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Formation Constants of Cyclodextrin Inclusion Complexes with Iodine in Aqueous Solutions

Isao SANEMASA,* Toyohisa KOBAYASHI, and Toshio DEGUCHI
Department of Chemistry, Faculty of Science, Kumamoto University, Kurokami 2-39-1, Kumamoto 860

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Formation constants of cyclodextrin (CyD) inclusion complexes with iodine were determined by measuring solubilities of iodine vapor in water. The formation constants at 25 °C are 8.3×10^3 (α-CyD), 1.0×10^2 (β-CyD), and 13 $dm^3\,mol^{-1}$ (γ-CyD). The temperature dependence of α-CyD–I_2 complexation was studied. ΔH and ΔS, being 9.52 kJ mol^{-1} and 107 J $K^{-1}\,mol^{-1}$ at 25 °C, respectively, are both largely dependent on temperature even within a rather small temperature range 15—35 °C studied. For the complexation with α-CyD, contribution of dehydration of iodine was estimated. The method proposed here is useful to study the formation of CyD association complexes with such substrates as are slightly soluble in water and easily vaporize from the aqueous phase.

The complex formation of cyclodextrin (CyD) with iodine has been studied with a view to understanding the far more complicated starch systems.[1,2] The molecular geometry of α-CyD–I_2 inclusion crystals has been determined by X-ray analysis as follows:[3] (a) The iodine molecule is coaxial with the host molecule, (b) one iodine atom of I_2 is situated near the opening on the primary alcohol side with a van der Waals contact with the cavity and the other is surrounded by six O(4) atoms with a contact greater than the van der Waals contact, and (c) the cavity is deep enough to enclose the whole iodine molecule. An iodine molecule can thus be suitably fitted with the α-CyD cavity. This may be responsible for giving the formation constant as large as 9.35×10^4 $dm^3\,mol^{-1}$ at 24 °C, the only data available so far in the literature.[2]

In our preceding paper[4] we reported a method of preparing an aqueous iodine solution saturated with its vapor. An important characteristic of this method is that the equilibrium solubility of iodine at a desired concentration can be obtained by adjusting the temperature of a solid iodine which is held separately isolated in space from an aqueous phase. The method seems to be suitable for studying possible interactions between iodine and a particular substance in an aqueous medium.

Here we have applied the method to aqueous CyD solutions. The equilibrium solubility of iodine vapor is increased by the presence of α-, β-, or γ-CyD, from which formation constants of inclusion complexes can be determined.

Experimental

Materials. Solid iodine of analytical reagent grade and cyclodextrins (α-, β-, and γ-CyD form Nakarai Chemicals) of guaranteed grade were used without further purification. A suitable amount of CyD, which had been dried over phosphorus pentaoxide, was weighed and dissolved in 1.0×10^{-3} mol dm^{-3} $HClO_4$ to prepare a CyD solution of known concentration. Perchloric acid was used instead of pure water to prevent hydrolysis of iodine.

Apparatus and Procedures. The apparatus used for preparing aqueous iodine solutions saturated with iodine vapor was essentially the same as that previously reported.[4] A 50 cm^3 aqueous CyD solution was placed in a separation funnel designated as the "solubility flask," and iodine crystals were packed in a column (ϕ 8 mm×200 mm) designated as the "solute reservoir." The temperatures of the solubility flask and the solute reservoir were held constant with water flows from separate thermostated baths circulating through their surrounding jackets. The assembled apparatus was placed in a chamber, where the temperature was kept higher than that of the solute reservoir. The iodine vapor, generated by a flow of air through the solute reservoir, was introduced into the solubility flask *via* a sintered glass ball and circulated by means of a Viton diaphragm air-pump. The circulation rate was set at 0.8 $dm^3\,min^{-1}$. At this rate, concentrations of iodine in CyD solutions had been found in advance to reach constant values after 60 min aeration. After attainment of solubility equilibrium, 10 cm^3 samples were withdrawn and the iodine concentrations were determined by solvent extraction-spectrophotometry at 514 nm. The solvent extraction was repeated twice for the same sample solution with a successive addition of 20 cm^3 of CCl_4.

Results and Discussion

Equilibrium Solubilities of Iodine Vapor in the Presence and Absence of Cyclodextrins. Solubility runs were made under the condition that the temperature of the solute reservoir was lower than that of the solubility flask, with the latter maintained constant. The vapor pressure of iodine at a given temperature of the solute reservoir was estimated from the equation, derived based on Ref. 5, $\log PT^{3/2}=16.945-3464/T$, where P is the vapor pressure in Pa and T is absolute temperature. At first, equilibrium solubilities were measured in the absence of CyD, and Henry's law constant, K_H, at each temperature of the aqueous phase was determined from the equation $K_H=P/X_2$, where X_2 is the mole fraction of dissolved iodine. The results are shown in Table 1, in which the K_H value obtained in iodic acid solution is also given since the use of HIO_3 was recommended in view of protecting iodine in aqueous medium from reduction.[2] If the reduction of iodine does occur in $HClO_4$ solution, an increase in

Table 1. Henry's law constants of iodine vapor in $HClO_4$ solutions[a)]

Temperature of aqueous phase °C	Henry's law constant[b)] 10^6 Pa	ΔG_{dehyd}[c)] kJ mol^{-1}
15.00	1.08 ± 0.04(0.995)	−5.67
20.00	1.36 ± 0.02(0.999)	−6.33
25.00	1.81 ± 0.03(0.999) 1.72 ± 0.02(0.999)[d)]	−7.15
30.00	2.32 ± 0.02(0.999)	−7.89
35.00	3.01 ± 0.02(0.999)	−8.69

a) The concentration of $HClO_4$ is 1.0×10^{-3} mol dm^{-3}. b) In parentheses are indicated the correlation coefficients derived from $K_H=P/X_2$. c) Estimated from K_H in atom units by using $\Delta G_{dehyd}=-RT\ln K_H$, where "dehyd" refers to the dehydration of iodine dissolved in the aqueous phase. ΔH_{dehyd} and ΔS_{dehyd} are estimated to be 38.2 kJ mol^{-1} and 152 J K^{-1} mol^{-1}, respectively, in the temperature range studied. d) Obtained in HIO_3 solutions of 0.20 mol dm^{-3}.

the apparent solubility of iodine would be expected from the equilibrium $I^- + I_2 \rightleftharpoons I_3^-$. Yet, as seen from Table 1, the K_H value observed in HIO_3 solution is rather small compared with that in $HClO_4$ at the same temperature of the aqueous phase. There was observed an increase by *ca.* 5% in the solubility of iodine in iodic acid medium of 0.2 mol dm^{-3} relative to that in perchloric acid of 1.0×10^{-3} mol dm^{-3}. The reason for this is not clear, but some interaction between IO_3^- and I_2 may be responsible.

Equilibrium solubilities of iodine vapor were measured in α-, β-, or γ-CyD solutions and the results expressed as S_{obsd} are shown in Table 2, where are also listed the equilibrium solubilities in the absence of CyD, expressed as S_o.

Iodine molecules dissolved in a CyD solution are equilibrated with CyD molecules to form associated complex(es), while those in the free form are equilibrated with iodine vapor in the gaseous phase. If it is assumed that the solubility of *free* iodine is little affected by the presence of CyD in the aqueous medium, the S_o value at a given temperature of the aqueous phase can be estimated from Henry's law constant provided the temperature of solid iodine is known.

Estimation of Formation Constants. α-CyD is reported to from a 1:1 complex with iodine,[1)] but there are no experimental data concerning the stoichiometry of β- and γ-CyD complexes. We have measured absorption spectra of iodine in CyD solutions of various concentrations; A clear isosbestic point was observed at 460 nm for α-CyD and a hardly recognizable one near 460 nm for β-CyD, but for γ-CyD the spectra appeared too closely superimposed to reveal any isosbestic point.

It may be valid to assume that, at the most, one CyD molecule is able to accept two iodine molecules, since even with γ-CyD the cavity is not large enough to receive more than three iodine molecules. Complex formation can then be written as

$$\mathrm{CyD} + I_2 \rightleftharpoons \mathrm{CyD}\cdot I_2, \quad K_1, \tag{1}$$

$$\mathrm{CyD}\cdot I_2 + I_2 \rightleftharpoons \mathrm{CyD}\cdot(I_2)_2, \quad K_2, \tag{2}$$

where K_1 and K_2 are stepwise formation constants. The total concentration of iodine present in the aqueous phase, C_{I_2}, and the total concentration of CyD, C_{CyD}, are expressed as

$$\begin{aligned} C_{I_2} &= [I_2] + [\mathrm{CyD}\cdot I_2] + 2[\mathrm{CyD}\cdot(I_2)_2] \\ &= [I_2](1+K_1[\mathrm{CyD}] + 2K_1K_2[\mathrm{CyD}][I_2]), \end{aligned} \tag{3}$$

$$\begin{aligned} C_{CyD} &= [\mathrm{CyD}] + [\mathrm{CyD}\cdot I_2] + [\mathrm{CyD}\cdot(I_2)_2] \\ &= [\mathrm{CyD}](1+K_1[I_2]+K_1K_2[I_2]^2), \end{aligned} \tag{4}$$

where $[I_2]$ and [CyD] denote free concentrations of I_2 and CyD, respectively. Here, $[I_2]$ and C_{I_2} are equal to S_o and S_{obsd}, respectively. Combining Eqs. 3 and 4, we have

$$\begin{aligned} &(S_{obsd}-S_o)/C_{CyD} \\ &\quad = K_1S_o(1+2K_2S_o)/\{1+K_1S_o(1+K_2S_o)\}. \end{aligned} \tag{5}$$

Suppose, as a first approximation, $1+2K_2S_o \approx 1+K_2S_o$, that is, the product K_2S_o is small compared with unity, and Eq. 5 becomes

$$(S_{obsd}-S_o)/S_o(C_{CyD}-S_{obsd}+S_o) = K_1 + nK_1K_2S_o, \tag{6}$$

where n takes the value of 1 or 2. It can be seen from Table 2 that for a particular type of CyD the left-hand side of Eq. 6 is almost constant independently of S_o at a given temperature of the aqueous phase. This means that the K_2 term need not be considered, *i.e.*, α-, β-, and γ-CyD form 1:1 complexes with iodine.

The formation constants K_f $(=K_1)=[\mathrm{CyD}\cdot I_2]/([\mathrm{CyD}][I_2])$ are summarized in Table 3. The K_f value obtained for α-CyD at 25 °C in 0.20 mol dm^{-3} HIO_3 solution is in good agreement with the literature value included in Table 3 despite different experimental approaches employed in these two studies. The reason that the K_f value observed in $HClO_4$ solution is somewhat smaller than that in HIO_3 is not clear at present, but may be due to an inhibition effect of perchloric acid. It is agreed that $HClO_4$ can enter the α-CyD cavity, the formation constant being reported to be 40 dm^3 mol^{-1}.[6)]

It can be seen from Table 3 that the formation constant of the complex with iodine decreases drastically on going from α- to γ-CyD. This is probably due to the size of the CyD cavity; β- and γ-CyD, especially the latter, have too large cavities to accommodate an iodine molecule tightly.

Thermodynamic Considerations of α-Cyclodextrin Complexation with Iodine. A striking feature of complex formation of α-CyD with iodine is the temperature dependence of the formation constant. Table 3 shows that with rising temperature the K_f value increases at first, and then decreases. The thermodynamic parameters of the complexation were estimated from the temperature dependence of K_f with the aid of the equations $\Delta G=-RT \ln K_f=\Delta H-T\,\Delta S$ and $dH/dT=\Delta C_p=A+BT$, where ΔC_p is the heat capacity change, A and B are constants, and the other symbols have their usual meanings. We can express K_f as a function of T as

$$\ln K_f = (A/B) \ln T + (B/2R)T - (C/R)T^{-1} + C' - A/R, \tag{7}$$

where C and C' are integration constants. The data shown in Table 3 are best fitted by the equation

$$\ln K_f = 140.0 \ln T - 1.441\,T - 87500\,T^{-1} - 65.60. \tag{8}$$

The result is shown in Fig. 1 by a solid curve. The ΔH and ΔC_p are expressed, respectively, by $\Delta H=87500\,R+140.0\,RT-1.441\,RT^2$ and $\Delta C_p=140.0\,R-2.882\,RT$. The thermodynamic parameters thus estimated for the α-CyD–I_2 complex are summarized in Table 3. It is noteworthy that ΔH and ΔS values are both strongly temperature dependent, changing from positive to negative.

A large number of ΔH and ΔS data concerning CyD

TABLE 2. SOLUBILITIES OF IODINE VAPOR IN THE PRESENCE OF CYCLODEXTRINS

Temperature of aqueous phase/°C	Temperature of solid iodine/°C	Vapor pressure of iodine/Pa	C_{CyD}a) / 10^{-3} mol dm^{-3}	Solubility of iodine 10^{-3} mol dm^{-3}		K_f d) / dm^3 mol^{-1}
				S_o b)	S_{obsd} c)	
α-Cyclodextrin in 1.0×10^{-3} mol dm^{-3} $HClO_4$ solutions						
15.00	10.17	10.97	0.9786	0.564	1.24	3.96×10^3
15.00	10.85	11.69	1.141	0.601	1.43	4.42×10^3
15.00	14.49	16.36	1.005	0.842	1.67	5.56×10^3
20.00	9.90	10.70	1.137	0.438	1.31	7.51×10^3
20.00	12.35	13.44	1.073	0.550	1.39	6.55×10^3
20.00	15.36	17.71	1.026	0.724	1.60	8.07×10^3
20.00	19.38	25.36	1.011	1.04	1.94	7.80×10^3
25.00	10.31	11.11	0.9971	0.340	1.09	8.93×10^3
25.00	14.89	16.97	1.005	0.519	1.35	9.20×10^3
25.00	17.96	22.36	1.040	0.684	1.56	7.80×10^3
25.00	19.43	25.47	1.053	0.779	1.69	8.24×10^3
25.00	19.43	25.47	1.527	0.779	2.10	8.24×10^3
25.00	19.50	25.63	1.217	0.784	1.83	7.80×10^3
25.00	23.67	36.80	1.059	1.13	2.08	7.71×10^3
30.00	19.93	26.61	1.040	0.636	1.50	7.72×10^3
30.00	23.48	36.05	1.024	0.861	1.75	7.65×10^3
30.00	28.30	54.32	1.001	1.30	2.20	6.85×10^3
35.00	10.12	10.91	1.005	0.201	0.813	7.75×10^3
35.00	18.58	23.63	1.046	0.436	1.21	6.53×10^3
35.00	24.40	39.16	1.001	0.723	1.54	6.14×10^3
35.00	29.65	60.71	1.201	1.12	2.17	6.21×10^3
α-Cyclodextrin in 0.20 mol dm^{-3} HIO_3 solutions						
25.00	14.75	16.75	1.071	0.540	1.45	1.05×10^4
25.00	17.99	22.42	1.065	0.723	1.64	8.57×10^3
25.00	21.88	31.54	1.036	1.02	1.96	9.60×10^3
β-Cyclodextrin in 1.0×10^{-3} mol dm^{-3} $HClO_4$ solutions						
25.00	10.40	11.21	1.454	0.343	0.386	88.8
25.00	16.28	19.24	1.827	0.589	0.700	110
25.00	19.30	25.18	2.007	0.771	0.900	89.1
γ-Cyclodextrin in 1.0×10^{-3} mol dm^{-3} $HClO_4$ solutions						
25.00	14.78	16.80	10.10	0.514	0.587	14.2
25.00	14.55	16.45	14.89	0.505	0.589	11.3
25.00	14.55	16.45	18.00	0.505	0.598	10.4
25.00	22.75	34.00	10.04	1.04	1.19	14.6

a) Concentration of CyD prepared by adding a known amount of dried CyD to the aqueous phase. b) The solubility of iodine in the absence of CyD. c) The solubility of iodine in the presence of CyD. d) $K_f=(S_{obsd}-S_o)/S_o(C_{CyD}-S_{obsd}+S_o)$, *i.e.*, the left-hand side of Eq. 6 in the text.

TABLE 3. FORMATION CONSTANTS OF CYCLODEXTRIN–IODINE COMPLEXES AND THERMODYNAMIC PARAMETERS

Temperature °C	Formation constant $dm^3\ mol^{-1}$	ΔG kJ mol^{-1}	ΔH kJ mol^{-1}	ΔS J $K^{-1}\ mol^{-1}$	ΔC_p J $K^{-1}\ mol^{-1}$
α-Cyclodextrin in 1.0×10^{-3} mol dm^{-3} $HClO_4$ solution					
15.00	$(4.6\pm0.7)\times10^3$	−20.1	68.1	306	−5.74
20.00	$(7.5\pm0.6)\times10^3$	−21.7	39.1	207	−5.86
25.00	$(8.3\pm0.5)\times10^3$	−22.4	9.52	107	−5.98
30.00	$(7.4\pm0.4)\times10^3$	−22.5	−20.7	5.94	−6.10
35.00	$(6.7\pm0.7)\times10^3$	−22.6	−51.5	−93.8	−6.22
α-Cyclodextrin in 0.20 mol dm^{-3} HIO_3 solution					
25.00	$(9.6\pm0.8)\times10^3$				
α-Cyclodextrin in 0.08 mol dm^{-3} HIO_3 solution[a]					
24	9.3×10^3				
β-Cyclodextrin in 1.0×10^{-3} mol dm^{-3} $HClO_4$ solution					
25.00	100 ± 10				
γ-Cyclodextrin in 1.0×10^{-3} mol dm^{-3} $HClO_4$ solution					
25.00	13 ± 2				

a) Taken from Ref. 2.

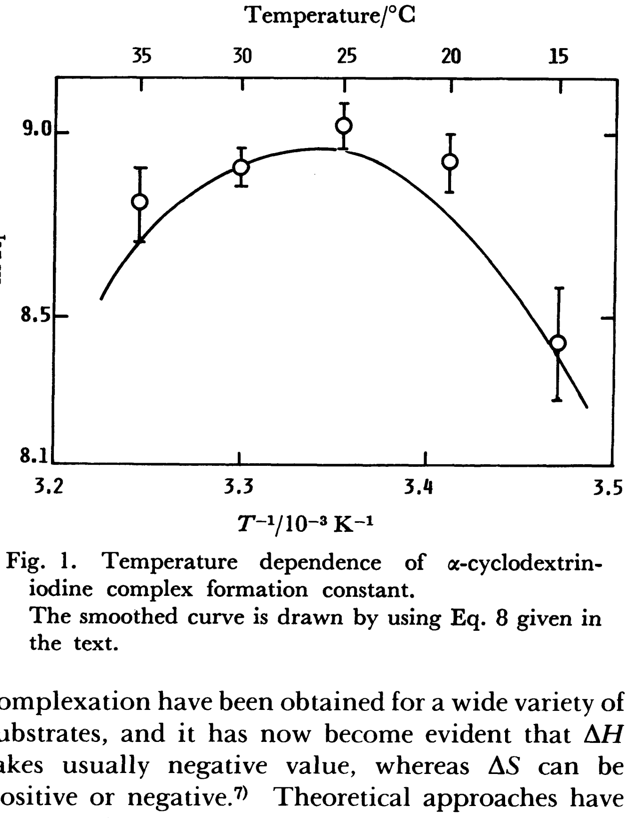

Fig. 1. Temperature dependence of α-cyclodextrin-iodine complex formation constant.
The smoothed curve is drawn by using Eq. 8 given in the text.

complexation have been obtained for a wide variety of substrates, and it has now become evident that ΔH takes usually negative value, whereas ΔS can be positive or negative.[7] Theoretical approaches have been made to elucidate the mechanism of CyD complexation with substrates,[8,9] but there are still some arguments in detail. It is now generally accepted that both the dehydration of a guest molecule on entering the CyD cavity and the interaction between a guest and CyD inside the cavity play an important role. The guest being hydrophobic, the interaction decreases with increasing temperature. On the other hand, the guest being a gaseous nonelectrolyte molecule, the dehydration increases with rising temperature, and in this case thermodynamic parameters can be easily determined by measuring the temperature dependence of the aqueous solubility of the guest in the absence of CyD. The results for iodine are shown in Table 1. Substracting the free energy change of dehydration from that of the overall process yields −14.4 (15 °C), −15.4 (20 °C), −15.3 (25 °C), −14.6 (30 °C), and −13.9 kJ mol^{-1} (35 °C). If it is assumed that these values provide a rough measure of iodine–CyD interaction, the order of the above figures at lower temperatures is not consistent with the view that the interaction can be explained by considering only hydrophobic interaction.

To shed light on what is really responsible for the present unusual temperature dependence of K_f observed for iodine, it seems desirable to study CyD complexations with nonelectrolytes, only sparingly soluble in water and volatile. For such a purpose the experimental technique proposed here is useful which utilizes vapor of nonelectrolyte.

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