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Detection of Odorant Molecules in the Gaseous Phase Using α-, β-, and γ-Cyclodextrin Films on a Quartz Crystal Microbalance

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Received: 13 June 2018; Accepted: 5 July 2018; Published: 6 July 2018



Abstract: There is an interest in sensors for the detection of odorant molecules in the gaseous phase, especially those related to the fragrance of fruits, because odorant sensing is useful for on-site quality control of agricultural products. Previously, gas-chromatographic methods requiring bench-top devices were used for odorant-molecule detection. Herein, we report an odorant sensor based on cyclodextrins (CDs) as a stable odorant receptor, using a highly mass-sensitive and quantitative 27-MHz quartz crystal microbalance (QCM) device, which has the advantage of possible incorporation into portable devices. When ethyl butyrate (a model odorant molecule for fruit fragrances) was flowed onto a QCM plate modified with α-, β-, or γ-CD network films, a decrease in frequency was observed (corresponding to an increase in mass), owing to the capture of odorant molecules by CD molecules. The CD films were capable of capturing and releasing odorant molecules, depending on the type of CD (α-, β-, or γ-CD). Thus, these sensors are reusable for odorant-molecule sensing, and are applicable to pattern recognition of odorant molecules. Thus, sensors based on CD films combined with a QCM handheld device could be applied to monitoring the condition of fruits.

Keywords: quartz crystal microbalance; cyclodextrin; odorant sensing; ethyl butyrate; limonene

1. Introduction

Chemical sensors and biosensors for the detection of volatile gaseous molecules attract research attention [1–3]. The gas-sensing of volatile organic compounds (VOCs), such as benzene, toluene, and xylene, is important for the air safety of indoor environments [4–6]. The detection and quantification of odorant molecules from fruits are useful for quality control in agriculture, due to reports that fragrance intensity may be related to the maturity of fruits [7,8]. As another example, in the food industry, odor evaluation is also required for the quality control of processed foods and drinks [2]. Thus, on-site sensor devices are desirable for the sensory analysis of odorants related to the fragrance of fruits.

In general, flavoring and aromatic volatile molecules can be quantitatively analyzed using gas chromatography (GC) or using GC coupled with mass spectrometry (GC/MS) [7]. These chromatographic methods are performed using bench-top devices that include gas cylinders to provide carrier gases, and also column ovens and detectors. However, handheld sensors are desirable

for on-site detection of volatile molecules. Quartz crystal microbalances (QCMs) [9,10], electrochemical analyzers for the detection of resistance changes in conducting polymers [11,12], and optical fibers [13] are candidates for handheld sensor devices, after previous experiments were performed combining electrospun nanofibers for the development of sensors that detect gases such as VOCs, NH_3, NO_2, alcohols, and CO_2 [14]. A QCM device, which is a mass-sensitive device, is advantageous owing to its potential for incorporation into portable devices [15]. Thus, a QCM combined with a receptor for odorant molecules could be applicable in portable olfactory devices.

Various inorganic and organic materials are employed as receptors for gases, including indium tin oxide for NO detection [16], graphene for NO_2 and NH_3 detection [17], polyacrylic acid (PAA) for NH_3 detection [9,10], and imprinted polymers of PAA or methacrylic acid for the detection of VOCs [18]. To capture organic and biological odorant molecules, various biomaterials are used, including lipids for fruit-flavor detection [19], enzymes for toluene detection [20], and olfactory receptors for the detection of various volatile molecules [3,21]. Although biomaterials exhibit highly sensitive and selective detection, they often lack the stability required for use as receptor materials in on-site sensors.

Cyclodextrins (CDs) are cyclic oligosaccharides composed of 6–8 α-1,4-D-glucopyranose units called α-, β-, and γ-CD, respectively. CDs have a cavity, similar to enzymes and olfactory receptors, that can capture small molecules, making them potential candidates for use as stable receptors. CDs are mainly applied to the detection of VOCs, such as benzene, toluene, and xylene [22–25]. CDs were also applied to the detection of fruit flavors, but this method used a UV-Vis spectrophotometric technique in aqueous solution, not in air [26].

We focused on the detection of odorant gaseous molecules related to the fragrance of fruits. In this study, we demonstrated the capture capability of CDs for ethyl butyrate and limonene, which were selected as model odorant molecules for fruit fragrances, using a highly sensitive 27-MHz QCM device [27–29] (Figure 1). CD thin films prepared with α-, β-, or γ-CD were expected to possess molecular-size selectivity, resulting in pattern recognition. Fruit fragrances generally contain several odorant molecules. Since a QCM can measure the captured molecules as a mass, it is possible to quantitatively compare the amounts which are captured by different receptors. Thus, it could be beneficial to utilize QCMs, equipped with multiple receptors such as CDs, as odor sensors for fruits.

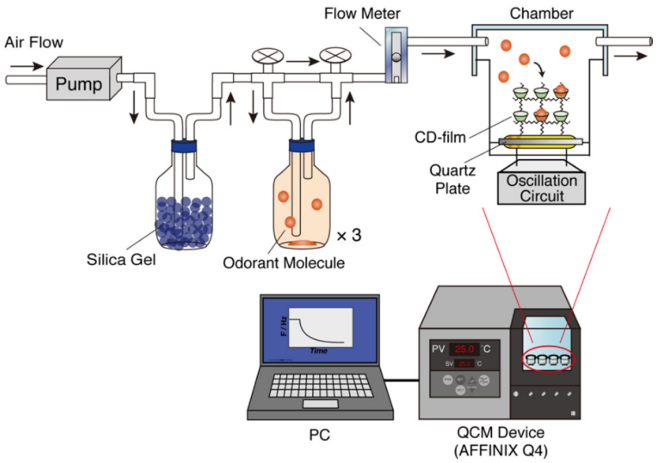


Figure 1. Schematic illustration of an airflow system combined with a quartz crystal microbalance (QCM) device modified with cyclodextrin (CD) films for odorant molecule detection.

2. Materials and Methods

2.1. Materials

Ethylene glycol diglycidyl ether (EGDE) and pentaerythritol were purchased from Tokyo Chemical Industry (Tokyo, Japan), while α-cyclodextrin (α-CD), β-cyclodextrin (β-CD), and ethyl butyrate were

purchased from Nakalai Tesque Inc. (Kyoto, Japan). Cystamine dihydrochloride, γ-cyclodextrin (γ-CD), limonene, and sodium hydroxide (NaOH) were purchased from Wako Pure Chemical Industries (Osaka, Japan). Sodium borohydride ($NaBH_4$) was purchased from Sigma-Aldrich Japan (Tokyo, Japan). Additionally, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) was purchased from Dojindo Laboratories (Kumamoto, Japan). All other reagents were purchased from Wako Pure Chemical Industries (Osaka, Japan). Type-1 ultrapure water (Milli-Q™ water, Merck Ltd., Tokyo, Japan) was used in all experiments.

2.2. Preparation of α-, β-, and γ-CD Films on QCM Sensor Surfaces

A QCM sensor cell designed for an AFFINIX Q4 system (Initium Co., Ltd., Tokyo, Japan) was employed in this study as a 27-MHz QCM device. The sensor cell, with a volume of 500 μL, was equipped with an AT-cut quartz plate with a diameter of 8.7 mm, which had a gold electrode of 5.7 mm^2 in area attached at the bottom of the cell [27–29]. CD films were prepared on the gold electrode (Figure 2). Firstly, the gold electrode was cleaned by treatment with fresh Piranha solution (concentrated sulfuric acid:hydrogen peroxide = 3:1; caution: this solution reacts violently with organic materials and must be handled with extreme care). The cleaned electrode was soaked in an aqueous solution of 5 mM cystamine for 1 h to immobilize amino groups on the electrode. After rinsing with Milli-Q water, the sensor cell was filled with 500 μL of EGDE solution (1 mM), buffered with 10 mM HEPES/NaOH (pH 8.0) for 1 h to immobilize epoxide groups on the sensor surface through reaction of EGDE with the amino groups. The sensor cell was rinsed with HEPES buffer, and then filled with 20 μL of CD solution, prepared by mixing 20 μL of 3 wt% EGDE aqueous solution with 100 μL of 8 M NaOH solution containing 5 mg of CD (α-, β-, or γ-CD) or pentaerythritol and 0.05 mg of $NaBH_4$. After incubating for 20 min at 20–23 °C, the sensor surface was rinsed three times with 500 μL of Milli-Q water to quench the reaction, and to remove unreacted reagents from the film.

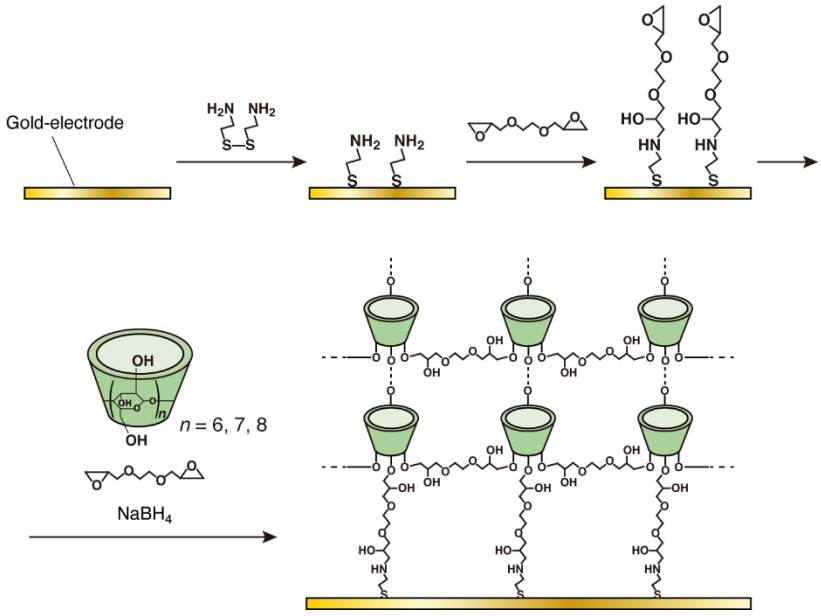


Figure 2. Schematic illustration of the process for preparing a CD film networked with ethylene glycol diglycidyl ether (EGDE) on a sensor surface.

2.3. QCM Setup and Odorant Molecule Detection

An AFFINIX Q4 system, capable of including four QCM sensor cells, was used to evaluate the amount of sensing film prepared on the sensor surface, and to carry out odorant-molecule detection. An airflow injection system was constructed for odorant-molecule detection, as shown in Figure 1.

The system consisted of a diaphragm air pump (discharge amount: 0–1000 mL min^{-1}), a silica bottle (volume: 1.15 L) to dry the air flow, flow-path switches, sample bottles (volume: 1.15 L × 3 bottles), a flow meter to control the air-flow rate, a measurement chamber (volume: 40 mL) to cover the four QCM cells, and an exhaust tube. These components were connected via tubes with inner diameters of 3 mm.

A QCM sensor cell, modified with the CD film on the electrode, was set in the cell holder of the AFFINIX Q4 system, and the cell cover was attached to form the measurement chamber. Dry air was flowed through a silica bottle at a rate of 100 mL min^{-1} to dry the films and to pre-equilibrate the system. After the resonance frequency of the QCM stabilized, in the range of ±2 Hz (±10 Hz h^{-1}), air containing a predetermined concentration of an odorant molecule (ethyl butyrate or limonene) was injected into the QCM chamber for 10 min. Frequency changes with time were then monitored. In order to prepare a bottle filled with different concentrations of an odorant molecule, it was necessary to obtain the liquid form of the odorant molecules as the required concentrations were poured into an empty bottle, and then vaporized. The bottle was connected to the flow system, and was used for the experiments of odorant-molecule detection.

The frequency value is known to decrease linearly following nanogram-level increases in the mass of the gold electrode attached to the quartz plate. The mass change (Δm) can be calculated from the frequency change (ΔF) using Equation (1). Specific details are described in previous papers [27–29].

$$\Delta m \text{ (ng cm}^{-2}\text{)} = -0.62\Delta F \text{ (Hz)}. \quad (1)$$

3. Results and Discussion

3.1. Reaction Time for CD-Film Preparation

The employment of a large amount of CDs as odorant-molecule receptors on a sensor surface is advantageous for detecting small molecules using a mass-sensitive QCM sensor. The hydroxyl groups of CD can react with epoxy groups to form ether bonds [30]. Therefore, we prepared networked CD films on the sensor surface of a QCM by using EGDE, which has epoxy groups at both ends, as a covalent linker (Figure 2). When the mass increase associated with the preparation of the β-CD film on the sensor surface was evaluated using the QCM device, we found that the amount of film was maximized at a reaction time of 20 min (Figure 3). At a reaction time of 30 min, the film amount decreased owing to hydrolysis of the produced ether bonds with time, under the strongly alkaline conditions (8 M NaOH). Therefore, a reaction time of 20 min was used to prepare each CD film. The mass of the β-CD film with a reaction time of 20 min was calculated to be 1860 ng cm^{-2} from the ΔF value using Equation 1 (Figure 2). The prepared CD film was estimated to be a multilayered CD film in comparison with the mass of a β-CD monolayer film (93 ng cm^{-2}), calculated as a closest-packing monolayer of β-CD molecules (diameter: 1.5 nm, M_w: 1135). Thus, the networked CD film can capture more odorant molecules than that of the monolayer film.

Each α-, β-, and γ-CD film was prepared on the sensor surface with a reaction time of 20 min. Pentaerythritol, which has four hydroxymethyl groups on one carbon atom, was used to prepare a control film. The amount of CD film deposited on the sensor surface depended on the size of the CD: α-CD (1500 ng cm^{-2}), β-CD (3130 ng cm^{-2}), and γ-CD (4230 ng cm^{-2}; Table 1). This tendency may be explained by the effect of the number of primary hydroxyl groups and steric hindrance on the ease of reaction with the linker reagent. The amount of pentaerythritol film was 2760 ng cm^{-2}. Pentaerythritol has a smaller number of hydroxyl groups, but they may react easily, in terms of steric hindrance. It was difficult to control the film amount owing to the severe reaction conditions. The average amounts, and the standard deviation of each α-, β-, and γ-CD film prepared three times were 1220 ng cm^{-2} ± 260, 3580 ng cm^{-2} ± 570, and 3250 ng cm^{-2} ± 850, respectively. Therefore, these films, with the varying amounts listed in Table 1, were used for odorant-molecule detection.

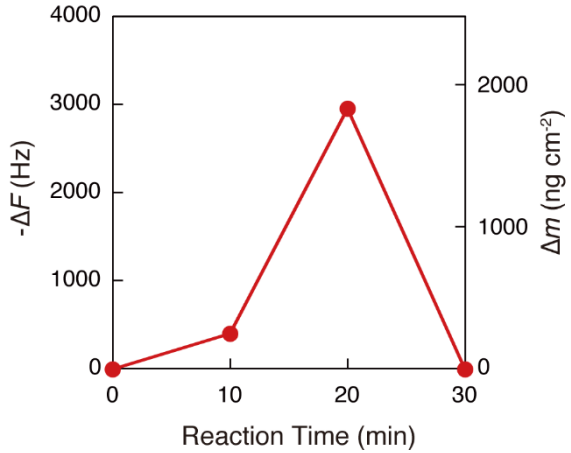


Figure 3. Dependence of the amount of β-CD film immobilized on the QCM sensor surface on the reaction time.

Table 1. Amount of odorant molecules captured on each cyclodextrin (CD) film.

Film	Δm_{film} (ng cm^{-2})	CD Content *1 [normalized] *2 (nmol cm^{-2})	Ethyl Butyrate *3			Limonene *3		
			Δm *4 [normalized] *2 (ng cm^{-2})	Molecule [normalized] *2 (nmol cm^{-2})	Occupancy *5 (normalized) *6	Δm *4 [normalized] *2 (ng cm^{-2})	Molecule [normalized] *2 (nmol cm^{-2})	Occupancy *5 (normalized) *6
α-CD	1500	1.23 [2.46]	14.9 [29.8]	0.128 [0.256]	0.10 (1)	53.3 [107]	0.391 [0.783]	0.32 (1)
β-CD	3130	2.21 [2.12]	102 [98.4]	0.875 [0.847]	0.40 (4.0)	283 [274]	2.08 [2.01]	0.95 (3.0)
γ-CD	4230	2.61 [1.85]	51.5 [36.8]	0.443 [0.317]	0.17 (1.7)	144 [103]	1.06 [0.757]	0.41 (1.3)

*1 Calculated as the content ratio of 80% of the film mass (Δm_{film}); *2 normalized to a film amount of 3000 ng cm^{-2}; *3 the odorant-molecule concentration was 0.66 mmol L^{-1}; *4 baseline corrected using the value for 0 mM of odorant molecules; *5 calculated with Equation (4), see text for details; *6 normalized with the value of α-CD set as 1.

3.2. QCM Response during Odorant-Molecule Detection

Ethyl butyrate is a fragrance component of various fruits, including banana and mango. We observed the adsorption behavior of ethyl butyrate on each CD film as a mass change using a QCM device (Figure 4). When dry air including 0.66 mmol L^{-1} of vaporized ethyl butyrate was added to the QCM chamber at 25 °C, the frequency of the QCM with the β-CD film decreased (corresponding to a mass increase), as shown in Figure 4, curve b. After 10 min, the flow was switched to dry air containing no odorant molecules, and the frequency returned to the baseline. Although small baseline shifts were observed, these binding and release behaviors were observed repeatedly in the flow experiments (Supplementary Materials Table S1). In the case of the pentaerythritol film, the frequency change corresponding to nonspecific binding to the linker and/or pentaerythritol (Figure 4, curve d) was smaller than that observed for the β-CD film. These results indicate that β-CD molecules in the film can capture and release the odorant molecules. In addition, the amount of odorant molecule adsorbed on the α-, β-, and γ-CD films increased in the order of α-CD < γ-CD < β-CD (curves a, c, and b, respectively). Although the differences in film thickness should be taken into consideration, these results suggest qualitatively that the odorant molecules can be captured strongly by β-CD, moderately by γ-CD, and weakly by α-CD. This trend may indicate that the α-, β-, and γ-CD films exhibit molecular-size selectivity.

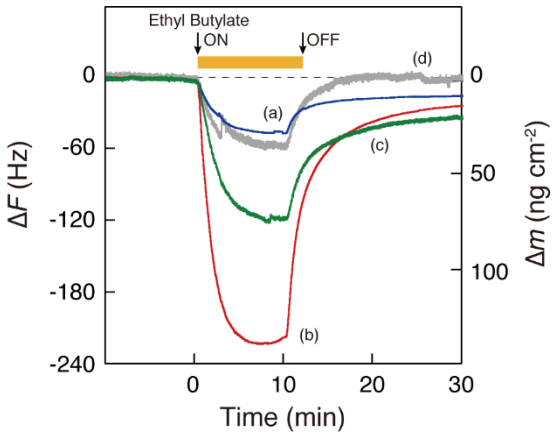


Figure 4. Time courses of the frequency change (Δ*F*) for QCM plates modified with (a) α-, (b) β-, and (c) γ-CD films, and (d) the pentaerythritol film, in response to a flow of 0.66 mmol L^{-1} vaporized ethyl butyrate in dry air at a flow rate of 0.1 L min^{-1} for 10 min, indicated by the orange bar at 25 °C.

3.3. Concentration Dependence of Odorant-Molecule Adsorption

We examined the relationship between the concentration of odorant molecules and the amount of molecules captured by the CD films. For comparison on each film, frequency changes (Δ*F*) observed at odorant-molecule concentrations in the range of 0–5.4 mmol L^{-1} were normalized to a film amount of 3000 ng cm^{-2} for each CD film ($\Delta F_{normalized}$), and were then plotted against concentration (Figure 5). The α-CD and γ-CD films only showed a slight dependence on the concentration. In contrast, the changes observed for the β-CD film with adsorption of ethyl butyrate were much greater. The saturation curves were fitted to the Langmuir adsorption isotherm, as shown by Equation (2).

$$\Delta m = \frac{\Delta m_{max} \cdot [OM]}{K_d + [OM]}, \quad (2)$$

where Δm and Δm_{max} are the mass of molecules captured on the film and the maximum value, respectively, [OM] is the concentration of odorant molecules, and K_d is the dissociation constant. The Δm_{max} value for the β-CD film was found to be 172 ng cm^{-2}, meaning that 0.7 molecules of ethyl

butyrate were captured by each molecule of β-CD when the CD content, subtracting the linker part from the film mass, was calculated as 80% of the mass of a 3000 ng cm^{-2} film, assuming that two to three linker molecules were contained per CD in a film (Figure 5A). The K_d value for the β-CD film and ethyl butyrate in the gaseous phase was calculated to be 0.61 mmol L^{-1}. K_d values of 18–480 mmol L^{-1} were reported for β-CD and various fruit flavors in aqueous solution [26]. The smaller K_d value (meaning larger affinity) observed in this study could be the result of odorant molecules being captured easily by β-CD molecules without replacing water molecules in the CD cavity. To determine the limit of detection (LOD) of the β-CD film on the QCM device for ethyl butyrate, we fitted the data linearly in the range of 0–0.66 mmol L^{-1}. The LOD value was calculated to be 0.2 mmol L^{-1} from the slope of the linear approximation and the standard deviation (SD) at 0 mM of ethyl butyrate, as shown in Figure 5B, using Equation (3).

$$\mathrm{LOD} = \frac{3.3\mathrm{SD}}{\mathrm{Slope}}. \tag{3}$$

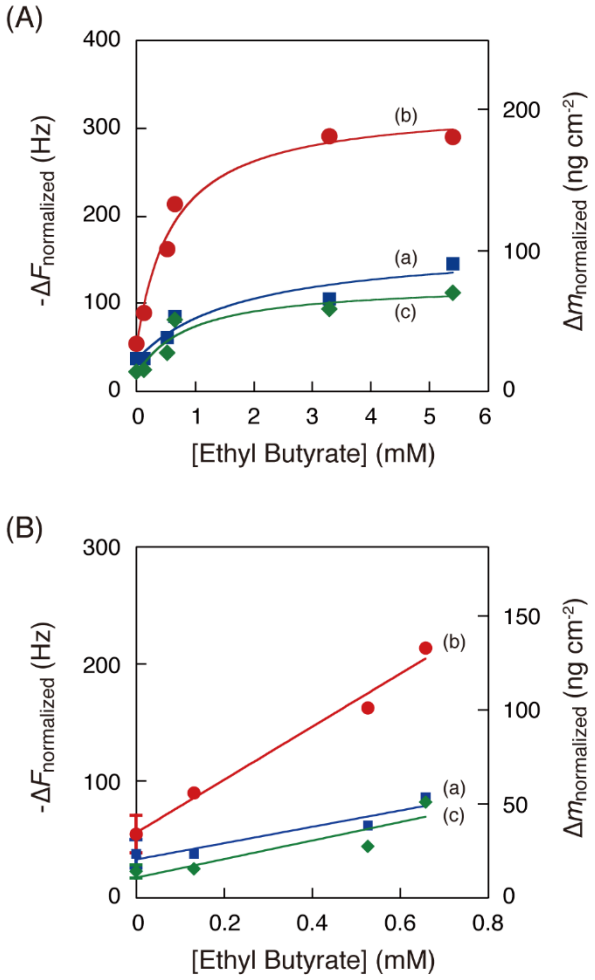


Figure 5. (**A**) Saturation curves for the adsorption of ethyl butyrate on (a: square) α-, (b: circle) β-, and (c: diamond) γ-CD films, as a function of concentration. (**B**) Linear approximation in the range of 0–0.66 mmol L^{-1} ethyl butyrate. The error bars at the origin indicate the standard deviation. The ΔF values were normalized to a film amount of 3000 ng cm^{-2}.

The total content of fragrance compounds in banana was reported to be 8–16 ng per g of fruit [31]. By using a 1-cm^2 sensing seal adhered to the surface of a fruit of ~1 g with close contact (10 μm) to form 10^{-6} L of space, the concentration in the space between the surface and a sensor was estimated to

be 8–16 mg L^{-1} (0.16–0.32 mmol L^{-1} for a molecular weight of 50). Thus, the LOD obtained in this study suggests the possibility of the detection of odorant molecules.

3.4. Response to Different Odorant Molecules

To assess the ability of the CD films to detect different odorant molecules, we investigated the response of the QCM device with each CD film toward limonene, which is a known fragrance compound in citrus fruits, such as lemon and orange. Vaporized limonene (0.66 mmol L^{-1}) was flowed into the chamber with QCM sensors modified with each CD film, and the frequency changes were observed in the same manner as for ethyl butyrate (Supplementary Materials Figure S1). Because the molecular weights of ethyl butyrate and limonene are different, the molecular occupancy, as defined by Equation (4), was calculated to compare the adsorption amounts of each odorant molecule.

$$[\text{molecular occupancy}] = \frac{[\text{odorant molecule}]_{adosorption}}{[\text{receptor molecule}]_{film}}, \quad (4)$$

where $[\text{odorant molecule}]_{adsorption}$ was obtained by dividing Δm for odorant molecules adsorbed on the film by the molecular weight of the odorant molecule, and $[\text{receptor molecule}]_{film}$ was calculated by dividing $\Delta m \times 0.8$ for the film on the sensor surface by the molecular weight of the CD, where the content of each CD was assumed to account for 80% of the film mass, subtracting the linker part from the film mass. These results are summarized in Table 1. Both odorant molecules exhibited greater adsorption on the β-CD film than on the α- and γ-CD films. The molecular occupancy value for limonene on the β-CD film was larger than that for ethyl butyrate, which suggests that limonene, which contains a cyclohexane ring, is the optimal size for capture by β-CD. This observation is consistent with a previous report that bulky moieties, such as six-membered rings, are preferable for binding in the cavities of β-CD molecules [32]. In addition, the occupancy patterns for ethyl butyrate and limonene were different from each other, which suggests that α-, β-, and γ-CD films could allow pattern-sensing of odorant molecules by comparing the different responses of these CD films.

4. Conclusions

We demonstrated that network films of α-, β-, or γ-CD with EGDE linkers are capable of sensing odorant molecules, such as ethyl butyrate and limonene in the gaseous phase, using a highly sensitive 27-MHz QCM device. The CD films showed capture and release within the order of several minutes, allowing their reuse for odorant-molecule sensing. The β-CD film exhibited the maximum capture ability for odorant molecules. The amount of odorant molecules captured on the γ- and α-CD films differed depending on the odorant molecule, indicating the possibility of using these films for pattern recognition of odorant molecules. The estimated LOD of 0.2 mmol L^{-1} for ethyl butyrate, as a model odorant molecule in the gaseous phase, suggests that this approach has the potential for application to the detection of odorant molecules using a small space on the fruit surface. We believe that the CD-film sensor combined with a handheld QCM device will enable the monitoring of fruit condition, without the need for bench-top devices.

Supplementary Materials: The following are available online at http://www.mdpi.com/2227-7080/6/3/63/s1, Table S1: Responses when the sensor was used repeatedly, Figure S1: Observation of binding behaviors of limonene with each CD film.

Author Contributions: K.S. performed the measurements, analyzed the experimental data, and wrote the manuscript. H.F. supervised the entire project, and wrote the manuscript. K.N. and S.T. participated in comprehensive discussions, and provided helpful advice and suggestions.

Funding: This research was funded by the Total Assistance for Seasonal Foods Transportation from Yamagata (TASTY) Program in YU-COE(C) of Yamagata University; grant number C27-3.

Acknowledgments: The authors acknowledge Professor Hideki Murayama of Yamagata University for valuable advice and suggestions regarding fruit fragrances.

Conflicts of Interest: The authors declare no conflict of interest.

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