Bull. Chem. Soc. Jpn., *71*, *1615—1618 (1998)*

Association Constants of Ferrocene with Cyclodextrins in Aqueous Medium Determined by Solubility Measurements of Ferrocene

Ji-Shi Wu, Kei Toda, Akira Tanaka, and Isao Sanemasa*

Department of Environmental Science, Faculty of Science, Kumamoto University,
Kurokami 2-39-1, Kumamoto 860-8555

(Received February 19, 1998)

The association constants of ferrocene with cyclodextrins (CyD's) in an aqueous medium at 25 °C have been determined by solubility measurements of ferrocene in both the absence and presence of CyD. The solubility of ferrocene in pure water was found to be $(4.25\pm0.02)\times10^{-5}$ mol dm^{-3} at 25.0±0.1 °C. The β- and γ-CyD's form only 1 : 1 complexes with ferrocene. The 1 : 1 association constants were determined to be $(1.39\pm0.21)\times10^{2}$ (α), $(1.65\pm0.04)\times10^{4}$ (β), and $(9.04\pm0.11)\times10^{2}$ dm^{3} mol^{-1} (γ). The 2 : 1 (CyD : ferrocene) association constant was $(2.36\pm0.06)\times10^{3}$ dm^{3} mol^{-1} (α). Ferrocene-included CyD precipitates were also prepared in water, and their stability upon drying in air was studied. The sublimation enthalpy of ferrocene in the temperature range of 290.65 to 298.15 K was estimated to be 74.2±1.5 kJ mol^{-1}.

Cyclodextrins (CyD's) act as hosts and form inclusion complexes with various organic and inorganic guest molecules. Complex formation occurs more favorably in an aqueous medium than in a nonaqueous solvent. As an example of organometallic guests, ferrocene has been extensively studied concerning complex formation with CyD's. Such studies, however, were carried out in solvents, such as ethylene glycol, dimethyl sulfoxide (DMSO), dimethyl formamide, and ethanol.[1,2] It became apparent from these studies that the complex-formation constant of β-CyD depends largely upon the solvent used. To date, the complex-formation constant of ferrocene with CyD's has not been determined in an aqueous medium, although the data concerning water-soluble ferrocene derivatives are available.[3]

Harada et al. have prepared ferrocene (and its derivatives) inclusion compounds with CyD's by three methods:[4] mixing an alcohol solution of ferrocene with an aqueous or alcohol solution of CyD or, alternatively, the addition of fine crystals of ferrocene directly to an aqueous CyD solution at 60 °C. They found that the latter method was the best, and that complexes of ferrocene with α- and γ-CyD could not be obtained in the presence of alcohol. These observations may indicate that the formation constant of ferrocene with these two CyD's in an aqueous medium is much lower than that with β-CyD.

Our major concern is with the evaluation of ferrocene–CyD complex formation in an aqueous medium. The formation constant was determined by solubility measurements based on the vapor-circulation technique, which has been described elsewhere.[5] The conventional shake-flask method, which is usually employed in the solubility measurement, was not used in this work. The reason is that CyD molecules may be adsorbed on the surface of solid ferrocene or may penetrate into the solid phase to cause a modification of its physicochemical properties, and consequently, its aqueous solubility. The vapor-circulation technique is particularly useful to prepare guest-included CyD precipitates. The enthalpy of sublimation of ferrocene can also be estimated by this technique.

Experimental

Reagents. The ferrocene and other reagents used were of analytical reagent grade. α-, β-, and γ-CyD's of guaranteed grade (Nacalai Tesque Co.) were used as received. Deionized distilled water was used throughout the experiments.

Apparatus and Procedures. The apparatus and procedure to prepare aqueous solutions saturated with ferrocene vapor were the same as those previously described.[5] The concentrations of ferrocene in both pure water and CyD solutions were measured with a Hitachi 100-50 spectrophotometer at 440 nm after extraction with cyclohexane; CyD present in the aqueous phase exhibits no effect on complete extraction of ferrocene. The ferrocene-CyD complex formation constants were determined based on increases in the solubility of ferrocene in solutions of various CyD concentrations of up to 2.6×10^{-3} M (1 M ≡ 1 mol dm^{-3}) for α, 5.0×10^{-4} M for β, and 2.4×10^{-3} M for γ. When the CyD concentration in solution exceeds 2.6×10^{-3} M, it becomes difficult to completely extract ferrocene from solution, because CyD begins to precipitate in the presence of the extractant (cyclohexane). In the case of β, ferrocene–CyD precipitates begin to occur at relatively low CyD concentrations.

Ferrocene-included CyD precipitates were prepared at concentrations of 5.0×10^{-2} M for both α- and γ-CyD's and 1.2×10^{-2} M for β-CyD. CyD precipitates were treated and analyzed as previously described.[5] A JASCO RI-930 differential refractometer was used to measure CyD in the precipitates and in the supernatant aqueous solutions. To study the stability of the included complex, a part of the precipitate was stored in air at room temperature for at most four weeks and analyzed every one week.

Results and Discussion

Solubility of Ferrocene in Water. The ferrocene vapor was circulated at ca. 0.5 $\mathrm{dm^3\,min^{-1}}$ through pure water or CyD solutions, and the solute concentration was measured as a function of the vapor-circulation time. The results are shown in Fig. 1. The solubility equilibrium was attained after 4 h; the time-course of this process was little affected by CyD (as an example, the case of β-CyD is plotted in Fig. 1). The solubility of ferrocene in pure water was found to be $(4.25\pm0.02)\times10^{-5}$ M at 25.0±0.1 °C. To our knowledge, the aqueous solubility of ferrocene has not been reported so far. In order to check the present solubility, the conventional shake-flask method was also used:[6] An excess quantity of ferrocene crystals was shaken with water for at least one day, and the supernatant solution was analyzed after the mixture was allowed to stand overnight. The solubility obtained by the shake-flask technique was $(4.27\pm0.02)\times10^{-5}$ M at 25.0±0.1 °C, which was in reasonable agreement with that obtained by the vapor-circulation technique.

Complex Formation Constants of Ferrocene with CyDs. The solubility method has been demonstrated to be useful for studying associations, particularly those with relatively large formation constants, between sparingly soluble guests and CyD's in an aqueous medium.[7] Since ferrocene (guest) has been known to form 1 : 1 and 2 : 1 (CyD : guest) complexes with CyD's, the equilibria that must be taken into account are as follows:

$$\mathrm{CyD} + \phi \rightleftharpoons \mathrm{CyD}\cdot\phi, \qquad K_1 \tag{1}$$

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

where ϕ refers to a ferrocene molecule. The 1 : 1 and 2 : 1 (CyD : ferrocene) association constants (K_1 and K_2) can be estimated from the solubility of ferrocene in pure water ($[\phi]_0$) and that in a CyD solution (C_ϕ), as follows:

$$\begin{aligned} C_\phi &= [\phi]_0 + [\mathrm{CyD}\cdot\phi] + [(\mathrm{CyD})_2\cdot\phi] \\ &= [\phi]_0(1 + K_1[\mathrm{CyD}] + K_1K_2[\mathrm{CyD}]) \end{aligned} \tag{3}$$

and

$$\begin{aligned} C_\mathrm{CyD} &= [\mathrm{CyD}] + [\mathrm{CyD}\cdot\phi] + 2[(\mathrm{CyD})_2\cdot\phi] \\ &= [\mathrm{CyD}](1 + K_1[\phi]_0 + 2K_1K_2[\phi]_0[\mathrm{CyD}]). \end{aligned} \tag{4}$$

Here, we assume that, in the presence of CyD, the $[\phi]_0$ value corresponds to the equilibrium concentration of free ferrocene, which remains unchanged irrespective of C_CyD.

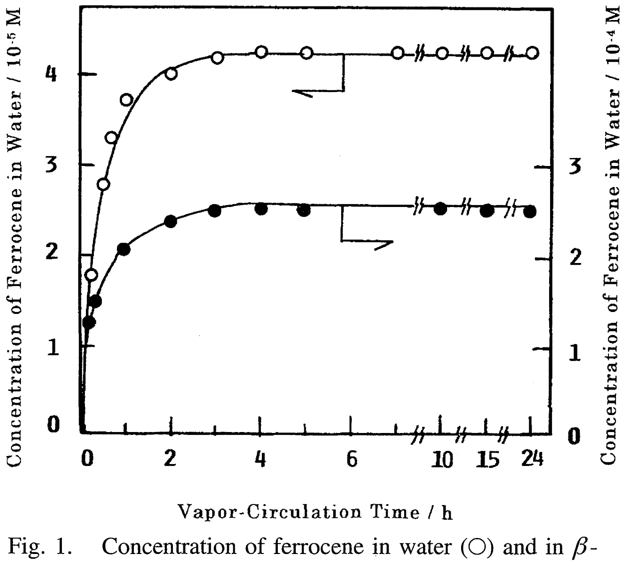

Fig. 1. Concentration of ferrocene in water (○) and in β-CyD ($C_\mathrm{CyD} = 5.00\times10^{-4}$ M) solution (●) at 25.0±0.1 °C as a function of ferrocene vapor-circulation time.

Since the equilibrium concentration of free CyD ([CyD]) is initially unknown, an iterative solution is used. As a first approximation, [CyD] is set to be equal to the initial CyD concentration (C_CyD) in Eq. 3 to obtain initial estimates of K_1 and K_2, which are then used in Eq. 4 to give improved estimates of [CyD], and so on. $C_\phi/[\phi]_0$ vs. [CyD] plots are shown in Figs. 2 and 3 (solid lines are drawn by the nonlinear least-squares method), which indicate that β- and γ-CyD's form only 1 : 1 complexes with ferrocene. The association constants are summarized in Table 1, where the related data reported in the literature are also listed. It is noteworthy that the association constants of β-CyD–ferrocene is large enough to be comparable to that of α-CyD–iodine (1.5×10^4 $\mathrm{dm^3\,mol^{-1}}$),[8] which is one of the most stable CyD complexes.

It is suggested that, if K_2 is larger than K_1, the cross-section of the secondary hydroxyl group sides of the two CyD molecules are situated parallel to each other at a suitable distance to form a hydrogen bond.[9] This suggestion is consistent with the ferrocene–α-CyD inclusion model proposed

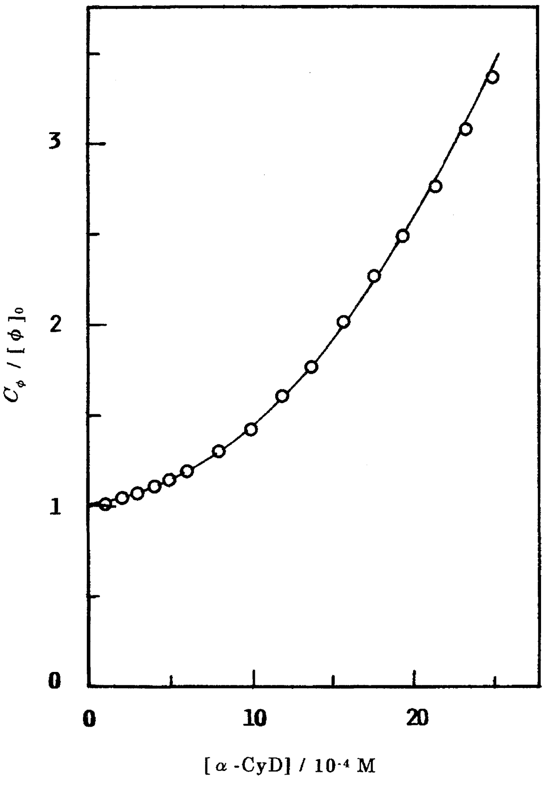

Fig. 2. Plots of $C_\phi/[\phi]_0$ vs. concentration of free α-CyD.

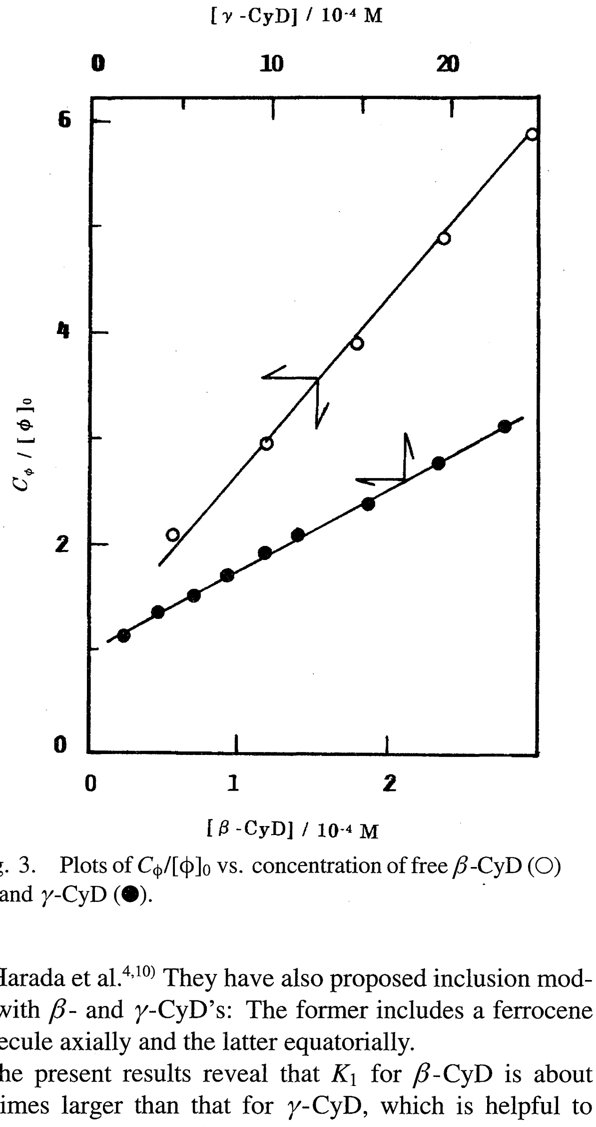

Fig. 3. Plots of $C_\phi/[\phi]_0$ vs. concentration of free β-CyD (○) and γ-CyD (●).

by Harada et al.[4,10] They have also proposed inclusion models with β- and γ-CyD's: The former includes a ferrocene molecule axially and the latter equatorially.

The present results reveal that K_1 for β-CyD is about 20-times larger than that for γ-CyD, which is helpful to understand some experimental results reported in the literature. Ueno et al. have recently prepared ferrocene-appended CyD's (one ferrocene molecule is attached to the entrance of the CyD cavity).[11] When these CyD's are in an aqueous solution alone, they form intramolecular self-complexes in which the pendant ferrocene moiety is included in the CyD cavity, and exhibits induced circular dichroism (ICD). When guest molecules are added to the solution, they replace the ferrocene moiety in the CyD cavity, and the resulting ICD intensity changes occur. The ferrocene-appended β-CyD has been found to be more selective than the corresponding γ-CyD: The former exhibits little response to such guests that weekly associate with β-CyD. This finding is consistent with our present results that ferrocene forms a more stable complex with β-CyD than with γ-CyD. Harada and Takahashi have measured the complex-formation constants of ferrocene in alcohol solutions for β-CyD, but not for γ-CyD, although they indicate that γ-CyD also forms inclusion complexes with ferrocene in ethylene glycol.[1]

The complex formation of water-soluble ferrocene derivatives, alkyldimethyl(ferrocenylmethyl)ammonium salts, with three CyD's in aqueous solution have recently been reported by Isnin et al.[3] They assumed that α-CyD forms inclusion complexes with the aliphatic region of the derivatives, while β- and γ-CyD's associate with the ferrocene subunit. As can be seen from Table 1, in an aqueous medium, α-CyD forms a 1 : 1 complex with the alkyl chain in preference to ferrocene. It is worth noting that the parent ferrocene molecule forms much more stable complexes with both β- and γ-CyD's than do the water-soluble derivatives. One reason for this discrepancy is ascribed to the difference in the hydrophobic nature of the guest molecule and the other to the steric hindrance between the CyD cavity and the substituent group of the water-soluble guests.

Ferrocene-Included CyD Precipitates and Their Stability in Air. Elemental analyses of Fe have revealed that the molar ratio (CyD : ferrocene) in the solid complex is 2 : 1 (α) and 1 : 1 (β and γ).[4] Our results, shown in Table 2, based on analyses of both CyD and ferrocene using crude complexes without purification, are in accord with a preceding study;[4] hence, Eqs. 3 and 4 derived from the postulated stoichiometry are reasonable. It can be seen from Table 2 that the ferrocene-included CyD complex isolated from water is

Table 1. Association Constants Obtained in This Work (Ferrocene–CyD in Aqueous Medium at 25 °C) and Those Reported in the Literature (Ferrocene–CyD in Nonaqueous Medium, Ferrocene-derivatives–CyD in Aqueous Medium)

Type of CyD	This work[a)]		Literature[c)]					
	Aqueous medium (Guest; ferrocene)		Nonaqueous medium (Guest; ferrocene)[d)] Solvent				Aqueous medium Guest[e)]	
			Ethyleneglycol	2-Methoxyethanol	DMSO	DMSO : water (8 : 2)	FC_1^+	FC_7^+
	K_1/dm^3 mol^{-1}	K_2[b)]/dm^3 mol^{-1}	K_1/dm^3 mol^{-1}					
α	$(1.39\pm0.21)\times10^2$	$(2.36\pm0.06)\times10^3$					240	420
β	$(1.65\pm0.04)\times10^4$	—	83, 77	40	48, 60, 40	320, 350	1900	1400
γ	$(9.04\pm0.11)\times10^2$	—					400	170

a) Total concentration of CyD; $(1.00—26.0)\times10^{-4}$ M (α), $(1.00—5.00)\times10^{-4}$ M (β), and $(1.00—24.0)\times10^{-4}$ M (γ). b) The dash sign indicates that K_2 was not evaluated. c) The temperature at which the data were obtained was not specified in the original papers. d) Taken from Refs. 1 and 2. e) Taken from Ref. 3; guests are alkyldimethyl(ferrocenylmethyl)ammonium salts, where the alkyl group is methyl (FC_1^+) or heptyl (FC_7^+).

Table 2. (Ferrocene/CyD) Molar Ratio of CyD Precipitates as a Function of Time Allowed to Stand in Air

Type of CyD	(Ferrocene/CyD) molar ratio after being allowed to stand for the following weeks:				
	0[a)]	1	2	3	4
α	0.47	0.43	0.43	0.44	0.46
β	1.03	1.01	0.98	0.96	0.98
γ	1.06	1.10	1.06	1.05	1.04

a) Measurements were made immediately after preparation of the precipitates.

Table 3. Concentration of Ferrocene in Water at 25.0±0.1 °C in Equilibrium with Ferrocene Vapor

Temperature of ferrocene	Vapor pressure of ferrocene[a)]	Concentration of ferrocene in water
°C	Pa	10^{-5} mol dm^{-3}
17.5	0.479	1.95
20.0	0.617	2.58
22.5	0.794	3.26
25.0	1.023	4.25

a) Taken from Ref. 12.

stable in air.

Harada et al. purified inclusion complexes, prior to their elemental analyses, by washing the products with water to remove the remaining CyD, and then the residue with tetrahydrofuran to remove uncomplexed ferrocene.[4)] It was found, however, to be quite difficult to purify the product in such a way: the product was readily dissolved by washing even with cold water.

Henry's Law Constant and Sublimation Enthalpy of Ferrocene. The sublimation enthalpy (ΔH_{sub}) of ferrocene has been determined by a measurement of the vapor pressure of solid ferrocene as a function of the temperature.[12,13)] As was shown in our previous papers,[6,14)] ΔH_{sub} can be easily estimated, using the vapor-circulation technique, by solubility measurements of a solid solute in water. In this technique, the temperature of the solvent (water) is held constant at 25.0±0.1 °C, while that of a solute reservoir, in which the solid solute to be studied is dispersed in water, is made to vary up to that of the solvent. The equilibrium solubility of ferrocene, that is the concentration of ferrocene in water in equilibrium with the vapor of solid ferrocene, was found to be proportional to the ferrocene vapor pressure (Table 3). That is, the solubility obeys Henry's law:

$$P = K_{\text{H}}X, \tag{5}$$

where P is the partial pressure of ferrocene, which is taken from Ref. 12, K_{H} is the Henry's law constant, and X is the mole fraction of ferrocene dissolved in water. From the data listed in Table 3, K_{H} was found to be $(1.34\pm0.01)\times10^{6}$ Pa at a water temperature of 25 °C.

The temperature dependence of the vapor pressure of a solid is given by

$$\mathrm{d}\ln P/\mathrm{d}T = \Delta H_{\text{sub}}/(RT^2), \tag{6}$$

where P is the sublimation vapor pressure, and T and R have their usual meanings. Here, we take P in Eqs. 5 and 6 to be equal to each other in its physical quantity. When $\log X$ was plotted against T^{-1}, we obtained a straight line with a slope corresponding to $-\Delta H_{\text{sub}}/(2.303\times8.314)$. ΔH_{sub} over the temperature range of 290.65 to 298.15 K is thus estimated to be 74.2±1.5 kJ mol^{-1}, which is in reasonable agreement with the literature values, 72.39±1.0,[12)] and 74.0±2.0[13)] kJ mol^{-1}.

References

1) A. Harada and S. Takahashi, *Chem. Lett.*, **1984**, 2089.

2) T, Matsue, U. Akiba, K. Suzufuji, and T. Osa, *Denki Kagaku*, **53**, 508 (1985).

3) R. Isnin, C. Salam, and A. E. Kaifer, *J. Org. Chem.*, **56**, 35 (1991).

4) A. Harada, Y. Hu, S. Yamamoto, and S. Takahashi, *J. Chem. Soc., Dalton Trans.*, **1988**, 729.

5) I. Sanemasa, Y. Wu, Y. Koide, M. Shigenaga, K. Ishibashi, and T. Deguchi, *Bull. Chem. Soc. Jpn.*, **66**, 1424 (1993).

6) I. Sanemasa, K. Ishibashi, M. Kumamaru, and T. Deguchi, *Bull. Chem. Soc. Jpn.*, **62**, 2908 (1989).

7) K. A. Connor, A. Pauloson, and D. Toledo-Velasquez, *J. Org. Chem.*, **53**, 2023 (1988).

8) I. Sanemasa, Y. Nishimoto, A. Tanaka, and T. Deguchi, *Bull. Chem. Soc. Jpn.*, **59**, 2269 (1986).

9) W. C. Cromwell, K. Bystr•m, and M. R. Eftink, *J. Phys. Chem.*, **89**, 326 (1985).

10) A. Harada and S. Takahashi, *J. Chem. Soc., Chem. Commun.*, **1984**, 645.

11) A. Ueno, Q. Chen, I. Suzuki, and T. Osa, *Anal. Chem.*, **64**, 1650 (1992).

12) M. A. V. Ribeiro Da Silva and M. J. S. Monte, *Thermochim. Acta*, **171**, 169 (1990).

13) M. Pelino, M. Tomassetti, V. Piacente, and G. D'ascenzo, *Thermochim. Acta*, **44**, 89 (1981).

14) Y. Wu, K. Ishibashi, T. Deguchi, and I. Sanemasa, *Bull. Chem. Soc. Jpn.*, **63**, 3450 (1990).