Dynamic Interaction between Cyclodextrin and Nonelectrolytes in Aqueous Solutions by Ultrasonic Relaxation Method

Sadakatsu Nishikawa* and Takaho Ugawa

Department of Chemistry and Applied Chemistry, Faculty of Science and Engineering, Saga University, Saga 840-8502, Japan

Received: October 14, 1999; In Final Form: January 20, 2000

Ultrasonic absorption coefficients were measured in aqueous β-cyclodextrin (host) solutions with 1-butyramide (guest), with methyl propionate (guest) and with methyl butyrate (guest) by pulse and resonance methods in the frequency range from 0.8 to 95 MHz at 25 °C. The cause of a single relaxational absorption observed was ascribed to a perturbation of a chemical equilibrium associated with β-cyclodextrin and nonelectrolyte interaction. From the concentration dependence of the ultrasonic parameters, the rate and equilibrium constants were determined. These results were compared with those reported already in other systems with β-cyclodextrin and were discussed in relation to the β-cyclodextrin and guest molecular structures. It was found that the interactions of β-cyclodextrin with the nonelectrolytes were dependent on the characteristics of hydrophobicity and functional group of the guests.

Introduction

Cyclodextrin (CD) (host) is cyclic oligomers composed of six (α-CD), seven (β-CD), eight (γ-CD), or more α-1,4-glucopyranose units. The cavity of the doughnut-shaped CD molecule accommodates a variety of other compounds (guest) to form inclusion complexes. A lot of equilibrium studies have been carried out using UV, NMR, fluoroscence, calorimetry, etc. in order to obtain the stability of complexes.[1−4] However, relatively little kinetic study has been achieved, because the dynamic characteristics differ too greatly, depending upon functions and structures of host and guest molecules.[5−10] Revealing the kinetic mechanism of complexation and decomplexation reaction between host and guest leads to a more accurate understanding of the inclusion complexes which are applied to drug delivery system, fabric softner, release ability of fragrance, and so on.

In our series of the dynamic studies for interactions between cyclodextrins and some alcohols by ultrasonic relaxation method,[5,11] it has been clarified that the rate of the decomplexation of host and guest is very dependent on the size and hydrophobicity of the guest molecules. Also, it has been speculated that the hydroxy groups in the guest molecules are still interacting with bulk water molecules or hydroxy groups at the rim of CD. Then, it is very interesting to see how functional group affects the dynamic characteristics of the complexation and decomplexation processes. To highlight this effect, β-cyclodextrin has been chosen as the host, and three nonelectrolytes (butyramide, methyl propionate, and methyl butyrate) have been taken as the guest. The sound absorption coefficient and velocity and the solution density have been measured as a function of the concentrations. The results are compared with those for other guests with β-cyclodextrin and are discussed in relation to the guest molecular structures and the kinetic characteristics.

* To whom correspondence should be addressed. E-mail: nishikas@cc.saga-u.ac.jp.

Experimental Section

β-Cyclodextrin was purchased from Wako Pure Chemical Co. Ltd. It was recrystallized once from water and then 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. Butyramide, methyl propionate, and methyl butyrate were also purchased from Wako Pure Chemical Co. Ltd. as the purest grade and were used without further purification. 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, a, were measured in the frequency range from about 0.8 to 9 MHz by a resonance method. A new resonance cell with 7 MHz x-cut fundamental crystal (2 cm diameter) was constructed in order to obtain the absorption coefficient in the range from 8 to 9 MHz. A pulse method was used in the frequency range from 25 to 95 MHz. More details about the absorption apparatus and the procedure for determining the absorption coefficient are described elsewhere.[12,13] Sound velocity values were obtained by the resonator at around 3 MHz. Density measurements were carried out using a vibrating density meter (Anton Paar DMA 60/602). The temperature for all of the resonator cells was controlled within ±0.01 °C (Lauda, RM20) and that for the pulse was maintained within ±0.1 °C (EYELA UNI ACE BATH NCB-2200). All measurements were performed at 25 °C.

Results

Kato et al. have reported that the relaxational absorption is found for aqueous β-CD solution in the concentration 0.013 mol dm^{-3}.[14] However, in the more dilute solution of β-CD, no relaxation exists as is reported previously.[11] Figures 1−3 show representative ultrasonic absorption spectra in aqueous solutions of butyramide, methyl propionate, and methyl butyrate in the presence or absence of β-CD, respectively. The frequency dependence of the absorption coefficient divided by the square of the frequency, a/f^2, was not observed in the solutions without

10.1021/jp993677l CCC: $19.00
Published on Web 03/11/2000

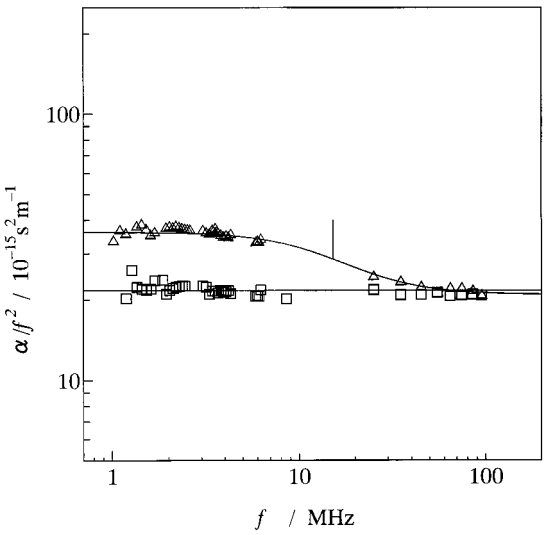

Figure 1. Ultrasonic absorption spectra in aqueous solutions of β-CD with butyramide and in aqueous solution of butyramide: (Δ) 0.0087 mol dm^{-3} β-CD and 0.040 mol dm^{-3} butyramide; (□) 0.090 mol dm^{-3} butyramide.

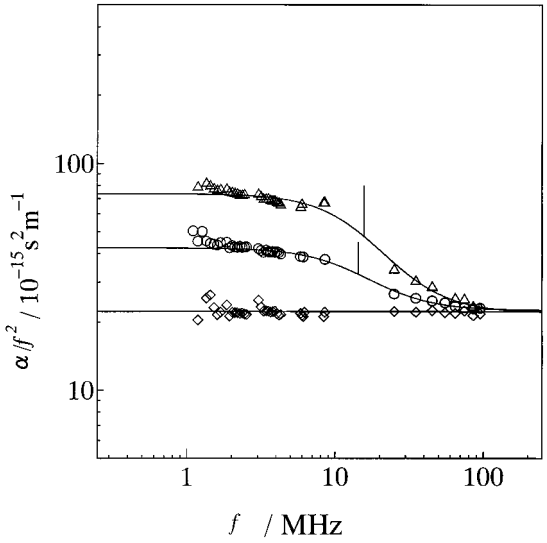

Figure 2. Ultrasonic absorption spectra in aqueous solutions of β-CD with methyl propionate and in aqueous solution of methyl propionate: (○) 0.0087 mol dm^{-3} β-CD and 0.016 mol dm^{-3} methyl propionate; (△) 0.0087 mol dm^{-3} β-CD and 0.060 mol dm^{-3} methyl propionate; (◇) 0.10 mol dm^{-3} methyl propionate.

β-CD in the concentration range investigated in this study. When both of the solutes, that is, β-CD and the individual nonelectrolyte, coexist in the solution, the values of a/f^2 are dependent on the frequency.

The frequency dependence of the absorption has been tested by a Debye-type relaxational equation,

$$a/f^2 = A/\{1 + (f/f_r)^2\} + B \quad (1)$$

where f_r is the relaxation frequency and A and B are constants. Equation 1 is a monotonic decreasing function with the frequency and, therefore, to give similar weight to the experimental data as a function of the frequency, the modified equation as $(a/f^2)f = Af/\{1 + (f/f_r)^2\} + Bf$ has been used for determining the ultrasonic parameters, f_r, A, and B, using a nonlinear least-mean-squares method. The solid curves in Figures 1−3 are generated from the obtained parameters, and it is seen that all the absorption data with the relaxational absorption have been

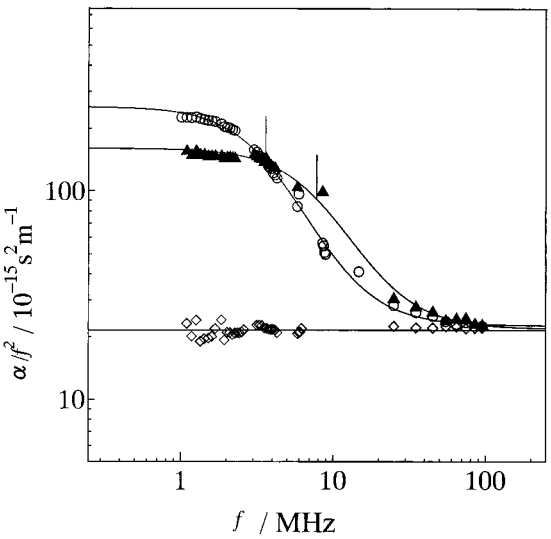

Figure 3. Ultrasonic absorption spectra in aqueous solutions β-CD solution with methyl butyrate and in aqueous solution of methyl butyrate: (○) 0.0087 mol dm^{-3} β-CD and 0.034 mol dm^{-3} methyl butyrate; (▲) 0.0087 mol dm^{-3} β-CD and 0.086 mol dm^{-3} methyl butyrate; (◇) 0.076 mol dm^{-3} methyl butyrate.

found to constitute a satisfactory fit to eq 1. In Table 1, the obtained ultrasonic relaxation parameters are listed along with the sound velocity and density data. From these experimental facts, the cause of the ultrasonic relaxation is considered to be associated with the interaction between β-CD and the nonelectrolytes. Thus, the perturbation of the following equilibrium by the ultrasonic wave is taken into account for the cause of the observed relaxation,

$$\mathrm{CD} + \mathrm{GST} \underset{k_b}{\overset{k_f}{\rightleftharpoons}} \mathrm{CDGST} \quad (2)$$

where CD is β-CD, GST is the nonelectrolytes, CDGST is the complex, and k_f and k_b are the forward and backward rate constants, respectively. We define the equilibrium constant, K, as $K = k_f/k_b = [\mathrm{CDGST}]/[\mathrm{CD}][\mathrm{GST}]$. As the solutes are nonelectrolytes and the concentrations are not so high, it may be approximated that the activities for the reactants are close to their concentrations. Then, the relationship for the relaxation time, τ, or the relaxation frequency with the reactant concentrations is derived, following the procedure of the relaxation method. It is, then, expressed by a function of the analytical concentrations of C_{CD} and C_{GST} for β-CD and the nonelectrolytes, respectively.[5]

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

When the concentration of β-CD is fixed, the relaxation frequency is only a function of the guest concentration, C_{GST}. Consequently, the parameters, K and k_b, can be estimated using a nonlinear least-mean-square method. Thus determined values are listed in Table 2 along with those for the solutions with other guests reported previously.[11] Figures 4−6 show the plots of $2\pi f_r$ vs $[\{1 + K(C_{CD} + C_{GST})\}^2 - 4K^2 C_{CD}C_{GST}]^{1/2}$ for three guests. It can be seen that the experimental data fall almost on a straight line which goes through a zero intercept, the results of which confirm that the cause of the relaxation is due to a perturbation of the equilibrium expressed by eq 2.

Another piece of information obtained by the absorption measurement is a standard volume change of the reaction, ΔV.

TABLE 1: Ultrasonic Thermodynamic Parameters for Aqueous Solution of 0.0087 mol dm^{-3} β-CD with the Nonelectrolytes[a]

C_{GST} mol dm^{-3}	f_r MHz	A 10^{-15} s^2 m^{-1}	B 10^{-15} s^2 m^{-1}	ρ^a kg dm^{-3}	c ms^{-1}
			butyramide		
0.010	15 ± 2	8.4 ± 0.7	21.5 ± 0.1	1.0010	1500.5 ± 0.9
0.030	20 ± 1	13.8 ± 0.8	21.0 ± 0.1	1.0011	1502.0 ± 1.0
0.040	15.2 ± 0.8	15.1 ± 0.5	20.95 ± 0.07	1.0011	1501.9 ± 1.0
0.060	18 ± 2	18 ± 2	20.1 ± 0.3	1.0010	1502.7 ± 0.9
0.075	19 ± 1	15.1 ± 1.0	21.3 ± 0.2	1.0010	1503.0 ± 1.0
0.10	24 ± 1	14.4 ± 0.7	20.1 ± 0.1	1.0010	1506.7 ± 0.6
0.15	23 ± 1	10.7 ± 0.5	22.04 ± 0.09	1.0010	1510.0 ± 0.6
0.20	22 ± 1	11.3 ± 0.4	19.8 ± 0.1	1.0010	1512.0 ± 1.0
			methyl propionate		
0.016	14.4 ± 0.4	19.9 ± 0.4	22.52 ± 0.05	1.0008	1499.8 ± 1.0
0.021	13.0 ± 0.8	23.2 ± 0.9	22.3 ± 0.1	1.0008	1499.8 ± 1.0
0.030	15.2 ± 0.6	40.1 ± 1.0	21.6 ± 0.1	1.0009	1502.0 ± 0.8
0.041	15.8 ± 0.5	39.7 ± 0.9	21.5 ± 0.1	1.0009	1502.0 ± 0.8
0.060	15.7 ± 0.5	52 ± 1	22.0 ± 0.2	1.0009	1501.9 ± 1.0
0.080	14.9 ± 0.8	41 ± 1	21.5 ± 0.2	1.0009	1501.0 ± 1.0
0.10	15.6 ± 0.4	59 ± 1	21.8 ± 0.2	1.0008	1503.9 ± 0.7
0.15	17.2 ± 0.5	53 ± 1	22.7 ± 0.2	1.0008	1505.2 ± 0.7
0.20	18 ± 1	49 ± 2	24.5 ± 0.4	1.0008	1505.8 ± 0.7
			methyl butyrate		
0.013	3.1 ± 0.1	110 ± 2	20.24 ± 0.08	1.0009	1500.0 ± 1.0
0.024	3.42 ± 0.07	239 ± 5	22.88 ± 0.09	1.0008	1500.4 ± 0.9
0.034	3.61 ± 0.07	232 ± 4	22.6 ± 0.1	1.0008	1500.9 ± 0.6
0.050	4.89 ± 0.10	203 ± 3	22.86 ± 0.08	1.0007	1498.9 ± 0.8
0.072	6.1 ± 0.2	151 ± 3	22.4 ± 0.1	1.0007	1502.0 ± 1.0
0.086	7.8 ± 0.3	138 ± 3	21.8 ± 0.2	1.0007	1501.5 ± 1.0
0.10	7.1 ± 0.2	160 ± 4	20.7 ± 0.2	1.0007	1505.8 ± 0.7

[a] The errors of the density values are with ±0.0001 kg dm^{-3}.

TABLE 2: Rate and Thermodynamic Constants for Complexation of β-CD with Some Guests at 25 °C

	k_f mol^{-1} dm^3 s^{-1}	k_b s^{-1}	K mol^{-1} dm^3	K^a mol^{-1} dm^3	ΔV 10^{-6} m^3 mol^{-1}
methyl propionate	(1.3 ± 0.1) × 10^8	(8.66 ± 0.10) × 10^7	1.5 ± 0.1		24 ± 3
methyl butryrate	(3.7 ± 0.3) × 10^8	(1.28 ± 0.03) × 10^7	29 ± 1		16 ± 2
1-butyramide	(2.7 ± 0.3) × 10^8	(9.8 ± 0.7) × 10^7	2.7 ± 0.3		12 ± 2
1-propanol	(5.1 ± 0.7) × 10^8	(1.21 ± 0.07) × 10^8	4.2 ± 0.6	3.72, 4.5	12.5 ± 0.3
1-butanol	(2.8 ± 0.8) × 10^8	(3.8 ± 0.6) × 10^7	7.2 ± 2	14.6, 16	11.1 ± 1

[a] The values in refs 19 and 20.

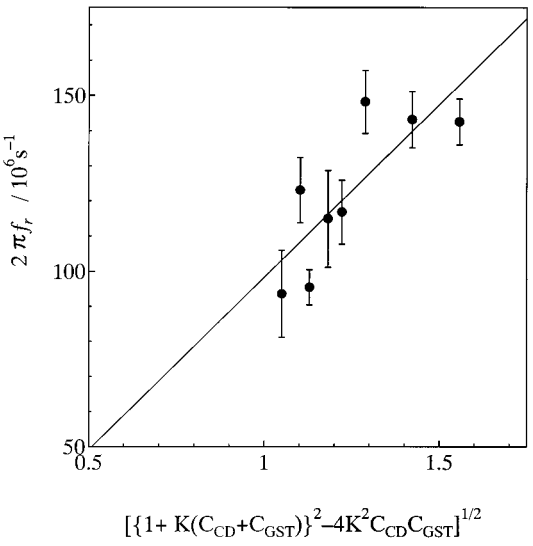

Figure 4. Plots of $2\pi f_r$ vs $[\{1 + K(C_{CD} + C_{GST})\}^2 - 4K^2C_{CD}C_{GST}]^{1/2}$ for aqueous solutions of butyramide in the presence of β-CD.

In the ultrasonic relaxation study, the maximum absorption per wavelength, $\mu_{max} = 0.5Af_rc$, is conventionally employed where c is the sound velocity. This quantity is connected with the solution density, the sound velocity, and the reactant concentrations by the next equation.[15]

$$\mu_{max} = \pi\rho c^2(1/[CD] + 1/[RCONH_2] + 1/[CDRCONH_2])^{-1}(\Delta V)^2/2RT \quad (4)$$

The individual reactant concentrations are calculated from the analytical concentrations of the host and the guest using the obtained equilibrium constant, K. The values of ρ and c are determined independently. Therefore, ΔV is calculated by eq 4 and they are also indicated Table 2.

Discussion

There are so many reports[4] concerning the equilibrium properties for the complexation between hosts and guests. However, few experimental studies have been carried out for amide and CD or ester and CD systems to our knowledge. The present study may, therefore, be the first report for butyramide-β-CD, methyl propionate-β-CD, and methyl butyrate-β-CD interactions.

It is considered that the inside of the CD cavity is a considerably hydrophobic environment, while the outside of the cavity is hydrophilic because hydroxyl groups align on the rims of both sides of the cavity. From the calculation of the complex formation energy, it is said that the hydrophobic groups of guests prefer to incorporate into the CD cavity.[10] Since the complexation and decomplexation reactions in the present study are

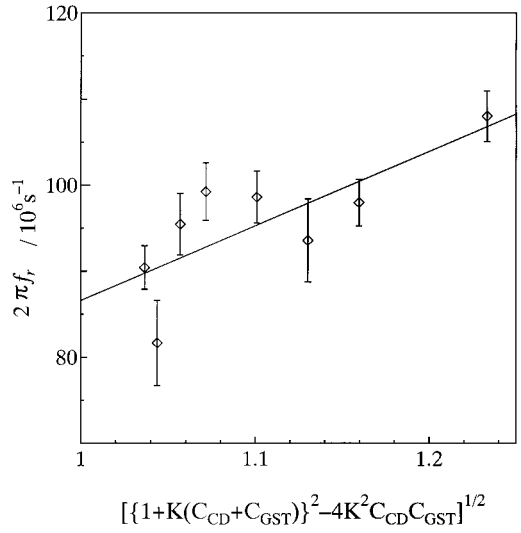

Figure 5. Plots of $2\pi f_r$ vs $[\{1 + K(C_{CD} + C_{GST})\}^2 - 4K^2C_{CD}C_{GST}]^{1/2}$ for aqueous solutions of methyl propionate in the presence of β-CD.

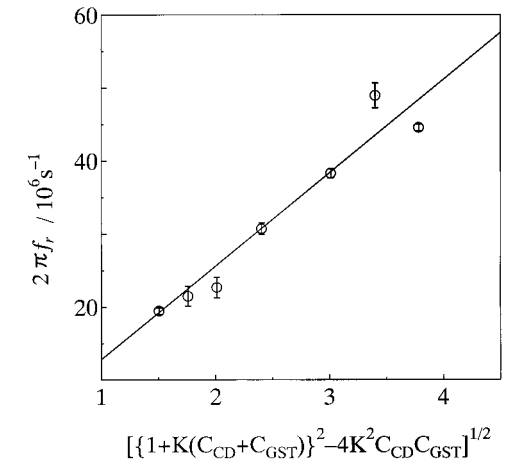

Figure 6. Plots of $2\pi f_r$ vs $[\{1 + K(C_{CD} + C_{GST})\}^2 - 4K^2C_{CD}C_{GST}]^{1/2}$ for aqueous solutions of methyl butyrate in the presence of β-CD.

proceeding in the aqueous media, the hydrophobic group of the nonelectrolytes is considered to be incorporated into the β-CD cavity.

As is seen in Table 2, the forward rate constants, namely, the measure of the incorporation rate into the β-CD cavity for the guests, are hardly dependent on the guest structures. It is of the order of 3×10^8 mol^{-1} dm^3 s^{-1}. These results are consistent with that predicted for the interactions between α- or β-CD's and some alcohols.[5,11] That is, the rate of the incorporation for small molecules is independent of the sizes of the host cavity and the hydrophobicity and hydrophilicity of the guests. This may be because the size of the cavity of the β-CD is big enough (about 7.0×10^{-10} m in the depth and diameter of the cavity) for the incorporation of these small guests.[16]

On the other hand, the backward rate constants are quite dependent on the structures of the guests as is seen in Table 2. The rate constants seem to be related to the hydrophobicity and the hydrophilicity of the guests. To see the effect of the hydrophobicity on the rate constant, the results in the solutions of methyl propionate and methyl butyrate may be compared with those in the solutions of 1-propanol and 1-butanol.[5] With increase of the number of carbon chain, it is found the rate constant, k_b, decreases considerably in the both cases. These decreases of the rate constants for the decomplexation cause the formation of the more stable complex (the increase of the equilibrium constant). That is, the hydrophobic group of the guest molecule plays an important role for the formation of the complex between CD and nonelectrolytes.

From the results for the solutions of methyl butyrate, 1-butyramide, and 1-propanol, it is possible to see the effect of the hydrophilicity on the interaction with the β-CD. The backward rate constant is the greatest for 1-propanol and the smallest for methyl butyrate in the three guests. As has been speculated,[10] the hydrophilic groups of guests are still interacting with the hydroxyl groups existing at the rims of CD. This interaction may also influence the rate of the departure of the guest from the cavity. The stronger the attractive interaction is between the polar group of the guests and the hydroxyl group of CD, the slower the rate constant, k_b, becomes. It is interesting to notice that the order of the polarity of functional groups is R−OH > R−CONH$_2$ > R−COOCH$_3$ and the order of the rate constant is the same as is seen in Table 2.

Next, we consider the result of the volume change of the reaction. It is considered that there are several water molecules in CD cavities. Fujiwara et al. have estimated that 1.4 water molecules in the cavity are released in average when one guest molecule moves into the α-CD.[17] Marini et al. have discussed that the hydrated β-CD can involve about seven water molecules, although the crystalline structure of β-CD involved two water molecules.[18] Therefore, even though some water molecules in β-CD are released when guest molecule is included in β-CD cavity, the observed volume changes seem to be considerably small (Table 2). This means that a part of the hydrophobic group of the guest molecule enters into the CD cavity while releasing some of water molecules, and the interactions are proceeding between the hydroxyl groups at the rims on β-CD and the functional groups of guests. This effect is also seen in the effect of the hydrophilic group on the backward rate constant. The volume change of the reaction for 1-butyramide is nearly equal to that of 1-propanol. This may arise from the expectation that the interaction between the hydroxy groups at the rims on β-CD and amide groups is not so different from that for 1-propanol. Also, the volume changes of the reaction for two methyl esters are relatively larger than the other guests. This may mean that the interaction between the hydroxy groups on the rims of CD and the methyl ester groups is considerably weaker than that for the other guests. Therefore, the ester is considered to incorporate further into the β-CD cavity.

Acknowledgment. This work was partly supported by a Grant-in-Aid for Science Research no. 09440202 from The Ministry of Education, Science and Culture of Japan.

References and Notes

(1) Tan, W. H.; Ishikura, T.; Muruta, A.; Yamamoto, T.; Matsui, Y. *Bull. Chem. Soc. Jpn*. **1998**, *71*, 2323.
(2) Mitra, S.; Das, R.; Mukherjee, S. *J. Phys. Chem. B* **1998**, *102*, 3730.
(3) Godinez, L. A.; Schwartz, L.; Criss, C. M.; Kaifar, A. E. *J. Phys. Chem. B* **1997**, *101*, 3376.
(4) Rekharsky, M. V.; Inoue, Y. *Chem. Rev.* **1998**, *98*, 1875.
(5) Nishikawa, S.; Yokoo, N.; Kuramoto, N. *J. Phys. Chem. B* **1998**, *102*, 4830.
(6) Turro, N. J.; Okubo, T.; Chung, C. *J. Am. Chem. Soc.* **1982**, *104*, 1789.
(7) Yoshida, N.; Yamaguchi, H.; Higashi, M. *J. Phys. Chem. A* **1998**, *102*, 1523.
(8) Rohrbach, R. P.; Rodriguer, L. J.; Eyring, E. M.; Wojcik, J. F. *J. Phys. Chem.* **1977**, *81*, 944.
(9) Hersey, A.; Rohmson, B. H.; Kelly, H. C. *J. Chem. Soc., Faraday. Trans. 1* **1986**, *82*, 1271.
(10) Harata, K. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2066.
(11) Nishikawa, S. *Bull. Chem. Soc. Jpn.* **1997**, *170*, 1003.

(12) Nishikawa, S.; Kotegawa, K. *J. Phys. Chem.* **1985**, *89*, 2896.
(13) Kuramoto, N.; Ueda, M.; Nishikawa, S. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1560.
(14) Kato, S.; Nomura, H.; Miyahara, Y. *J. Phys. Chem.* **1985**, *89*, 5417.
(15) Blndamar, M. J. *Chemical Ultrasonics*; Academic Press: New York, 1973.
(16) Bender, M. L. *Cyclodextrin Chemistry*, Springer-Verlag: New York, 1978.
(17) Fujiwara, H.; Arakawa, H.; Murata, S.; Sasaki, Y. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3891.
(18) Marini, A.; Berbenni, V.; Bruni, G.; Mossarotti, V.; Mustarelli, P. *J. Chem. Phys.* **1995**, *103*, 7532.
(19) Rekharsky, M. U.; Schwarz, F. P.; Tewari, Y. B.; Goldbarg, R. N. *J. Phys. Chem.* **1994**, *98*, 10282.
(20) Matsui, Y.; Mochida, K. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2808.