Dynamic Analyses on Induced-Fit Gaseous Guest Binding to Organic Crystals with a Quartz-Crystal Microbalance

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Abstract: The inclusion behavior of gaseous guest molecules in a solid apohost, an orthogonal anthracene-bis(resorcinol)tetraol (**1**), was investigated with a quartz-crystal microbalance (QCM). Compound **1** forms crystals composed of molecular sheets bound together by an extensive hydrogen-bonded network. An apohost of **1** was cast onto a QCM and the binding of gaseous guest molecules was followed as a function of time by observing the decrease in the oscillation frequency, which is directly related to the increase in mass. Ethyl acetate and methyl ethyl ketone were significantly included into the apohost, whereas benzene and cyclohexane were simply adsorbed onto the surface of the solid; all these guests have similar vapor pressures at 25 °C. On the other hand, a host analogue **2**, a tetramethoxy derivative of **1**, barely included these guest molecules. The inclusion amount and the rate of inclusion of ethyl acetate or methyl ethyl ketone showed a drastic increase above a threshold concentration of guests in the gas phase. Thus, the structure of the apohost changed cooperatively in order to bind guest molecules above the threshold guest concentration. This cooperativity of the binding behavior was kinetically analyzed.

Keywords: host–guest chemistry · hydrogen bonding · kinetics · quartz-crystal microbalance

Introduction

Induced-fit molecular recognition between proteins and their substrates has been the focus of much attention for many years. Solid-phase complementary host–guest and cocrystal systems have been employed as model systems in recent years.[1–18] From a functional point of view, the process of binding guest molecules should be reversible. Thus, the cavities are maintained after the removal of the guests, or the cavities that have collapsed on account of crystal-packing forces could be restored upon guest binding.[19, 20] Hopefully, the induced-fit behavior may occur if guest molecules are included into the empty cavities, in a similar manner to proteins. Solid organic hosts linked through hydrogen-bonding networks are potential candidates for this purpose, because the collapse and reconstruction of their cavities would be controlled through switchable formation of hydrogen bonding.

Although these dynamic characteristics seem to be very important, the guest binding to organic crystals has mainly been studied with conventional static methods: the host–guest complex has been obtained as precipitated crystals from solutions and analyzed by X-ray diffraction, or the extracted guests from crystals have been analyzed by NMR spectra in solution. Theses static methods present some difficulties in kinetic studies of host–guest chemistry in which the host and guest concentrations are changed. It is favorable to study the inclusion behavior of guest molecules in the host crystals in the gaseous phase to avoid the effects of solvation or crystal-packing forces on guest inclusion.[21, 22] However, there have been only a few kinetic investigations of the guest inclusion process into organic crystals because of the lack of detection methods.[23] Nassimbeni and co-workers have studied the kinetics of the inclusion of acetone vapor in an solid organic host by means of a conventional balance system.[24]

A quartz-crystal microbalance (QCM) is a very sensitive mass measuring device because its resonance frequency decreases linearly as the mass on the QCM plate increases so that it can be used on the nanogram scale in the gas phase as well as with aqueous solutions.[25–38] The QCM technique also allows us to monitor the mass changes continuously. Therefore, QCM provides a powerful technique to analyze molecular interactions kinetically. A QCM has been widely

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used with various sensing systems,[26–31] and we have already shown its validity for the detection of molecular interactions, for example, molecular adsorption to cast films in gas[32] and aqueous[33] phases, in-situ characterization of Langmuir–Blodgett films,[34] DNA hybridization,[35] DNA–protein interactions,[36] and molecular recognition at the air–water interface.[37] Recently, we combined a QCM technique and a flow cell to detect the molecular recognition of gaseous guests on a functionalized monolayer.[38]

In this paper, we report the dynamic studies of gaseous guest binding to the apohost crystals immobilized on a QCM (see Figure 1). We chose crystals of anthracene-bis(resorcinol) (**1**) as the host; it forms molecular sheets held together by

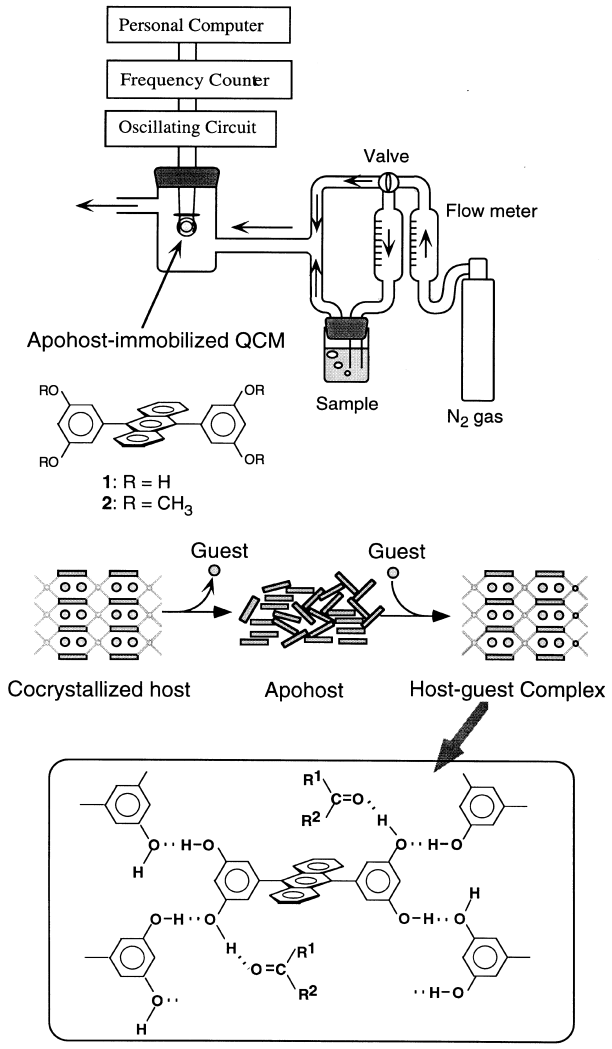

Figure 1. A schematic illustration of the in-situ detection of gaseous guest binding on apohost **1** immobilized on a quartz-crystal microbalance (QCM).

an extensive hydrogen-bonded network and has large (≈10 Å) cavities similar to those of organic zeolites.[2a–d] The host–guest complex of **1** was obtained by cocrystallization from a solution that contained the guest, and the guest-free apohost was readily prepared by heating the host–guest complex under vacuum. We have already reported on the static binding properties of guests into the apohost **1**, investigated with powder X-ray analysis, that showed that the cavities of the apohost, which had collapsed as a result of crystal-packing forces, could be restored upon guest binding.[2] In the present QCM study, we observed that the structure of the apohost changed drastically and cooperatively above a threshold guest concentration in order to bind guests. We report here on a kinetic study of this cooperative binding behavior.

Experimental Section

The QCM employed in this study was a commercially available 9 MHz, AT-cut quartz (diameter 9 mm, purchased from Showa Crystals, Chiba). Au electrodes were deposited onto both sides of the quartz-crystal plate (area 16 mm^2). The 9 MHz QCM was driven by a handmade oscillator, and the frequency changes were followed by a universal counter (Hewlett Packard Co. Ltd., Tokyo, model 53131A) attached to a microcomputer system. Equation (1) was established for AT-cut shear mode QCM. [25]

$$\Delta F = \frac{-2F_o^2}{A\sqrt{\rho_q \mu_q}}\Delta m \qquad (1)$$

In Equation (1) ΔF is the measured frequency shift [Hz], F_o the parent frequency of the QCM (9×10^6 Hz), Δm the mass change [g], A the electrode area (0.16 cm^2), ρ_q the density of quartz (2.65 $g\,cm^{-3}$), and μ_q the shear modulus of quartz (2.95×10^{11} dyne cm^{-2}). The QCM was calibrated by the LB-film transfer method[34] to give Equation (2).

$$\Delta m = -(0.95 \pm 0.01) \times 10^{-9}\Delta F \qquad (2)$$

Syntheses of the host compound **1** and host analogue compound **2** have been described elsewhere.[2c] A solution of host **1** in ethyl acetate (1 $mg\,mL^{-1}$) was cast onto both sides of the gold electrode of the QCM at room temperature. It has been confirmed from powder X-ray analyses that the host **1** is cocrystallized with the guest in the cavities with a molecular ratio of 2:1.[2a] When 2 μL solution was cast onto the electrode and dried in air, the frequency decreased by 3030 ± 10 Hz to give $\Delta m =$ 2880 ± 10 ng in air. This is assumed to be a total mass of 2000 ng (5.08 mol) of the cast host **1** and 880 ± 10 ng (10.0 mol) of cocrystallized ethyl acetate, that is, with a molar ratio of guest:host = 2:1. When the host–guest complex on the QCM was dried under vacuum at 140 °C for 4 h, the frequency increased by 930 ± 10 Hz (mass decrease of $\Delta m = 880 \pm 10$ ng), which agrees with the expected mass of included ethyl acetate. Thus, the so-cast crystal of **1** contained ethyl acetate as a guest with a molar ratio of 2:1 (guest:host), and ethyl acetate was completely evaporated after drying in vacuo to give apohost **1** on the QCM plate. Immobilization of the host analogue **2** was also carried out a similar way to that descried above.

The QCM immobilized with the solid apohost **1** was placed in a flow cell (70 cm^3), through which a mixture of a saturated vapor of guest molecules and dry N_2 gas was passed at a rate of 2 $L\,min^{-1}$. The binding kinetics were obtained from the time-resolved decrease in the oscillating frequency (mass increase) of the QCM. The temperature was maintained at 25 °C during the experiments. The concentration of guest molecules in the flow cell was controlled by changing the mixture ratio of the saturated vapor of guest and dry N_2 gas. In order to avoid the influence of water molecules, the guest molecules were dried and the flow cell was purged with sufficient dry N_2 gas before the experiments. The saturated vapor pressure of the guests at 25 °C were as follows: ethyl acetate 96.8 mm Hg, methyl ethyl ketone 90.4 mm Hg, benzene 95.2 mm Hg, cyclohexane 97.6 mm Hg, methyl acetate 216.6 mm Hg, and methyl propionate 81.6 mm Hg.

Infrared spectra were measured with A-100 IR Spectrometer (JEOL, Japan). The apohost of **1**, dispersed in CCl_4 and ethyl acetate, was sealed between NaCl plates for the measurement. The sample of the ethyl acetate/**1** (2:1) complex was prepared by sealing it immediately after exposure of apohost **1** to ethyl acetate vapor for one hour.

Results and Discussion

General behavior of guest binding: Figure 2 shows typical time-resolved changes in the frequency of the QCM immobilized with the apohost **1** or the host analogue **2** (2000 and 2290 ng, respectively, 5.08 mol) as they respond to exposure of the same concentration (5 mM, 350 nmol in 70 cm^3) of ethyl acetate, methyl ethyl ketone, benzene, and cyclohexane in the gas phase at 25 °C. These gaseous guest molecules were chosen because they have a similar vapor pressure at 90–98 mm Hg at 25 °C, since the adsorption of gaseous molecules onto a solid surface largely depends on their condensation ability which is reflected in their vapor pressure.[38b] Ethyl acetate and methyl ethyl ketone were significantly included into the apohost **1** and reached equilibrium within few minutes. These changes can be approximated by first-order kinetics and the curve obtained was fitted by Equation (3), in which Δm_t and Δm_{max} are the amounts of bound guest at t and infinite time, respectively.

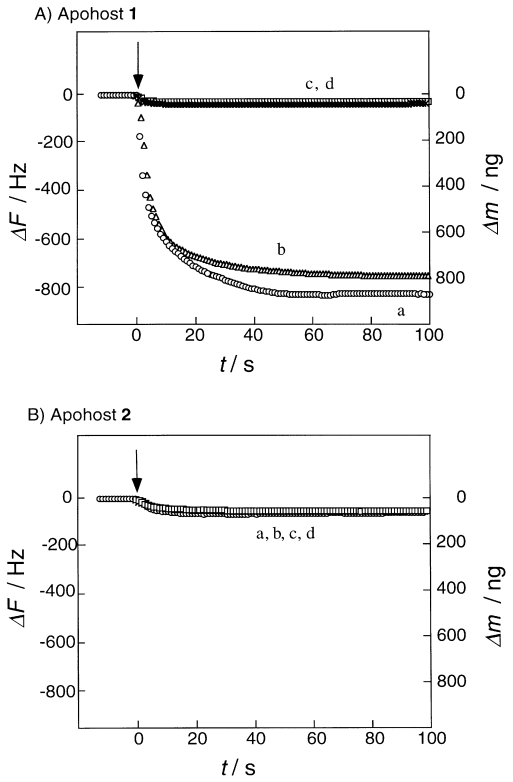

Figure 2. Time-resolved changes in the frequency of the QCM immobilized with A) the apohost **1** (2000 ng, 5.08 nmol) and B) apohost **2** (2290 ng, 5.08 nmol) as they respond to the exposure to saturated vapor of guest molecules (5 mM, 350 μmol in 70 cm^3) at 25 °C: a) ethyl acetate, b) methyl ethyl ketone, c) benzene, and d) cyclohexane.

$$\Delta m_t = \Delta m_{max}[1 - \exp(-t/\tau)] \quad (3)$$

Parameter τ is the relaxation time on the binding. Curve fitting was satisfactory in all cases (correlation coefficient, $r > 0.98$). The Δm_{max} values, obtained from Figure 2A, were 880 ± 10 ng (10.0 nmol) and 800 ± 10 ng (11.1 nmol) for ethyl acetate and methyl ethyl ketone, respectively. Since 5.06 mol of apohost was cast on the QCM, ethyl acetate or methyl ethyl ketone was included by the apohost **1** in 2:1 (guest:host) stoichiometry at saturation. This was in good agreement with the observation of the host–guest complex (1:2) by X-ray analyses,[2a] and with the evaporated mass when the cocrystallized host–guest complex was dried in vacuum (see the Experimental Section).

In contrast, benzene and cyclohexane were hardly included by apohost **1**, although these four guests have a similar vapor pressure (90–98 mm Hg) at 25 °C. This selective binding behavior agrees with the finding that no cocrystals were obtained from these solvents.[2a] Hydrocarbons, such as benzene and cyclohexane, which do not have a hydrogen-bonding ability were only adsorbed very weakly and/or adsorbed near the surface.

Figure 3 shows the IR spectra of the apohost **1**, the host **1** with included ethyl acetate in a 2:1 ratio (guest:host), and ethyl acetate only. In the apohost **1**, the sharp absorptions of ν_{OH} at 3490 and 3300 cm^{-1} indicated both free OH and the hydrogen-bonded OH groups, respectively. When ethyl acetate was included into the apohost, the free OH group at $\tilde{\nu} = 3490$ cm^{-1} disappeared and the hydrogen-bonded ν_{OH} shifted to a lower wave number (3220 cm^{-1}) than that of the apohost. Moreover, $\nu_{C=O}$ of ethyl acetate at $\tilde{\nu} = 1720$ cm^{-1} shifted to 1700 cm^{-1}, which indicates the formation of a hydrogen bond to the host. These IR shifts fundamentally agree with those observed for cocrystals of **1** and benzoates.[2a, 2b] It was reported from X-ray crystal analyses that apohost **1** contains columns held together by O–H···O–H hydrogen bonding which alternate with anthracene face-to-face arrays, and that ketone and ester guests can bind to the crystal through hydrogen bonding of C=O to the remaining H in O–H···O–H bonds with accommodation of the bulky parts between anthracene rings (see Figure 1).[2a] Agreement in the IR data

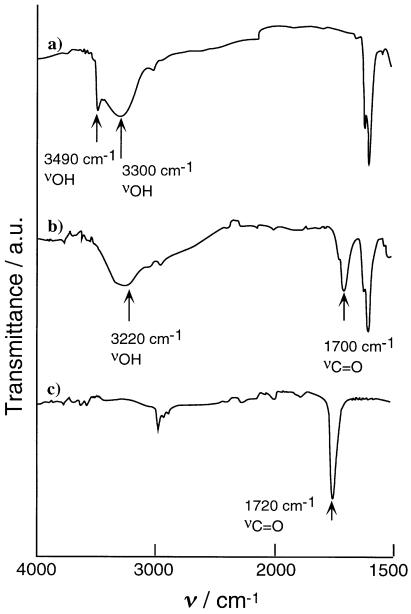

Figure 3. IR spectra of a) apohost **1**, b) inclusion complex of ethyl acetate and host **1** (2:1), and c) ethyl acetate at 25 °C.

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supports the indication that the structure of the cast film of the apohost complex on the QCM is the same as that in the cocrystal system.

In contrast, host analogue **2**, in which four hydroxyl groups were substituted by methoxy groups, was barely able to include all the guest molecules (Figure 2B). It has been confirmed that the methoxy derivative **2** does not contain a hydrogen-bonded network and such cavities.[2a] Thus, the formation of a cavity-forming hydrogen-bonded network plays an important role in the inclusion of gaseous guests in apohost **1**.

Figure 4 shows the effect of cast amount (thickness) of the apohost on the QCM plate on the equilibrium amount of included guest (Δm_{max}). In the case of ethyl acetate or methyl ethyl ketone as guests, the Δm_{max} increased linearly as the

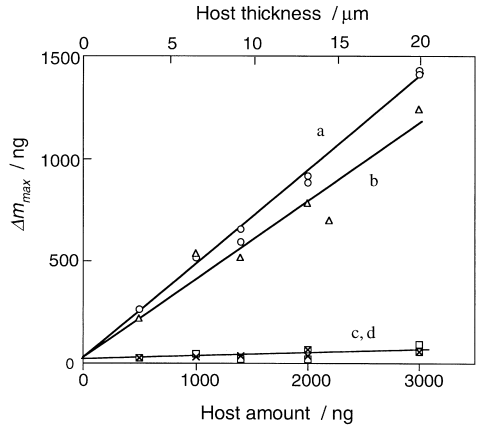

Figure 4. Effects of the amount (thickness) of apohost **1** on the equilibrium inclusion amount in the gas phase at [Guest] = 5 mM and 25 °C: a) ethyl acetate, b) methyl ethyl ketone, c) benzene, and d) cyclohexane.

amount (thickness) of the cast apohost increased (slope ≈ 2). The fitting parameters were 0.97 – 0.99. These results indicate that ethyl acetate and methyl ethyl ketone adsorb and penetrate deeply and completely into the solid apohost, even through 20 μm thickness (3 μg on 16 mm^2 electrode), to form a complex in which two guest molecules fit into one host site. On the other hand, for benzene or cyclohexane as the guest, the equilibrium inclusion amount was independent of the apohost thickness, which shows that there is simple surface adsorption.

Binding curve and cooperativity: Effects of the concentration of guests in the gas phase on the Δm_{max} of the apohost **1** (2000 ng, 5.08 nmol) at 25 °C are shown in Figure 5A. The amounts of adsorbed benzene and cyclohexane were very small and increased only slightly as the guest concentration increased. In contrast, the inclusion amount of ethyl acetate and methyl ethyl ketone increased sigmoidally with increasing gaseous concentration with threshold concentrations of 2.0 and 3.0 mM, respectively. The binding behavior of methyl acetate was not of the Langmuir type either, and the binding of methyl propionate seemed to obey a simple saturation-type with a small binding constant. The cooperativities on binding ethyl acetate and methyl ethyl ketone suggest that at low concentrations the guest molecules just adsorb near the solid

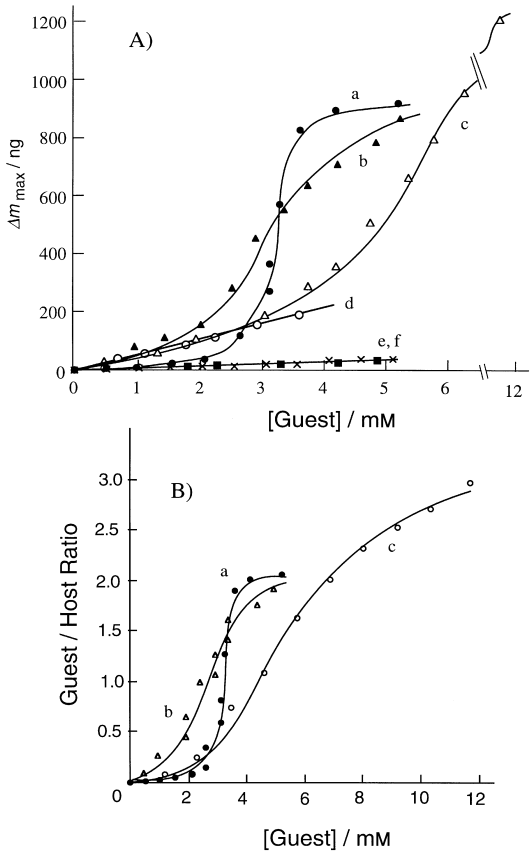

Figure 5. A) Effects guest concentration in the gas phase on the equilibrium inclusion amount (Δm_{max}). B) Plots of guest/host ratios against guest concentrations in the apohost **1** (2000 ng, 5.08 nmol). All measurements were made at 25 °C: a) ethyl acetate, b) methyl ethyl ketone, c) methyl acetate, d) methyl propionate, e) benzene, and f) cyclohexane.

surface of the collapsed crystal structure of the apohost. The cooperativities also suggest that above the threshold guest concentration, an extensive hydrogen-bonded network is formed to give an expanded, porous crystal structure, as shown schematically in Figure 1.

The cooperative binding behavior was analyzed more precisely, as shown in Figure 5B where guest/host ratios are plotted as a function of guest concentration, according to the Hill equation [Eq. (4)], in which n is the cooperativity factor, K is the binding constant, y and y_∞ are the amount of bound guest per host (guest/host) at [Guest] and infinite guest concentration, respectively.[39]

$$y = y_\infty \frac{K[\mathrm{Guest}]^n}{1 + [\mathrm{Guest}]^n} \quad (4)$$

Curves fitted by Equation (4) are shown in Figure 5B and the obtained parameters are summarized in Table 1. Values of the binding stoichiometry (y_∞) were 2.02, 1.95, and 3.38 for

Table 1. Binding parameters obtained from the binding curves shown in Figure 5B.

Guest	Guest/Host (y_∞)	n	K/M^{-n}	r
ethyl acetate	2.02 ± 0.07	13.8 ± 6.7	1.4×10^{36}	0.991
methyl acetate	3.38 ± 0.19	2.6 ± 0.2	7.5×10^{5}	0.998
methyl ethyl ketone	1.95 ± 0.77	2.3 ± 0.5	4.8×10^{5}	0.991

ethyl acetate, methyl ethyl ketone, and methyl acetate, respectively. The results for ethyl acetate and methyl ethyl ketone showed a good agreement with the binding stoichiometry obtained from X-ray structural analysis where two molecules of ethyl acetate bind to each molecule of **1**.[2a] The smaller methyl acetate showed a larger binding stoichiometry ($y_\infty = 3.38$) compared with ethyl acetate. This finding is in agreement with the formation of 3:1 and 4:1 (guest:host) complexes with smaller acetone and diethyl ketone molecules, respectively, while most bulky ketones prefer a 2:1 complex.[2]

A more interesting result appears for the cooperative factor, *n*. In all cases, *n* values are larger than unity, which indicates that the system has a positive cooperativity on binding. Unexpectedly, a large *n* value (13.8) was observed for the binding of ethyl acetate. The cooperative factor does not usually exceed the binding stoichiometry, as seen in the binding of oxygen to hemoglobin: the binding site stoichiometry is 4 and the cooperative factor is 2.8.[40] The large cooperative factor for ethyl acetate to the apohost **1** is probably attributable to the continuity of host structures. A cooperative factor larger than its stoichiometry was also reported for adenine binding to a host-site array assembled on a monolayer of orotate-type lipid.[41] Guest binding to the apohost **1** would be driven by reconstruction of the collapsed host structure. If the collapsed apohost maintains a partial hydrogen-bonding network and the sheet structure within the network intercalates with each other, only a small number of bound guests would by required to recreate a large number of active binding sites by opening intercalated sheet structures.[2a] According to IR observation of the apohost, the intense peak of the hydrogen-bonded OH group still exists, which indicates the preservation of hydrogen bonded network even in the apohost cast film. In these systems, the induction period was not observed as seen in Figure 2A. It suggests that the structural change of the host upon binding is relatively quick. This finding also supports partial preservation of network structure in the apohost and energy-unconsummated recreation of active binding sites.

Kinetic aspects of guest binding: The cooperativity was also observed in the binding rates. The inverse relaxation time of binding (τ^{-1}) was plotted against the guest concentration (Figure 6). If there is simple equimolar binding then the plot would be a straight line with a slope of k_1 (binding rate constant) and an intercept of k_{-1} (dissociation rate constant).[38] However, τ^{-1} values increased abruptly above a certain threshold concentration, that is, the values depend on the multiplied term of the guest concentration. This behavior would be also attributed to cooperativity on guest binding. With cooperative factor *n*, Equation (5) then holds.

$$\tau^{-1} = k_1[\mathrm{Guest}]^n + k_{-1} \quad (5)$$

Experimental data was fitted to this equation with the *n* values listed in Table 1. Fitting of the data with Equation (5) was satisfactory in the other two cases and the obtained parameters are summarized in Table 2. The ratio of k_1 to k_{-1} should be equal to the apparent binding constant *K*. The calculated ratios from Table 2 are in of a similar order of size to the values listed in Table 1, except for the data of ethyl acetate. This agreement indicates that both binding curve and kinetic analyses support the cooperative binding mechanism.

Table 2. Kinetic parameters obtained from Equation (5).[a]

Guest	k_1 [$M^{-n}s^{-1}$]	k_{-1} [s^{-1}]	*n*	*r*
ethyl acetate	$(9.4 \pm 3.3) \times 10^{30}$	0.298 ± 0.061	13.8	0.818
methyl acetate	$(3.5 \pm 1{,}1) \times 10^{4}$	0.285 ± 0.057	2.64	0.873
methyl ethyl ketone	$(6.1 \pm 0.5) \times 10^{4}$	0.017 ± 0.008	2.30	0.988

[a] Flow rate: 2 L min^{-1} at 25 °C.

The dissociation rate constants k_{-1} can be compared with each other if they have the same unit (s^{-1}). The k_{-1} values for ethyl acetate, methyl acetate, and methyl ethyl ketone are 0.298, 0.285, and 0.017 s^{-1}, respectively. Methyl acetate has a larger dissociation rate constant than methyl ethyl ketone, while both have the similar *n* values. The difference could be attributed to the saturation vapor pressure: methyl acetate has a higher vapor pressure (216.6 mm Hg at 25 °C) than methyl ethyl ketone (90.4 mm Hg at 25 °C). The larger dissociation rate constant of methyl acetate is probably caused by its greater ability to vaporize. Ethyl acetate has a similar vapor pressure (96.8 mm Hg at 25 °C) to methyl ethyl ketone; however, it has a larger dissociation rate constant (0.298 s^{-1}). This finding may be may be the reason for the difference in cooperativity. Ethyl acetate has a significantly higher cooperativity than other guests, which suggests that the small number of bound guests can reconstruct the crystal structure to create many binding sites. Dissociation of ethyl acetate might not affect the collapse of host structures and release of ethyl acetate has a low energy barrier.

We have already reported preliminary results on the kinetics of guest binding studied by the exposure of ground apohost crystals to guest vapor.[2a] Guest binding to the ground crystals needed 30 – 40 hours for saturation and the associate rate was independent of time almost up to binding saturation. This indicates that the guest binding to the ground crystals is significantly slow and the rate is not affected by the number of unbound sites. The observed difference would be attributed to the size of apohost. The size of the ground crystals is probably in the order of μm, which is much larger than the guest molecule. After guest molecules have bound to

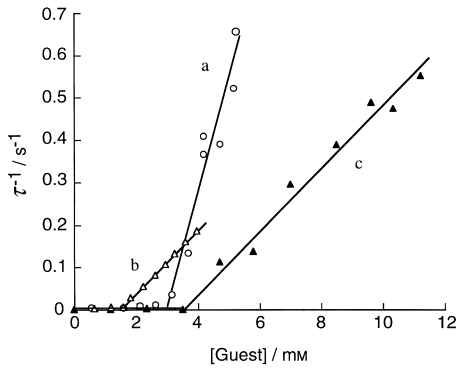

Figure 6. Correlations between τ^{-1} values and guest concentrations in the gas phase at 25 °C and concentration of apohost **1** = 2000 ng, 5.08 nmol: a) ethyl acetate, b) methyl ethyl ketone, and c) methyl acetate.

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the surface site, they have to diffuse into the crystal to reach the deeper binding sites. The latter step is rate-determining, which is slow and independent of the number of unbound sites. In contrast, the apohost cast film probably exists as nanometer-size crystals, because the molecularly-dispersed solution of host molecules was cast directly and the solvent was evaporated rapidly. Most of the binding sites are located near to the surface of the very small crystals and diffusion of the guest is not important. Therefore, the kinetics of guest binding to the apohost film is fast and is first order with respect to the number of remaining sites. These results suggest the importance of host dimensions in gas–solid molecular recognition.

Conclusions

We have observed the inclusion behavior of gaseous guest molecules into a solid apohost, the orthogonal anthracene-bis(resorcinol) derivative **1**, by means of a QCM method. Ethyl acetate and methyl ethyl ketone were significantly included by the apohost, whereas benzene and cyclohexane were simply adsorbed onto the solid surface even though all of these guests have a similar vapor pressure at 25 °C. Their binding stoichiometries agree with the results previously obtained from X-ray analyses, and indicate the validity of the QCM method for the quantitation of guest binding in a gas–solid system. The QCM method is simple to use and allowed us to analyze the kinetic binding behavior by following the time-resolved change of the frequency. The most profound finding in this study was the cooperativity on gaseous guest binding. The binding of guest molecules, such as ethyl acetate, to the apohost showed a sigmoidal binding curve that can be analyzed with a cooperativity factor. The kinetic parameter τ was also analyzed with the cooperativity. These two methods of analysis do not conflict each other.

So far, mainly static methods, such as cocrystallization and X-ray crystal analysis, have been used to investigate the crystalline host–guest complex. As demonstrated in this paper, a QCM mass-detection analysis is a useful method to analyze the dynamic characteristics of molecular recognition on solid host molecules.

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