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Viscosity *B*-Coefficients, Apparent Molar Volumes, and Activity Coefficients for α- and γ-Cyclodextrins in Aqueous Solutions

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The viscosities and densities at 15, 25, and 35 °C, and activity coefficients at 25 °C for the aqueous solutions of α- and γ-cyclodextrins were measured, and the results were interpreted in terms of solute-solvent and solute-solute interactions. The concentration and temperature dependences of viscosities and apparent molar volumes are almost similar to those of linear saccharides, *i.e.* maltose and maltotriose, indicating that α- and γ-cyclodextrins are structure forming solutes. However, the concentration dependences of activity coefficients of cyclodextrins are significantly different from those of maltose and maltotriose. The results were tentatively assigned to the formation of dimer in aqueous solutions.

Cyclodextrins are the condensed ring compounds of D-glucopyranoses through α-1,4-glucosidic linkage and are called α-, β-, and γ-cyclodextrins (CD) in accordance with the numbers of glucose residues, 6, 7 and 8, respectively. CD has been well-known to form inclusion complexes with a wide varieties of molecular species irrespective of hydrophobic or ionic in nature.[1)]

In contrast to the numerous studies on the complex formation, the studies on the solution of CD seem to be sparse. However, the thermodynamic properties of aqueous solutions must play an important role on the complex formation, because the complex formation usually takes place in aqueous solution. Furthermore it is also interesting to compare the solution properties of CD with those of linear di- and trisaccharides reported previously.[2)]

In these viewpoints, we determined the viscosity *B*-coefficients and the apparent molar volumes at 15, 25, and 35 °C, and the activity coefficients at 25°C for α- and γ-CD in aquous solutions, and discussed the effects of CD on the water structure.

Experimental

Materials. Reagent grade α- and γ-CD purchased from Nakarai Chemical Co. Ltd., were recrystallized twice from water according to French *et al.*[3)] and were dried *in vacuo* for 5h at 110 °C before use. After drying, the water contents of crystalline compounds determined by the Carl Fisher method were found to be less than 0.2% for each CD. The concentration correction was made on every solution. Reagent grade sodium chloride purchased from Matsunaga Chemical Co. Ltd., was used after drying without purification. CD and sodium chloride solutions were prepared with water purified by distillation and deionization.

Methods. The viscosity and density measurements were carried out at 15, 25, and 35 °C by using the apparatus described in a previous paper.[2)] Vapour pressure over aqueous solution was measured at 25 °C with an osmometer model 117 manufactured by Corona Electric Co. Ltd. Sodium chloride was used as a standard substance for the measurement of the instrument constant. The instrument constant thus obtained was almost unchanged in a set of measurements. But the constant was changed slightly in another set of measurements. Consequently, the instrument constant was determined for every set of measurements.

Results

Viscosity. The reletive viscosity, η_{rel} of a non-electrolyte solution can be expressed by

$$\eta/\eta_0 = \eta_{\text{rel}} = 1 + Bc + Dc^2, \tag{1}$$

where η_0 and η are the viscosities of the solvent and the solution, respectively, and c is the concentration in mol dm^3. B and D are the characteristic constants depending on the solute and the solvent at constant temperature and pressure. The plots of $(\eta_{\text{rel}}-1)/c$ *vs.* c for α- and γ-CD at 25 °C are shown in Fig. 1, indicating that Eq. 1 is valid up to about 0.05 mol dm^{-3}. The B and D coefficients determined from the intercepts and slopes at 15, 25, and 35 °C are listed in Table 1. The points in low concentration, which considerably deviate from the lines because of the experimental error, were neglected, and the standard deviation of each plot up to 0.05 mol dm^{-3} was calculated to be within 0.014 mol^{-1} dm^3. Therefore, the experimental errors in B and D are estimated to be less than 0.03 mol^{-1} dm^3 and 1.0 mol^{-2} dm^6, respectively.

The increment of B-coefficient arising from the structural change of water, B_{st}, may be obtained by

$$B_{\text{st}} = B - \nu V/1000. \tag{2}$$

The second term of the right hand side of Eq. 2 expresses the contribution of the hydrodynamic obstruction effect according to Einstein and Shimha.[4)] On the assumptions that a certain number of water molecules is packed in a cavity and the shape of the molecule is approximated by an oblate ellipsoid, the ν value of α-CD was estimated on the basis of Scheraga's table[5)] using the numerical value of axial ratio obtained from the molecular model,[6)] resulting in 2.26. The molar volume of the oblate, V, is calculated by

$$V = \bar{V}^\circ + N\bar{V}_{\text{w}}, \tag{3}$$

where $\bar{V}^\circ$ and $\bar{V}_{\text{w}}$ is the partial molar volume of α-CD at infinite dilution and molar volume of water, respectively. N is the number of water molecules in the cavity. An α-cyclodextrin hexahydrate crystal contains two water molecules in the cavity.[7)] By assuming that the number of water molecules in the cavity of α-CD molecule in solution state is the same as that in solid state, the value of B_{st} of α-CD was found to be 0.71. The B_{st} value of γ-CD could not be obtained because

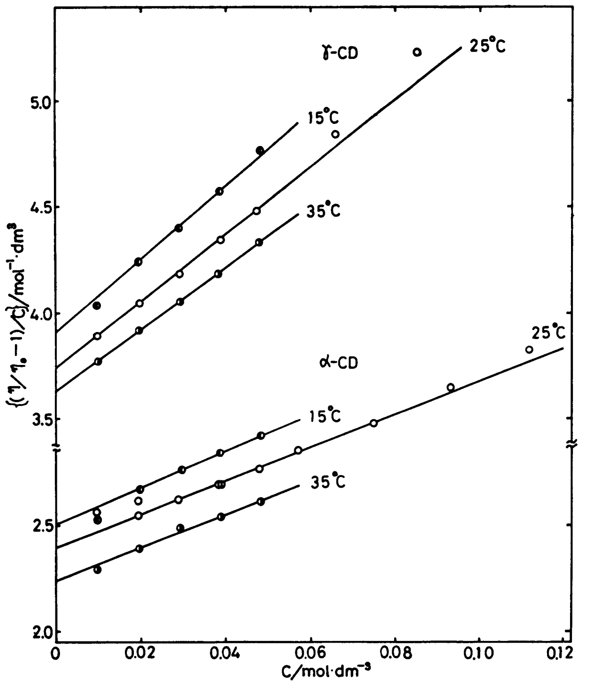

Fig. 1. Relations between $(\eta/\eta_0-1)/c$ and c for cyclodextrins at ◐ 15, ○ 25, and ◑ 35 °C.

Table 1. The values of B, D, dB/dT, $\bar{V}^\circ$ and α^* for cyclodextrins

	Temp/°C	α-CD	γ-CD
B / mol^{-1} dm^3	15	2.50	3.90
	25	2.39	3.74
	35	2.24	3.62
D / mol^{-2} dm^6	15	8.6	17.4
	25	7.8	15.7
	35	7.8	14.7
(dB/dT)×10^2 / mol^{-1} dm^3 K^{-1}	25	−1.3	−1.4
$\bar{V}^\circ$ / cm^3 mol^{-1}	15	598.5	788.5
	25	606.0	803.0
	35	612.0	805.3
α^*×10^3 / cm^3 mol^{-1} K^{-1}	25	1.1	0.8

the N value is not available.

Figure 2 shows the temperature dependence of B values. As seen in Fig. 2, the value of B decreases with increase of temperature for both CDs. The values of dB/dT at 25 °C are shown in Table 1.

Density. Apparent molar volume of solute, ϕ_v, was calculated by

$$\phi_v = \frac{1000(d_0-d)}{cd_0} + \frac{M_2}{d}, \tag{4}$$

where d_0 and d are the densities of the solvent and the solution, respectively, and M_2 is the molecular weight of the solute. As shown in Fig. 3, ϕ_v at each temperature is linearly related to c:

$$\phi_v = \bar{V}^\circ + b_v c, \tag{5}$$

where $\bar{V}^\circ$ is the partial molar volme at infinite dilution

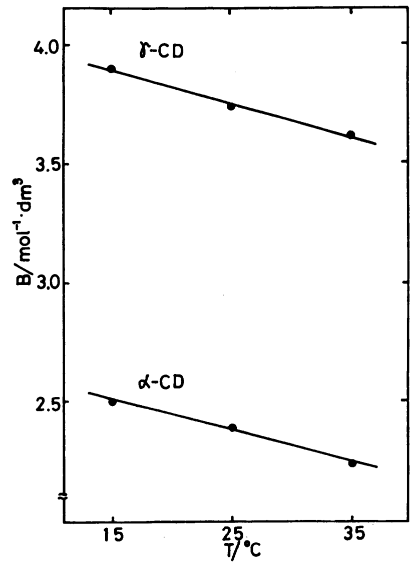

Fig. 2. Temperature dependenc of B-coefficients for cyclodextrins.

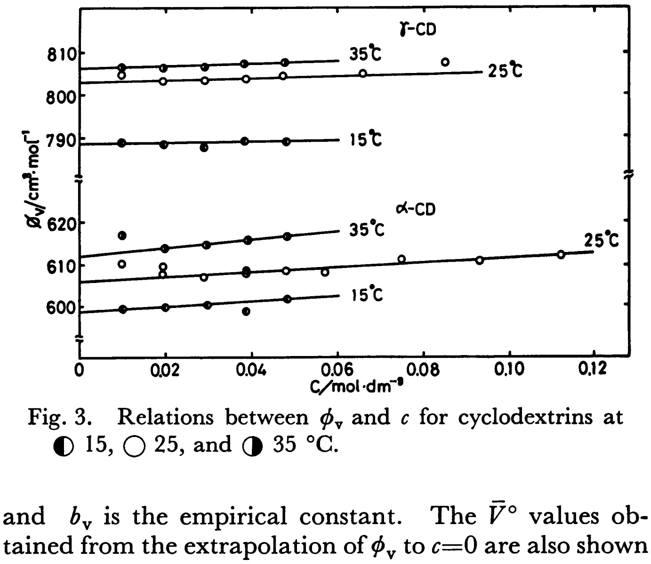

Fig. 3. Relations between ϕ_v and c for cyclodextrins at ◐ 15, ○ 25, and ◑ 35 °C.

and b_v is the empirical constant. The $\bar{V}^\circ$ values obtained from the extrapolation of ϕ_v to c=0 are also shown in Table 1. The values of b_v for the CDs are positive at every temperature. In Fig. 3, the positive deviations of ϕ_v from the lines in low concentration may be due to experimental error. The standard deviation of each plot was within 0.3 cm^3 mol^{-1}, if the points deviating extremely in low concentration were neglected. The experimental error in $\bar{V}^\circ$ is estimated to be less than 0.6 cm^3 mol^{-1}.

The temperature dependence of $\bar{V}^\circ$ is shown in Fig. 4. The values of $\bar{V}^\circ$ of α- and γ-CD increase nonlinearly with temperature, and the curves display upward curvatures. The thermal expansion coefficient, α^*, is defined by

$$\alpha^* = (\partial \bar{V}^\circ/\partial T)_p/\bar{V}^\circ. \tag{6}$$

The values of α^* at 25 °C are given in Table 1.

Activity Coefficient. The relations between the osmotic coefficient, ϕ, and the concentration in mol kg^{-1}, m, at 25 °C are shown in Fig. 5. By the least-squares fitting, ϕ's are expressed in terms of m as

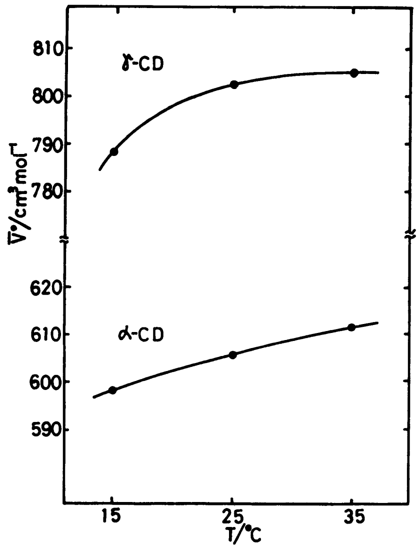

Fig. 4. Temperature dependence of $\bar{V}^\circ$ for cyclodextrins.

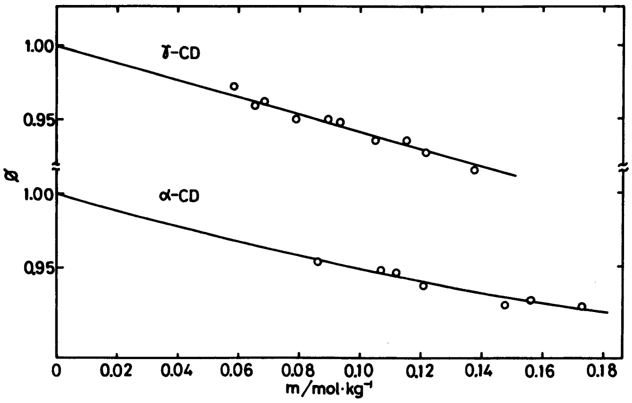

Fig. 5. Osmotic coefficients of cyclodextrins at 25 °C.

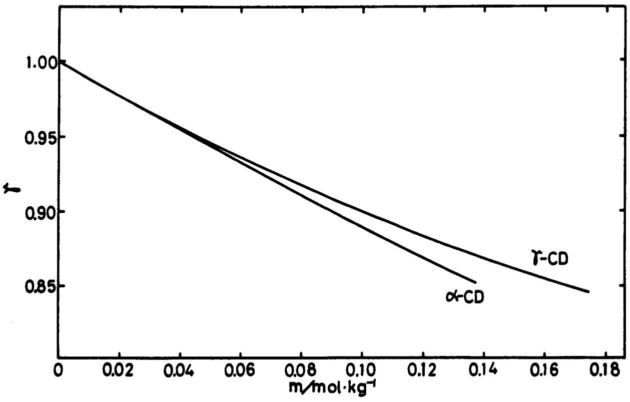

Fig. 6. Activity coefficients of cyclodextrins at 25 °C.

$$\left.\begin{aligned}\phi &= 1 - 0.585\,m \quad \text{for } \alpha\text{-CD},\\ \phi &= 1 - 0.588\,m + 0.789\,m^2 \quad \text{for } \gamma\text{-CD}.\end{aligned}\right\} \tag{7}$$

The activity coefficients, γ, were calculated from the osmotic coefficients by the following equation:

$$\ln \gamma = (\phi - 1) + \int_0^m \frac{\phi - 1}{m}\,\mathrm{d}m. \tag{8}$$

Introducing Eqs. 7 into Eq. 8, and integrating, we obtain

$$\left.\begin{aligned}\ln \gamma &= -\,1.170\,m \quad \text{for } \alpha\text{-CD},\\ \ln \gamma &= -\,1.176\,m + 1.148\,m^2 \quad \text{for } \gamma\text{-CD}.\end{aligned}\right\} \tag{9}$$

As seen in Figs. 5 and 6, the osmotic and activity coefficients decrease with increase of the concentration.

Discussion

As stated in a previous paper,[8] the signs and the magnitudes of B_{st} and $\mathrm{d}B/\mathrm{d}T$ are the useful criterion for the classification of solute property in water. As seen in Table 1, both α- and γ-CD are structure makers because of their negative $\mathrm{d}B/\mathrm{d}T$ values. The negative values of $\mathrm{d}B/\mathrm{d}T$ increase with the number of glucose regardless of linear[2] or cyclic, indicating that glucose residue has a structure forming ability. On the other hand, Hepler[9] proposed other criterion for the classification of solutes as structure makers or breakers. His criterion is that the structure making solutes have the positive sign of $(\partial^2\bar{V}^\circ/\partial T^2)$ while the structure breaking solutes the negative sign. As shown in Fig. 4, the signs of $(\partial^2\bar{V}^\circ/\partial T^2)$ for CDs are negative. If we adopt Hepler's criterion, CDs are structure breakers in disagreement with the conclusion obtained from B_{st} and $\mathrm{d}B/\mathrm{d}T$. As for hydrophilic nonelectrolytes, the values of $(\partial^2\bar{V}^\circ/\partial T^2)$ for urea,[10] maltose and maltotriose[2] are negative, and that for D-glucose[2] is nearly zero. These experimental results are in conflict with Hepler's criterion, because it has been proved by many studies that urea is a structure breaker, while D-glucose, maltose and maltotriose are structure makers. Therefore, Hepler's criterion seems to be inapplicable to hydrophilic nonelectrolytes such as sugars and urea.

As seen in Fig. 7, the B-coefficients of linear maltodextrins[11] increase almost linearly with the degree of polymerization (n) and the point of the B-coefficients for cyclic dextrins, *i.e.* α- and γ-CD, locate below the B *vs.* n curve for linear maltodextrins. The shape and the size of the hydrated molecule or ion affect mainly the sign and magnitude of the B-coefficient. The partial molar volumes of linear polysaccharides are not so

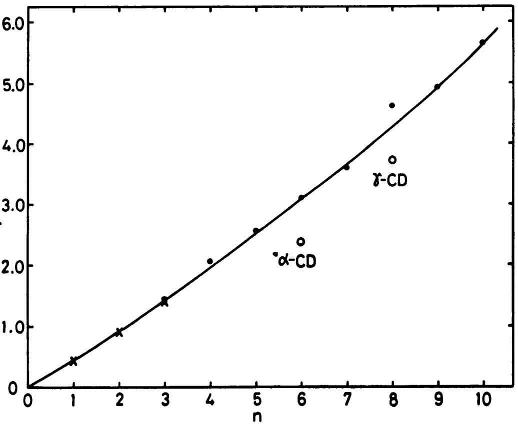

Fig. 7. Relation between B-coefficients and the number of glucose residues (n) for maltodextrins at 25 °C.
●: Calculated values from Thoma's table.[11] × : Our values in a previous paper.[2] ○: Cyclodextrin.

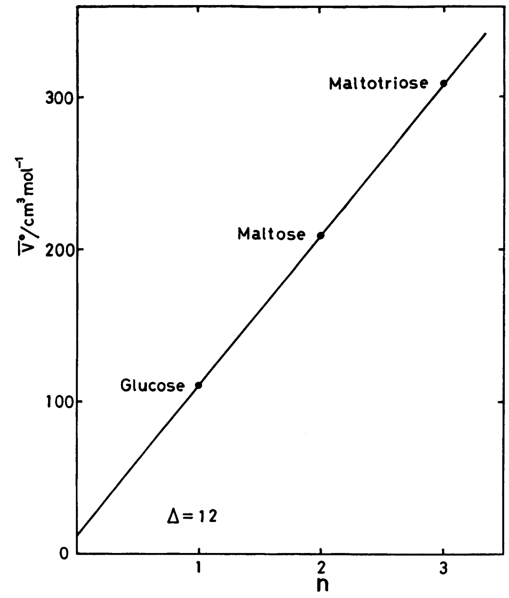

Fig. 8. Relation between $\bar{V}^{\circ}$ and n at 25 °C.

much different from those of the corresponding cyclic dextrins as will be seen later, and the hydrodynamic rigid volumes of the cyclic types are lager than those of the linear types based on the assumption that the exchange of water molecules between cavity and bulk has no influence on the hydrodynamic process. This assumption is supported by the fact that the point for γ-CD is more close to the B *vs.* n curve than that for α-CD in Fig. 7, because γ-CD has a larger cavity than α-CD.[12] The above discussion leads to the conclusion that the small values of the B-coefficients for cyclic dextrins, as compared with those of the corresponding linear ones, are due to the difference in shape, *i.e.* rod-like and oblate type molecules.

The partial molar volume at infinite dilution of a linear polymer, $\bar{V}^{\circ\mathrm{lin}}(n)$, is expressed as

$$\bar{V}^{\circ\mathrm{lin}}(n) = n\bar{V}^{\circ\mathrm{m}} - (n-1)\Delta = n(\bar{V}^{\circ\mathrm{m}} - \Delta) + \Delta, \tag{10}$$

where n is the degree of polymerization, $\bar{V}^{\circ\mathrm{m}}$ the volume of the monomer *i.e.* D-glucose, and Δ is the volume change on the formation of the α-1,4 ether linkage. On the other hand, the partial molar volume at infinite dilution of a cyclic polymer, $\bar{V}^{\circ\mathrm{cyc}}(n)$, is expressed as

$$\bar{V}^{\circ\mathrm{cyc}}(n) = n\bar{V}^{\circ\mathrm{m}} - n\Delta. \tag{11}$$

The Δ value was found to be 12 cm^3 mol^{-1} form the intercept and the slope of the $\bar{V}^{\circ\mathrm{lin}}(n)$ *vs.* n curve as seen in Fig. 8. The value of $\bar{V}^{\circ\mathrm{cyc}}(n)$ was calculated from Eq. 11 using the Δ value, resulting in 596 and 795 cm^3 mol^{-1} for α-CD and γ-CD, respectively. These calculated values are smaller than the experimental values of $\bar{V}^{\circ\mathrm{cyc}}(n)$ by 10 to 8 cm^3 mol^{-1}. This result may be due to the formation of intramolecular hydrogen bonding[13] and the bulkiness of water in the cavity in which hydrophobic environment is formed.

The thermal expansion coefficient of α-CD at 25 °C is close to that of D-glucose (1.0×10^{-3}) and smaller than that of maltose (1.3×10^{-3}) or maltotriose (1.4×10^{-3}). This fact may be related to the torsional rotation around the α-1,4-linkage which brings about the increase of unstructured water having high thermal expansibility because D-glucose has no α-1,4-linkage and the rotations of glucose residues in the CD molecule are almost hindered. The small value of α* of γ-CD may be due to the large cavity, in which bulky water is packed.

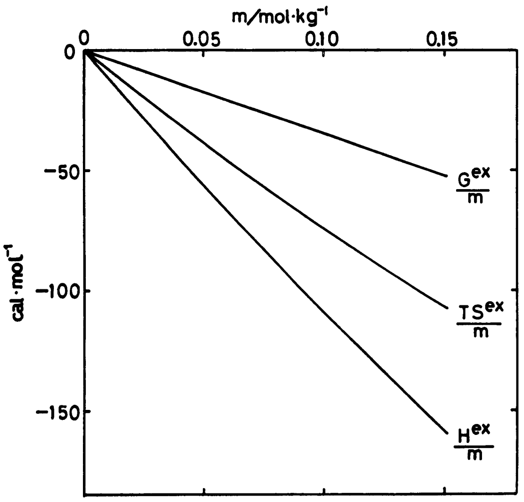

Fig. 9. Thermodynamic quantities of α-CD at 25 °C.

As seen in Figs. 5 and 6, the concentration dependences of the osmotic and activity coefficients for α- and γ-CD are strikingly different from those for linear oligosaccharides, such as maltose and maltotriose. The coefficients of the CDs decrease with increase of concentration. In general, the decrease in activity coefficients with the increase of concentration is possibly interpreted in terms of two different effects, *i.e.* structure breaking effect and the association of the solutes.

Using the data of the heat of dilution, ΔH^{dil},[14] excess thermodynamic quantities of α-CD are calculated from

$$G^{\mathrm{ex}} = mRT(1 - \phi + \ln\gamma), \tag{12}$$

$$H^{\mathrm{ex}} = -\Delta H^{\mathrm{dil}}, \tag{13}$$

and

$$G^{\mathrm{ex}} = H^{\mathrm{ex}} - TS^{\mathrm{ex}}. \tag{14}$$

As seen in Fig. 9, the sign of each quantity is negative, being opposite to that of D-glucose.[15] The negative sign of G^{ex} is based on the predominance of the negative value of H^{ex} over the negative value of TS^{ex}. The negative value of H^{ex} means the endothermic heat on the dilution process. Judging from the TS^{ex}/m *vs.* m curve in Fig. 9, excess partial molar entropy of water, $\bar{S}^{\mathrm{ex}}_{\mathrm{w}}$, would be positive, suggesting that the ordering of water molecules decreases with increase of solute concentration as far as solute-solute interactions are weak or absent. However, the possibility that the CD is a structure breaker would be small, because such a large decrease of γ in low concentration is unlikely to take place as a result of solute-solvent interaction alone, and α-CD is a hydrodynamically structure maker as stated in the preceding section.

From these considerations, we regard the positive value of $\bar{S}^{\mathrm{ex}}_{\mathrm{w}}$ as the result of the association of solute, and obtain the dimerization constant graphically using Eq. 13.[16]

$$K = (1 - \phi)/m\phi^2. \tag{13}$$

The K values of α- and γ-CD were found to be 0.66 and 0.55 mol^{-1} kg, respectively. These K values indicate that about 10 molecules out of 100 molecules form a dimer at 0.1 mol kg^{-1}.

The effect of the association of CD is considered to be reflected in Figs. 1 and 3. As mentioned above, B and $\bar{V}^\circ$ express the solute-solvent interactions at infinite dilution, where the association does not occur. The values of B and $\bar{V}^\circ$ are actually determined by the extrapolations of $(\eta_{\text{rel}}-1)/c$ and ϕ_v to $c=0$. Therefore, the discussions of the nature of CD based on these values are not influenced by the association of CD. On the other hand, D and b_v are regarded to express the solute-solute interactions. Accordingly, the effect of the association of CD is reflected in the values of D and b_v, *i.e.* the slopes of the lines in Figs. 1 and 3. But it is difficult to derive the evidences of the association of CD from the values of D and b_v, because these coefficients are also influenced by other complicated factors such as structural interactions.17,18)

We have no other evidence that CD forms a dimer in aqueous solutions at the present stage. But some kinds of compounds are included in β-CD dimer of head to head type, in which two secondary OH groups of β-CD are hydrogen bonded.19)

In conclusion, α- and γ-CD promote the structure of water and may possibly form a dimer in aqueous solutions, resulting in the increase of excess partial molar entropy of water.

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