Dynamic Study of Interaction between β-Cyclodextrin and Aspirin by the Ultrasonic Relaxation Method

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A single ultrasonic relaxational phenomenon was observed in aqueous solutions containing both β-cyclodextrin (β-CD) as host and nonionized or ionized acetylsalicylic acid (aspirin) as guest. The observed relaxation was responsible for a dynamic complexation reaction between β-CD and aspirin molecules, concomitant with a volume change during the reaction. The kinetic and equilibrium constants for the complexation in the acid (nonionized) form of the aspirin system were derived from the guest concentration dependence of the relaxation frequency. The equilibrium constant for the carboxylate (ionized) form of aspirin was determined from the concentration dependence of a maximum absorption per wavelength, and the rate constants were calculated by using the determined equilibrium constant and the observed relaxation frequencies, which remained nearly almost constant over the concentration range studied. The results showed that the effect of charge on the aspirin molecule was reflected only in the dissociation process from the β-CD cavity, while no remarkable change was seen in the association process whose rate was diffusion controlled. The results could be explained on the basis of the difference of the hydrophobic moieties in the two guests that were included in the host cavity. The results of the standard volume change for the complexation reaction were closely related to the number of expelled water molecules originally located in the β-CD cavity and the volume of the aspirin molecule incorporated into the β-CD cavity.

Introduction

Cyclodextrins (CDs) consisting of several glucose units possess hydrophobic cavities. The most important feature of CDs is their ability to include a variety of organic compounds as guests in the cavity through noncovalent forces.[1−9] The association and dissociation processes can be monitored by ultrasonic relaxation methods. In our previous studies[10−15] of the complexation reaction between CDs and organic compounds, it was clearly shown that CDs could recognize guest molecules and especially that the effect of the molecular recognition is reflected specifically on the dissociation process of the complex.

Our interests in the application of CDs as a vehicle molecule for drug delivery have led us to select a drug compound, acetylsalicylic acid (aspirin), as the guest for the β-cyclodextrin (β-CD) host which is comprised of seven glucose units. Aspirin is in the class of nonsteroidal anti-inflammatory drugs (NSAIDs). One of the methods tested for reduction of gastric irritation is the complex formation of NSAIDs and CDs.[5] Kinetic studies were conducted only on the reaction mechanism of the degradation of drug compounds, which takes place at a very slow time course. Detailed kinetic information for the complexation reaction between CDs and drug molecules is important for the application of CDs to drug-delivery systems. However, the rates of such reactions cover the range from microseconds to nanoseconds.[3,10−16] To investigate the kinetic characteristics for the complexation between β-CD and aspirin, in this report, two different pH conditions were applied: acidic conditions corresponding to the endogastric conditions and neutral conditions similar to the intestinal ones. The kinetic results obtained under the two conditions are compared also with those for other systems reported so far and are discussed in relation to the guest molecular structures in the present paper.

Experimental Section

Chemicals. The host chemical, β-CD, was purchased from Wako Pure Chemical Co. Ltd., was recrystallized once from distilled water purified by a Milli-Q SP-TOC filter system from Japan Millipore Ltd, and then was dried in vacuo at 45 °C to constant weight. The aspirin was also obtained from Wako Pure Chemical Co. Ltd. as the purest grade (the purity was confirmed to be >99%) and was used without further purification. The distilled and filtered water was also used as a solvent for all solutions after degassing under reduced pressure. A solution of aspirin as the acid (nonionized) form (>99%) was prepared by adjusting the pH to ≈1.7 with a concentrated aqueous solution of HCl. The solution with the carboxylate (ionized) form of aspirin (>99%) was obtained by adjusting the pH to ≈6.0 with NaOH solution. All sample solutions were freshly prepared by weighing just before the experimental measurements because the most important reaction contributing to the instability of aspirin in an aqueous medium is hydrolysis of its phenyl ester.

Apparatus. Ultrasonic absorption coefficients, α, were measured by a resonance method in the frequency range from about 0.8 to 7.5 MHz. The temperature for the resonator cells was maintained within ±0.01 °C (Lauda RM20). A pulse method equipped with 5 MHz fundamental *x*-cut crystal was used in the range from about 25 to 95 MHz, and the temperature for the pulse cell was maintained within ±0.1 °C (EYEYA UNI ACE BATH NCB-2200). More details for the apparatus are described elsewhere.[17,18] Sound velocity values were obtained

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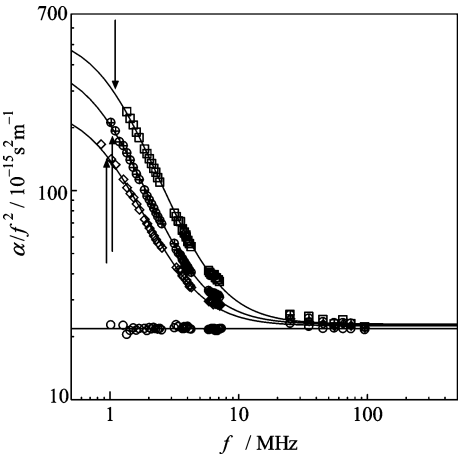

Figure 1. Representative ultrasonic absorption spectra in aqueous solutions of nonionized aspirin in the presence and absence of β-CD at pH ≈1.7 and 25 °C: (○) 0.0120 mol dm^{-3} aspirin; (◇) 0.0030 mol dm^{-3} aspirin + 0.0087 mol dm^{-3} β-CD; (⊕) 0.0050 mol dm^{-3} aspirin + 0.0087 mol dm^{-3} β-CD; (□) 0.0120 mol dm^{-3} aspirin + 0.0087 mol dm^{-3} β-CD. The arrows indicate the location of the relaxation frequency.

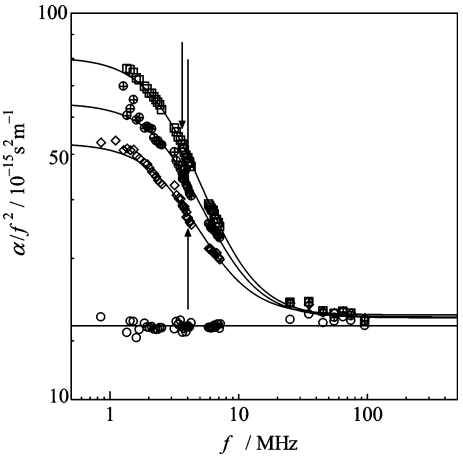

Figure 2. Representative ultrasonic absorption spectra in aqueous solutions of ionized aspirin in the presence and absence of β-CD at pH ≈6.0 and 25 °C: (○) 0.0120 mol dm^{-3} aspirin; (◇) 0.0050 mol dm^{-3} aspirin + 0.0087 mol dm^{-3} β-CD; (⊕) 0.0080 mol dm^{-3} aspirin + 0.0087 mol dm^{-3} β-CD; (□) 0.0120 mol dm^{-3} aspirin + 0.0087 mol dm^{-3} β-CD.

by the resonance method at around 3 MHz. Solution densities were measured by a vibrating density meter (Anton Paar NMA 60/602). Solution pHs were measured by using a glass electrode (HM-60S Toa Denpa pH meter) in the same thermostatic bath used in the pulse method. All experiments were carried out at 25 °C.

Results

The kinetic constants for the hydrolysis for free aspirin, k_{obsd}, as a function of pH at 25 °C were reported; $k_{obsd} = 2.18 \times 10^{-3}$ h^{-1} at pH 1.95, and $k_{obsd} = 1.4 \times 10^{-2}$ h^{-1} at pH 5.96.[19] These rates are sufficiently slow to not influence the ultrasonic absorption measurements.

Representative ultrasonic absorption spectra in aqueous solutions of nonionized (at pH ≈1.7) and ionized aspirin (at pH ≈6.0) in the presence and absence of β-CD are shown in Figures 1 and 2, respectively. The theory of the ultrasonic relaxation is described in detail elsewhere.[20−22] The frequency dependence of the absorption coefficient divided by the square of the measurement frequency, α/f^2, was not observed in nonionized or ionized aspirin aqueous solutions without β-CD. When β-CD and aspirin are both present in water, relaxational absorption is clearly observed. The frequency dependence of α/f^2 was analyzed by a Debye-type single relaxational equation as $\alpha/f^2 = A/\{1 + (f/f_r)^2\} + B$, where A, f_r, and B are the relaxational amplitude, the relaxation frequency, and the background absorption, respectively. A nonlinear least-mean-squares method was applied to obtain the best fit of the experimental data to yield the three parameters (f_r, A, and B). The calculated lines are well fitted to the experimental values of α/f^2, as seen in Figures 1 and 2. The obtained parameters are summarized in Table 1 along with the experimental values of the solution density, ρ, and the sound velocity, v.

As the relaxation is only observed in solutions containing both β-CD and aspirin, the cause of the relaxation may be due to a perturbation of a chemical equilibrium associated with an interaction between these two solute molecules as

$$\mathrm{CD} + \mathrm{GST} \underset{k_b}{\overset{k_f}{\rightleftharpoons}} \mathrm{CDGST} \qquad (1)$$

where CD indicates β-CD as the host, GST is aspirin as the guest, CDGST is the host−guest inclusion complex, and k_f and k_b are the forward and backward rate constants, respectively. The relaxation time, τ, or the relaxation frequency is derived for the perturbation of the above equilibrium as[23]

$$\tau^{-1} = 2\pi f_r = k_b\{(KC_{CD} + KC_{GST} + 1)^2 - 4K^2C_{CD}C_{GST}\}^{1/2} \qquad (2)$$

where K is the equilibrium constant defined as $K = k_f/k_b$ = [CDGST]/[CD][GST] and C_{CD} and C_{GST} are the initial concentrations of the host and the guest, respectively. When C_{CD} is fixed, f_r ought to be dependent only on C_{GST}.

First, the analysis of the results in the nonionized aspirin system is carried out. As the relaxation frequencies were dependent on C_{GST}, the constants, K and k_b, were determined using eq 2 by a nonlinear least-mean-squares method. From the definition of K, the k_f value was also calculated. The results thus obtained are indicated in Table 2, and the plots of $2\pi f_r$ versus $\{(KC_{CD} + KC_{GST} + 1)^2 - 4K^2C_{CD}C_{GST}\}^{1/2}$ are shown in Figure 3. The good agreement between the calculated line and the experimental data supports the validity of the proposed reaction mechanism.

The concentration dependence of the maximum absorption per wavelength, $\mu_{max} = 0.5Af_rv$, can also be interpreted, and it is given by eq 3 for the above-proposed reaction.

$$\mu_{max} = \pi\rho v^2\{1/[\mathrm{CD}] + 1/[\mathrm{GST}] + 1/[\mathrm{CDGST}]\}^{-1}(\Delta V)^2/2RT \qquad (3)$$

where ΔV is a standard volume change of the reaction and the contribution of the enthalpy term to μ_{max} is negligibly small in aqueous solution.[20,21] Plots of $2RT\mu_{max}/\pi\rho v^2$ versus $\{1/[\mathrm{CD}] + 1/[\mathrm{GST}] + 1/[\mathrm{CDGST}]\}^{-1}$ are shown in Figure 4; from the slope of the lines, the value of ΔV was calculated.

Next, the analysis for the aqueous solution of ionized aspirin and β-CD is performed. The relaxation frequencies are independent of C_{GST}. However, the relaxational amplitude, A, increased monotonically with C_{GST} and a similar tendency was also seen when amino acids (L-leucine and L-methionine) were the guests for β-CD.[12,14] The equilibrium concentrations of the reactants in eq 1 can be obtained if the K value is known. Thus, a trial-and-error procedure was used to obtain the K value which provided the best match to the experimental plots of $2RT\mu_{max}/$

TABLE 1: Ultrasonic Relaxation and Thermodynamic Parameters in Aqueous Solutions of Aspirin with β-CD at 25 °C

C_{CD} (mol dm^{-3})	C_{GST} (mol dm^{-3})	f_r (MHz)	A (10^{-15} s^2 m^{-1})	B (10^{-15} s^2 m^{-1})	ρ (kg m^{-3})	v (m s^{-1})	pH
			β-CD + Nonionized Aspirin System				
0.0087	0.003	1.01 ± 0.05	231 ± 19	22.5 ± 0.1	1001.47 ± 0.01	1493.6 ± 0.8	1.75
0.0087	0.005	0.95 ± 0.05	388 ± 35	22.9 ± 0.1	1001.54 ± 0.01	1496.9 ± 0.8	1.74
0.0087	0.008	0.92 ± 0.02	569 ± 16	22.6 ± 0.1	1001.61 ± 0.01	1493.6 ± 0.7	1.76
0.0087	0.010	0.98 ± 0.03	584 ± 30	22.7 ± 0.1	1001.68 ± 0.01	1497.3 ± 0.8	1.74
0.0087	0.012	1.08 ± 0.05	541 ± 44	23.0 ± 0.1	1001.73 ± 0.01	1498.4 ± 0.8	1.74
			β-CD + Ionized Aspirin System				
0.0087	0.003	4.17 ± 0.22	19.7 ± 1.1	22.2 ± 0.1	1001.20 ± 0.01	1494.0 ± 0.8	6.09
0.0087	0.005	3.94 ± 0.16	30.1 ± 1.3	22.7 ± 0.1	1001.35 ± 0.01	1495.7 ± 0.8	6.02
0.0087	0.008	4.09 ± 0.16	41.8 ± 1.6	22.4 ± 0.1	1001.57 ± 0.01	1497.5 ± 0.8	5.97
0.0087	0.010	3.81 ± 0.07	51.3 ± 1.0	22.5 ± 0.1	1001.76 ± 0.01	1494.7 ± 0.8	5.95
0.0087	0.012	3.76 ± 0.13	58.1 ± 2.0	22.5 ± 0.1	1001.84 ± 0.01	1496.1 ± 0.8	6.05

TABLE 2: Rate and Thermodynamic Constants for Host−Guest Complexation at 25 °C

guest	k_f (10^8 mol^{-1} dm^3 s^{-1})	k_b (10^6 s^{-1})	K (mol^{-1} dm^3)	ΔV (10^{-6} m^3 mol^{-1})
nonionized aspirin	7.21 ± 0.04	1.31 ± 0.03	549 ± 2	15.5 ± 0.1
ionized aspirin	7.8 ± 0.5	15.2 ± 1.1	51	8.5 ± 1.1
nonionized propionic acid[a]	3.6 ± 0.1	67 ± 1	5.3 ± 0.2	17.8 ± 0.7
ionized propionic acid[a]	1.9 ± 0.1	81.9 ± 0.4	2.4 ± 0.1	16.2 ± 0.1

[a] Reference 13.

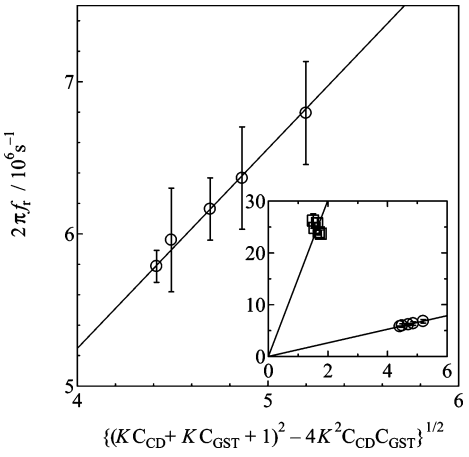

Figure 3. Plots of $2\pi f_r$ vs $\{(KC_{CD} + KC_{GST} + 1)^2 - 4K^2C_{CD}C_{GST}\}^{1/2}$ for aqueous solutions of aspirin in the presence of 0.0087 mol dm^{-3} β-CD at 25 °C: (○) nonionized aspirin system; (□) ionized aspirin system.

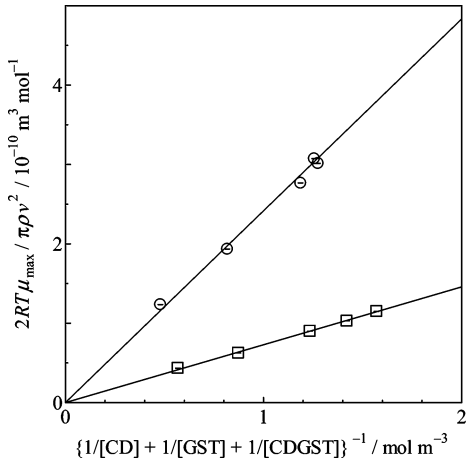

Figure 4. Plots of $2RT\mu_{max}/\pi\rho v^2$ vs $\{1/[CD] + 1/[GST] + 1/[CDGST]\}^{-1}$ for aqueous solutions of aspirin in the presence of 0.0087 mol dm^{-3} β-CD at 25 °C: (○) nonionized aspirin system; (□) ionized aspirin system.

$\pi\rho v^2$ versus $\{1/[CD] + 1/[GST] + 1/[CDGST]\}^{-1}$, with the line passing through the origin. The best fit is obtained when K = 51 dm^3 mol^{-1}, which is shown in Figure 4. The ΔV value in Table 2 was calculated from the slope of the line. Previously, eq 2 was simplified to $2\pi f_r \approx k_b$ for the solutions with L-leucine and L-methionine. However, it is inappropriate to apply the same approximation to the ionized aspirin system, since the hydrophobicity of aspirin (mainly due to the phenyl ring) is very high and the value of k_b might be much smaller than those for the solutions with the amino acids. Therefore, the equation in which the relaxation frequency was related to the rate constants and the reactant concentrations was used to obtain the reverse rate constant as

$$k_b = 2\pi f_r/[K\{[CD] + [GST]\} + 1] \quad (4)$$

The mean value of the calculated k_b's is shown in Table 2. Similar plots of $2\pi f_r$ versus the concentration term, $\{(KC_{CD} + KC_{GST} + 1)^2 - 4K^2C_{CD}C_{GST}\}^{1/2}$, for the ionized aspirin system are also shown in Figure 3.

Discussion

The association rate constants, k_f, obtained for both aspirin systems are virtually the same, approximately 7.5 × 10^8 mol^{-1} dm^3 s^{-1}. To examine whether the process is a diffusion-controlled reaction, we applied Smoluchowski's equation, giving the rate constant as[24]

$$k_D = 4\pi N_A(D_{CD} + D_{GST})(r_{CD} + r_{GST}) \quad (5)$$

where N_A is Avogadro's number, D_{CD} and D_{GST} are the diffusion coefficients for the reactants, and r_{CD} and r_{GST} are the estimated radii of the reacting molecules. The value of the diffusion coefficient[25] of *o*-amino benzoic acid in water at 25 °C and 0.24 wt % (0.84 × 10^{-9} m^2 s^{-1}) was used instead of that of aspirin, since the value for aspirin was not reported to the best of our knowledge. Also, the diffusion coefficients for similar compounds fall into a similar range.[26−30] The radius of the aspirin molecule in water, r_{GST}, was estimated by using molecular modeling computation software, WinMOPAC v.3.0 (Fujitsu, Co. Ltd), to be approximately 0.41 nm. Other reference values, D_{CD} and r_{CD} could be found in the literature.[31,32]

Applying the necessary conditions[14] for forming the inclusion complex (the inclusion of the guest occurs at the entrances of the β-CD cavity, and the rate constant is diminished by the power of the ratio of the entrance area to the total surface area of the β-CD molecule), we obtained $k_D \approx 8.4 \times 10^8$ mol^{-1} dm^3 s^{-1}. The calculated value is very similar to those obtained in this study for both aspirin systems.

The k_D values calculated through eq 5 for other CD systems in our previous studies[14,15] are on the order of $(8-9) \times 10^8$ mol^{-1} dm^3 s^{-1}, while the average k_f value obtained by the ultrasonic experiment is about 3×10^8 mol^{-1} dm^3 s^{-1}.[10-15] This difference is considered to be due to the hydrophobicity of the guest molecules. Most of the guest molecules in the previous studies possessed relatively small hydrophobic groups. The smaller k_f values obtained experimentally suggest that a part of the guest molecule with the small hydrophobicity is included into the CD cavity. On the other hand, the hydrophobicity of the phenyl ring in aspirin is so high that once the aspirin molecule comes close to the entrance of the β-CD cavity, almost all of the aspirin molecule is considered to be included into the cavity.

The dissociation rate constants, k_b, obtained in this study are considerably smaller than those reported for other CD systems.[10-15] As mentioned, the hydrophobicity in the guest molecules is the most important factor for the k_b value, the smaller value of which leads to the more stable inclusion complex, since the k_f value was not so sensitive to a structure of host and guest molecules (2-3 times the k_f value). It can be seen in Table 2 that the k_b value decreases drastically with an increase in the hydrophobicity of the guest molecules. The k_b value for the nonionized propionic acid system is smaller than that of the ionized system,[13] although the difference is not sufficient to see the existence of charge, as seen in Table 2. The k_b values in this study are significantly different; the k_b value for the nonionized system is more than 10 times smaller than that of the ionized system. This may be because the charged group in the ionized aspirin can be easily drawn to solvent bulk water. It is also reported that ionization of NSAID drugs such as aspirin, ibuprofen, and naproxen greatly reduces the stability constant for their complexation reaction with the host, hydroxypropyl-β-CD.[4,5] The much smaller k_b value and the greater equilibrium constant, K, under acidic conditions compared to those under neutral conditions suggest that most of the aspirin molecule is captured by the β-CD cavity, which results in less contact with the gastric wall.

Next, the results regarding the standard volume change of the reaction, ΔV, are considered. It was proposed that approximately five to seven water molecules are originally located inside the β-CD cavity in aqueous solutions and some of the molecules are expelled when a guest molecule enters into the cavity.[31,33-35] The positive contribution for the ΔV value is the volume nV_{H_2O}, where n is the number of the ejected water molecules, and the negative contribution is the included volume of a guest molecule into the cavity, V_{incl}. Consequently, the ΔV value is simply expressed by the equation as $\Delta V = nV_{H_2O} - V_{incl}$. Loftsson et al.[5] carried out structural analysis for the inclusion complex between β-CD and aspirin at 24 °C by ^{1}H NMR. Their experimental conditions are comparable to those of the present study. It was concluded that the phenyl ring of aspirin is completely included into the cavity and the ester group stands somewhat out of the cavity. The molar volume of benzene in water at 25 °C is about 83×10^{-6} m^3 mol^{-1},[36,37] which turns out to be the V_{incl} value in the nonionized system. The sign of the ΔV value which can be obtained from ultrasonic measurements is not known (i.e., it is the absolute value). When β-CD and other β-CD derivatives are used as hosts for their inclusion complexes, it is believed that the ΔV value is positive.[34,38] Hence, the number of expelled water molecules is calculated to be $n \approx 5.5$ for the nonionized aspirin system. In contrast, it can be considered that the ionized aspirin molecule is, to a certain degree, pulled out from the β-CD cavity when compared to the complex between nonionized aspirin and β-CD. Therefore, the included portion of the aspirin molecule should be smaller than that under acidic conditions. Consequently, the value of n for the ionized aspirin system is estimated to be less than 5.1.

Conclusions

The observed ultrasonic relaxation in an aqueous solution containing β-CD and aspirin has been found to be due to the complexation reaction between β-CD and aspirin. The rate constants for the formation and the dissociation of the complex were obtained from the concentration dependence of the relaxation frequency and the maximum absorption per wavelength. The rate of the complex formation is found to be diffusion controlled from Smoluchowski's equation, taking into account the reaction site. A clear charge effect in the guest molecules is reflected in the dissociating process of the guest from the inclusion complex. Further, from the experimental values of the standard volume change of the reaction, it has been concluded that about five water molecules are expelled on complexation of aspirin into the β-CD cavity.

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