Kinetic Study for Complexation between α-Cyclodextrin and Alcohols in Water by the Ultrasonic Relaxation Method

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Ultrasonic absorption measurements in the frequency range from 1 to 95 MHz were carried out in aqueous α-cyclodextrin solutions with 1-propanol or ethanol at 25 °C. A single relaxational absorption was observed, and the cause of the relaxation was attributed to a perturbation of a chemical equilibrium associated with a complexation reaction between α-cyclodextrin (host) and alcohols (guest). Rate and equilibrium constants for the complexation reaction were determined from the concentration dependence of the relaxation frequency for the solutions. A standard volume change of the reaction was also obtained from a maximum absorption per wavelength. These results were compared with those for the complexation between *β*-cyclodextrin and some alcohols and were discussed in relation to cyclodextrin and alcohol molecular structures. It was found (1) that the formation rate of the complex was slightly dependent on the cavity size of the cyclodextrins, but the rate of departure of alcohols from the cavity of the cyclodextrins was very dependent on the structure of the cyclodextrins and alcohols, and (2) that a part of the hydrophobic group in alcohols incorpoarated into the cavity of cyclodextrins even if water molecules also participated in the complexation reaction between cyclodextrins and alcohols.

Introduction

Recently, cyclodextrins have been widely used in various fields, such as a drug delivery system, a separation system, and a model for enzymatic specificity. An origin for such interesting applicabilities arises from a specific inclusion ability of cyclodextrins (hosts) for various compounds (guests). A lot of equilibrium studies have been carried out using UV, NMR, titration calorimetry, and so on in order to determine the stability of complexes formed by hosts and guests.[1−5]

Kinetic information plays an important role for understanding more precisely why the stability of the complexes depends on guest or host structures and how long the included molecules can stay in cyclodextrin cavities.

The ultrasonic relaxation method is useful for probing the microscopic solution structure and can be used to study fast processes with characteristic time constants of 10^{-6}−10^{-10} s. The method has also been applied to a fast reaction of the complexation between cyclodextrin and alcohols,[6,7] and it has been proposed that the stability of the complexes formed by cyclodextrin and alcohols is controlled by a rate constant of departure of guest molecules from the cavity of hosts. This has been concluded from the kinetic results for the complexation of *β*-cyclodextrin with 1-propanol and 1-butanol. It should be then clarified how the size of the cavity affects the stability of the complex from a dynamic point of view. To see this, α-cyclodextrin (α-CD), of which the cavity is smaller than that of *β*-cyclodextrin, has been chosen as a host, and 1-propanol and ethanol have been taken as guests in this study. The ultrasonic absorption, velocity, and density have been measured as a function of their concentrations. The results are compared with those for systems with *β*-cyclodextrin.

Experimental Section

α-Cyclodextrin was purchased from Wako Pure Chemical Co. Ltd. It was recrystallized once from water and then was dried in a vacuum oven kept at 45 °C until the weight of the sample powder reached a constant value. After that, it was kept in a desiccator. 1-Propanol and ethanol were also purchased from Wako Pure Chemical Co. Ltd. and were distilled once at normal pressure. The sample solutions were prepared by weighing with distilled and filtered water from a MilliQ SP-TOC system of Japan Millipore Ltd.

Ultrasonic absorption coefficients, α's, were measured in the frequency range from 1 to 7 MHz by a resonance method and in the range from 15 to 95 MHz by a pulse method. In the former equipment, 3 and 5 MHz x-cut quartz crystals were utilized, and they overlapped the measuring frequency range from 3.6 to 4.6 MHz. In the latter, a 5 MHz crystal was used and was driven at odd harmonics. More details about the absorption apparatus and the procedure for determining the absorption coefficient are described elsewhere.[8,9] Sound velocity was obtained by the resonator at around 3 MHz. Density measurements were carried out using a vibrating density meter (Anton Paar DMA60/602). Sample liquids in the cells for all of the apparatus were controlled at a constant temperature (25 °C) within ±0.01 °C.

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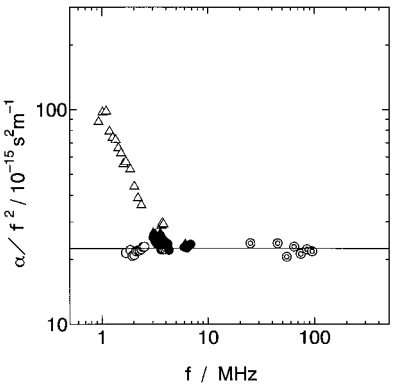

Figure 1. Ultrasonic absorption spectra in aqueous solutions of α-CD at 25 °C: (Δ) the results obtained by the resonator with the 3 MHz x-cut crystal at 0.015 mol dm^{-3} α-CD; (▲) those by the resonator with the 5 MHz crystal at 0.015 mol dm^{-3} α-CD; (○) the results by the 3 MHz crystal resonator at 0.012 mol dm^{-3} α-CD; (●) those by the 5 MHz at 0.012 mol dm^{-3} α-CD; (◎) those by the pulse method at 0.012 mol dm^{-3} α-CD.

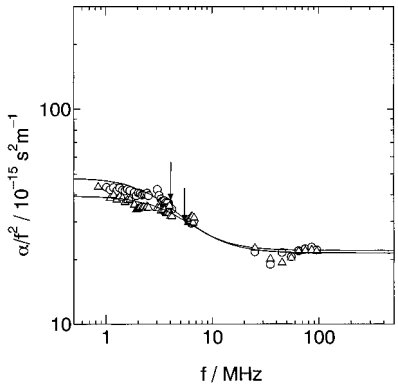

Figure 2. Ultrasonic absorption spectra in an aqueous solution of α-CD with 1-propanol. The arrows indicate the positions of the relaxation frequency: (Δ) 0.0100 mol dm^{-3} α-CD and 0.0750 mol dm^{-3} 1-propanol; (○) 0.0120 mol dm^{-3} α-CD and 0.0400 mol dm^{-3} 1-propanol.

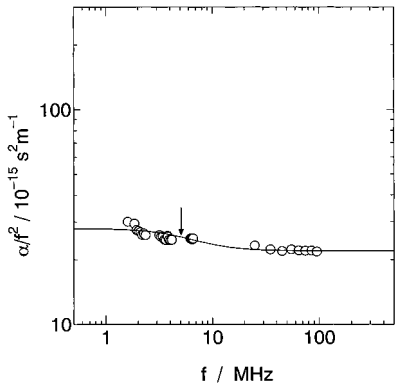

Figure 3. Representative ultrasonic absorption spectrum in an aqueous solution of 0.0100 mol dm^{-3} α-CD and 0.0300 mol dm^{-3} ethanol.

Results

The ultrasonic absorption data and the analysis of the frequency dependence of the absorption are presented. Figure 1 shows representative ultrasonic absorption spectra in α-CD aqueous solutions. As is seen in this figure, the absorption coefficients divided by the square of the frequency, (α/f^2)'s, are independent of the frequency at concentrations less than 0.0120 mol dm^{-3} in the entire frequency range measured (1−95 MHz). On the other hand, they are surely dependent at 0.0150 mol dm^{-3}. Namely, a relaxational absorption was found, the result of which was also reported by Rohrbach et al.[10] in the frequency range from 10 to 205 MHz and by Kato et al.[11] in the range from 0.8 to 135 MHz. However, the concentrations tested by them are higher than those examined by this study. The cause of the relaxation has been proposed to be due to a reaction associated with isomerization of α-CD, but more accumulation of the absorption data seems to be desired for the detailed clarification of the relaxational absorption mechanism. When the concentration of α-CD is restricted below 0.012 mol dm^{-3}, no excess absorption is observed. We have focused these relatively dilute α-CD solutions in the present study because the aim of this study is the examination of the interaction between cyclodextrins and alcohols.

When 1-propanol or ethanol was added to the solutions with α-CD, the frequency dependent (α/f^2)'s were found as seen in Figures 2 and 3. It should be noticed that the difference between high- and low-frequency values of (α/f^2) is quite small when ethanol is added, comparing with those with 1-proanol. The frequency dependence was tested by a Debye-type relaxational equation:

$$\alpha/f^2 = A/[1 + (f/f_r)^2] + B \qquad (1)$$

where f_r is the relaxation frequency and A and B are constants. Equation 1 is a decreasing function with the frequency, and therefore, the modified relation $(\alpha/f^2)f = (A/[1 + (f/f_r)^2] + B)f$ was used to determine the ultrasonic parameters, f_r, A, and B, using a nonlinear least-mean-squares method. Still, the procedure for the determination of the ultrasonic parameters may happen to be inappropriate when a position of the relaxation frequency is near or beyond the lower or upper limit of the measurement frequency and the amplitude of the ultrasonic relaxation, A, is small. When the relaxation frequencies are located at less than 3 MHz, which is found in the case for the solutions with 1-propanol, the above procedure has likely given curious parameters, such as negative values. In such a case, we used the linear plots of $(\alpha/f^2 - B)^{-1}$ vs f^2, because the background absorption, B, was easily estimated from the results in the frequency range more than 35 MHz, where the absorption was close to that of the solvent water.[12] The absorption data below 0.0225 mol dm^{-3} 1-propanol were analyzed by the above procedure, and therefore the probable errors for the background absorption were not given in Table 1. The data above that concentration of 1-propanol were analyzed by the nonlinear least-mean-squares method. To ascertain these procedures, both calculations were carried out at the concentration of 0.0251 mol dm^{-3} 1-propanol, the results of which are indicated in Table 1. The same ultrasonic parameters were obtained. The obtained parameters were used to draw theoretical curves. Some representative ones are shown in Figure 2 by the solid curves. It can be seen that agreement between the experimental and theoretical values is excellent. This means that a Debye-type single relaxational absorption is observed in α-CD solution with 1-propanol.

Although the amplitude of the relaxational absorption was so small in the solution with ethanol, the parameters were determined using the modified equation shown below eq 1, because the location of the relaxation frequency is around 8 MHz.

The mechanism of the observed relaxational absorption is now considered. From the facts that the relaxation was not found in the individual solutions of α-CD and alcohols in the concentration ranges studied here and that the relaxation clearly existed when 1-propanol or ethanol was added to the aqueous

TABLE 1: Ultrasonic Parameters for α-Cyclodextrin Aqueous Solutions of 1-Propanol and Ethanol at 25 °C

concn/mol dm^{-3}		f_r/MHz	10^{-15} s^2 m^{-1} A	B	c/m s^{-1}	ρ/kg dm^{-3}
			α-CD, 1-Propanol			
0.0100	0.0101	2.3 ± 0.3	40 ± 2	20.4	1494	1.0005
0.0100	0.0201	3.2 ± 0.4	29 ± 3	20.2	1496	1.0004
0.0100	0.0225	5.4 ± 0.1	16 ± 0.4	20.2	1496	1.0003
0.0100	0.0251	4.6 ± 0.8	18 ± 3	21.3	1497	1.0003
		4.5 ± 0.9	16 ± 3	21.3 ± 0.1		
0.0100	0.0375	5.3 ± 1.3	17 ± 3	20.7 ± 0.1	1498	1.0002
0.0100	0.0500	5.0 ± 1.3	19 ± 4	21.1 ± 0.1	1501	1.0002
0.0100	0.0750	6.0 ± 2.0	15 ± 3	21.1 ± 0.1	1498	1.0000
0.0120	0.0400	4.0 ± 0.6	26 ± 4	20.0 ± 0.1	1497	1.0009
0.0120	0.0750	5.4 ± 1.0	18 ± 3	22.0 ± 0.1	1499	1.0008
			α-CD, Ethanol			
0.0100	0.0300	5.1 ± 0.6	6.0 ± 0.5	22.0 ± 0.1		
0.0100	0.0400	5.9 ± 0.4	7.8 ± 0.4	21.9 ± 0.1		
0.0100	0.0500	9.0 ± 0.9	6.6 ± 0.3	21.9 ± 0.1		
0.0100	0.0600	7.9 ± 0.6	6.1 ± 0.2	21.9 ± 0.1		
0.0100	0.0800	7.4 ± 0.5	7.7 ± 0.3	21.9 ± 0.1		

TABLE 2: Rate and Thermodynamic Constants for the Complexation Reaction of Cyclodextrins with Alcohols at 25 °C

	β-cyclodextrin		α-cyclodextrin	
	1-propanol	1-butanol	1-propanol	ethanol
k_f/mol^{-1} dm^3 s^{-1}	(5.1 ± 0.7) × 10^8	(2.8 ± 0.8) × 10^8	(2.7 ± 1.2) × 10^8	(2.8 ± 0.4) × 10^8
k_b/s^{-1}	(1.21 ± 0.07) × 10^8	(3.8 ± 0.6) × 10^7	(1.7 ± 0.3) × 10^7	(2.9 ± 0.4) × 10^7
K/mol^{-1} dm^3	4.2 ± 0.6	7.2 ± 2	16 ± 7	
K^a/mol^{-1} dm^3	3.72,[4] 4.5[5]	16.6,[4] 16[5]	23.4,[4] 29.1,[15] 13 ± 7[16]	9.7[17]
ΔV/10^{-6} m^3 mol^{-1}	12.5 ± 0.3	11 ± 1	5.0 ± 0.6	3.5 ± 0.2

[a] The values in the literature.

solution of α-CD, a perturbation of the following equilibrium by ultrasonic waves is proposed.

$$\mathrm{CD} + \mathrm{ROH} \underset{k_b}{\overset{k_f}{\rightleftharpoons}} \mathrm{CDROH} \qquad (2)$$

where CD is α-CD, ROH is 1-propanol or ethanol, CDROH is the complex, and k_f and k_b are the forward and backward rate constants, respectively. We define the equilibrium constant as $K = k_f/k_b$ = [CDROH]/[CD][ROH] where the activities are assumed to equal the reactant concentrations. This is because the substances used herein are nonelectrolytes and their activity coefficients are close to unity at the low molarities in this experiment.[13] Following the chemical relaxation procedure, a relaxation time, τ, or the relaxation frequency is related to the reactant concentrations and the rate constants and is expressed as a function of the analytical concentrations of α-CD, C_{dx}, and 1-propanol or ethanol, C_{al}, as follows:[6]

$$\tau^{-1} = 2\pi f_r = k_f\{[\mathrm{CD}] + [\mathrm{ROH}]\} + k_b$$
$$= k_b[\{1 + K(C_{dx} + C_{al})\}^2 - 4K^2C_{dx}C_{al}]^{1/2} \qquad (3)$$

Using a nonlinear least-mean-squares method for eq 3, the parameters k_b and K were determined at $C_{dx} = 0.0100$ mol dm^{-3} for the solution of 1-propanol. The results are indicated in Table 2 along with those for β-CD solutions for comparison. The equilibrium constant thus obtained is quite close to the literature values, as is seen in the table.

The forward rate constant, k_f, was calculated from the definition of the equilibrium constant with the use of the backward rate constant, k_b. The relatively large errors for α-CD and 1-propanol solution arose from the large errors of the ultrasonic relaxation parameters because of the positions of the relatively low relaxation frequency and the small amplitude of the relaxation. The absorption measurements were carried out at a different α-CD concentration, results of which are also listed in Table 1. Once the equilibrium constant is obtained, it is possible to calculate the individual reactant concentrations, and Figure 4 shows the plots of $2\pi f_r$ vs {[CD] + [ROH]} for some concentrations of α-CD and 1-propanol. Even if the concentration of α-CD was different, the $2\pi f_r$ values fell on the same straight line. This confirmed that the cause of the observed relaxational absorption was associated with the complexation reaction between α-CD and 1-propanol.

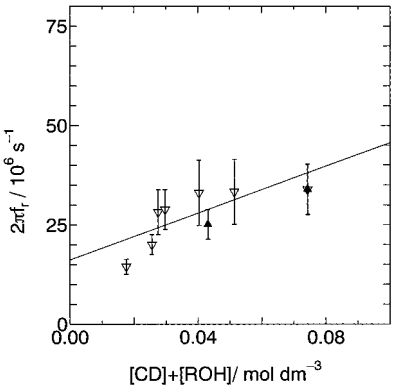

Figure 4. Reactant concentration dependence of the $2\pi f_r$ for α-CD aqueous solutions of 1-proapnol: (▽) 0.0100 mol dm^{-3} and (▲) 0.0120 mol dm^{-3} of α-CD, respectively.

In the solutions of ethanol, the relaxation frequency also tends to increase with the concentration, although the amplitude of the relaxational absorption was very small, as seen in Table 1. However, the same procedure for determining the parameters K and k_b could not be applied to this system because the minimum mean-square error was not reached. Therefore, the literature value of the equilibrium constant[17] was used to calculate the concentration term in the right-hand side of eq 3, and the reverse rate constant was determined from the slope of

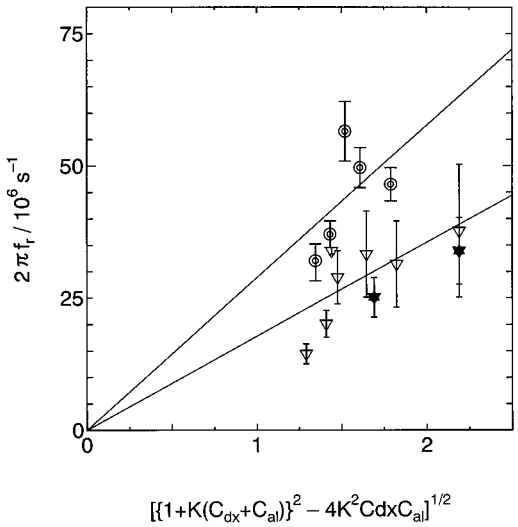

Figure 5. Plots of $2\pi f_r$ vs $[\{1 + K(C_{dx} + C_{al})\}^2 - 4K^2C_{dx}C_{al}]^{1/2}$ for α-CD aqueous solutions of 1-proapnol (▽, ▲) and ethanol (◎). The backward rate constant was determined from the slope for the solution of ethanol. Key: (▽) 0.0100 mol dm^{-3}, (▲) 0.0120 mol dm^{-3}, and (◎) 0.0100 mol dm^{-3} of α-CD.

the plots of $2\pi f_r$ vs the concentration term. They are also shown in Figure 5 along with those for the solution of 1-propanol.

A standard volume change of the reaction is also obtainable from the absorption data with the help of solution density and velocity values.[6] The maximum absorption per wavelength, $\mu_m = 0.5Af_rc$, is given by the following relation under the assumption that a thermal relaxational term is negligible in aqueous media.

$$\mu_m = \pi\rho c^2(1/[CD] + 1/[ROH] + 1/[CDROH])^{-1}(\Delta V)^2/2RT \quad (4)$$

where ρ is the solution density and ΔV is the standard volume change of the reaction. The contribution of the density and sound velocity to the determination of the volume change is found to be very small. Therefore, the ΔV for the complexation reation between α-CD and ethanol was calculated using the values of density and sound velocity for the solvent, water. The obtained value, ΔV, is also shown in Table 2. It was found that the volume changes of the complexation of α-CD and 1-propanol or ethanol were quite small when compared with those for β-CD and two alcohols.

Discussion

It is interesting to notice that the forward rate constant, k_f, exists in the range, $(3-5) \times 10^8$ mol^{-1} dm^3 s^{-1} and it is not very dependent on the size of the cyclodextrin cavity or the structure of the alcohols, as can be seen in Table 2. On the contrary, the backward rate constant, k_b, is very dependent on both the size of the cavity and the guest structures. When the size of the cavity of cyclodextrin is larger, the rate of the departure of 1-propanol from the cavity is greater. When the cavity size is the same, the backward rate for the smaller guest tends to be greater than that for the larger guest. That is, one of the main factors for the stability of the complex is the size of the cavity, and the guest molecules can stay longer in the cavity when the interaction between the host and guest increases in the cavity. Then, it is considered that the main interaction is a hydrophobic one because the stability of the complex is greater when the guest hydrophobicity increases. The interaction of this kind has also been proposed from the static experimental studies, and the interaction mechanism has been proved dynamically in this study.

Next, the result of the volume change of the reaction is concerned. Even if the guest is the same, the volume change of the complexation reaction depends on the size of the cavity. When the cavity is the same, on the other hand, the volume change is almost the same or increases slightly with an increase of the hydrophobicity of alcohol. As has been predicted in our previous kinetic study,[7] the complexation reaction may involve the participation of water molecules. It is generally said that there are several water molecules in cyclodextrin cavities.[14] When the guest molecule is incorporated into a cyclodextrin cavity, water molecules in the cavity are ejected into the bulk solvent.[15,17] According to an X-ray study, two water molecules exist in one α-CD cavity.[18] Fujiwara et al.[17] have estimated that 1.4 water molecules are released in average when one 1-propanol or ethanol molecule moves into the α-CD cavity. If the whole 1-propanol or ethanol molecule is included in the cavity, and 1.4 water molecules leave it, then the larger volume change of the reaction ($\Delta V \sim 50 \times 10^{-6}$ m^3 mol^{-1}) should be expected because the molar volumes of 1-propanol, ethanol, and water are approximately estimated to be 75×10^{-6}, 59×10^{-6}, and 18×10^{-6} m^3 mol^{-1}, respectively. If the volumes of less hydrogen-bonded water molecules in the cavity were smaller and they were released to the fully hydrogen-bonded bulk water,[17,19] a similar volume change should have been considered because the ejected water molecules play a role in the volume change. However, the experimental result gave a much smaller value for the complexation reaction between α-CD and 1-propanol or ethanol. This means that a part of the hydrophobic group of alcohols incorporates into the cavity and that the hydroxy group is still interacting with bulk water molecules or hydroxy groups at the rim of α-CD.

Finally, the reason the volume change for the reaction with β-CD is larger than that with α-CD is taken into account briefly. The size of the β-CD cavity is greater than that of α-CD. A quite recent study by Gonzalez-Gaitano et al.[20] has proved that the β-CD cavity can include 6.5 water molecules on average and the volume change of the complexation reaction between β-CD and decyltrimethylammonium bromide is 18.5×10^{-6} m^3 mol^{-1}. The volume change obtained in this study is smaller than that value. We consider that alcohol molecules may be digging into the cyclodextrin cavities but are not piercing the cavities because 6.3 methylene groups can be occupied by one β-CD cavity. Then, it is considered that two or three water molecules may be expelled when 1-propanol or 1-butanol is incorporated into β-CD cavities. However, the extent of the incorporating volume of alcohols into β-CD may be greater than that for α-CD. Then the larger volume change due to the interaction between β-CD and the alcohols is likely to be observed.

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