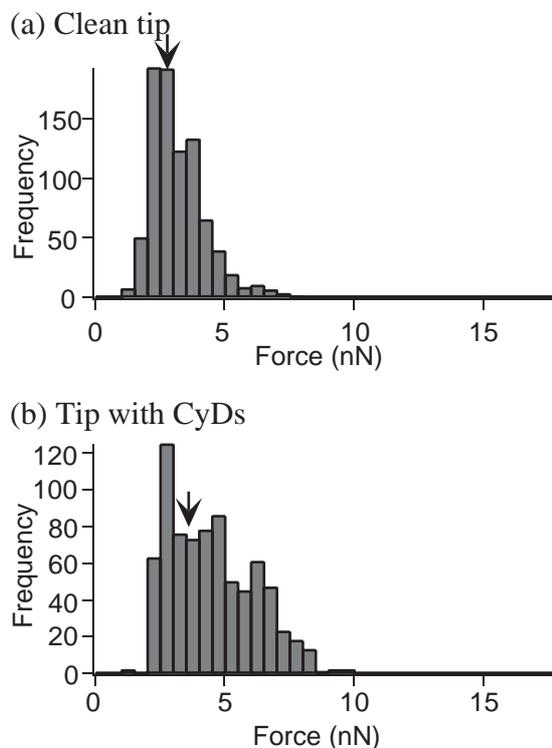
Fig. 2. Force distributions measured on fleshly cleaved HOPG surface (a) before and (b) after force curve measurements on a CyD thin film surface.

Fig. 3. Force distributions measured on (a) α-CyD and (b) β-CyD self-assembled film surface.

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force for α- and β-CyDs showed opposite results to those described above. Namely, besides the effect of the meniscus force, the intrinsic adhesion forces between CyDs could be observed. In fact, as mentioned above, according to the STM images, β-CyDs are more densely packed than α-CyD,[7] indicating that the interaction between β-CyDs is stronger than that of α-CyDs.

Next, in order to analyze the interaction between CyDs more in detail, we analyzed the influence of guest molecules. Figures 4 and 5 show the force distributions of α- and β-CyDs with guest molecules of (a) *p*-NP and (b) DABCO, respectively. Schematics of the molecular structures used are also shown in Figs. 4 and 5. The obtained values are summarized in Table I. In the case of α-CyD, the average value of the adhesion force increased with *p*-NP (~ 7.2 nN), while that with DABCO decreased (~ 5.8 nN) compared to the case with H_2O (~ 6.1 nN). (In the case of DABCO, there was another small peak at ~ 12.3 nN. Since the adhesion force of the pure DABCO was greater than that of α-CyDs, the small peak was considered to be influenced by pure DABCO such as by its clusters.) Namely, the adhesion forces changed drastically depending on the guest molecules. On the other hand, in the case of β-CyD, the average value of the adhesion force did
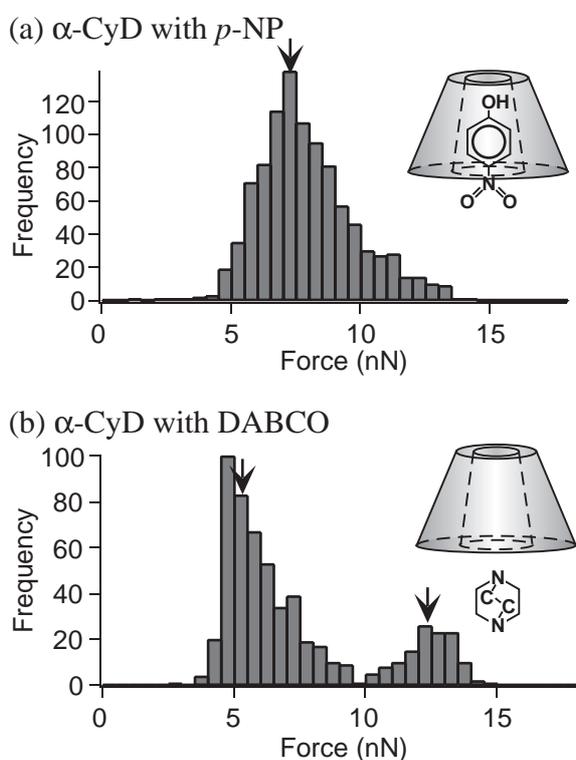
not change as much (~ 7.2 nN for H_2O, ~ 7.3 nN for *p*-NP, and ~ 7.4 nN for DABCO).

In order to understand the effect of the guest molecules on the CyDs, characteristic structures of the α- and β-CyDs are summarized first. As is well known, CyD molecules have intramolecular hydrogen bonds between O-2 hydroxyl groups of a glucose molecule and O-3' hydroxyl groups of the adjacent glucose molecule.[11] In the case of β-CyD, the distance between O-2 and O-3' on the adjacent two glucose molecules is short enough to form a hydrogen bond, and a rigid round structure is maintained without distortion. However, in the case of α-CyD, the CyD ring is distorted from the regular polygonal symmetry to form the hydrogen bond because the original distance between O-2 and O-3' on the adjacent two glucose molecules is too great. As a result of the distortion, two intramolecular hydrogen bonds in α-CyD are disrupted because of the inclination of the related glucose units.

When α-CyD includes *p*-NP, the distortion of the CyD structure is eliminated and the structure becomes more symmetric. According to the recent results of theoretical calculation, CyD molecules have a large dipole moment.[9,12] Also, an electrostatic potential gradient is present in the cavity of α-CyD molecules.[13] Therefore, electrostatic interaction exists between α-CyD molecules and guest molecules when they form the inclusion complexes. In addition, when they include large guest molecules such as *p*-NP, the guest molecules change the inclination of the glucose units and the CyDs take the symmetric macrocyclic structure. The theoretical calculation shows that the direction and magnitude of the dipole moment of α-CyD molecules is changed by the guest inclusion.[9,12] This change must influence the intermolecular

Table I. Average values of the adhesion force obtained for the inclusion complexes (nN).

Host	Guest		
	H_2O	*p*-NP	DABCO
α-CyD	6.1	7.3	—
β-CyD	7.2	7.3	7.4

Fig. 4. Force distributions measured on self-assembled film surfaces of α-CyDs with guest molecules ((a) *p*-NP and (b) DABCO). Insets are the schematics of each inclusion complex.
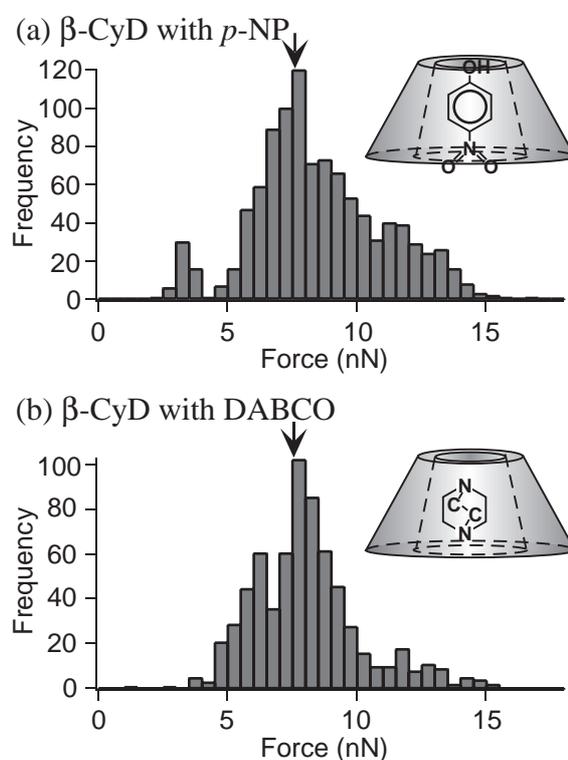
Fig. 5. Force distributions measured on self-assembled film surfaces of β-CyDs with guest molecules ((a) *p*-NP and (b) DABCO). Insets are the schematics of each inclusion complex.

interaction of the CyDs.

On the other hand, the structure of β-CyD is symmetric and very rigid from the beginning, and inclusion of *p*-NP and DABCO does not have a significant influence on the structure. β-CyD molecules have a large dipole moment, however, little electrostatic potential gradient is present in the cavity of the β-CyD molecules.[12] Therefore, β-CyDs interact less electrostatically with guest molecules even if they form inclusion complexes. Accordingly, it is considered that the change in the dipole moment induced by guest inclusion, which is observed for α-CyD, does not occur in the case of β-CyD. On the basis of the above discussion, the change in the dipole moment induced by the structural change of host CyD molecules is considered to be the major factor in the observed difference between the observed adhesion forces. This is in good agreement with the STM results which show that the structural arrangement of the CyD inclusion complexes can be explained on the basis of the change in the dipole moment induced by the guest molecules.

When DABCO molecules were mixed with α-CyD molecules, they did not form inclusion complexes because of the steric hindrance between the size of the cavity of α-CyD and DABCO molecules. Therefore, DABCO molecules are considered to prevent the interaction between α-CyD molecules, and the adhesion force of the mixture of α-CyD and DABCO molecules was reduced compared to the complexes of α-CyD with H_2O and *p*-NP molecules.

4. Conclusions

Change in the intermolecular interaction between CyDs with guest materials was observed by measuring the adhesion force using AFM in air. The observed adhesion force with water as the guest material is weaker for α-CyD than for β-CyD, contrary to the fact that α-CyD is more hydrophilic than β-CyD, indicating that the intrinsic interaction of molecules

could be obtained separately from the meniscus force even in air. In addition, the adhesion force depends on the type of guest molecules (H_2O, para-nitrophenol, and triethylendiamine) for α-CyDs, but not for β-CyDs. The observed change was explained well by the change in the dipole moment induced by the structural deformation due to the guest materials.

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