Preparation and Properties of Inclusion Compounds of Ferrocene and its Derivatives with Cyclodextrins

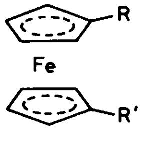
Akira Harada,* Ying Hu, Shyoko Yamamoto, and Shigetoshi Takahashi
The Institute of Scientific and Industrial Research, Osaka University, Ibaraki, Osaka 567, Japan

Inclusion compounds of ferrocene and its derivatives with α-, β-, and γ-cyclodextrins have been prepared in a crystalline state in high yields. β-Cyclodextrin and γ-cyclodextrin formed 1 : 1 stoicheiometric inclusion compounds. α-Cyclodextrin formed 2 : 1 (host : guest) complexes with ferrocene and its monosubstituted derivatives, but did not form complexes with 1,1′-disubstituted derivatives. The complexes of α- and β-cyclodextrin with ferrocene are thermally stable and do not liberate ferrocene on heating at 100 °C *in vacuo*. The inclusion compounds were characterized by ^{1}H n.m.r., i.r., u.v., and circular dichroism spectroscopy. A large positive induced Cotton effect was observed in the case of complex of β-cyclodextrin with ferrocene, while the complex of γ-cyclodextrin showed a negative spectrum. The binding mode is discussed.

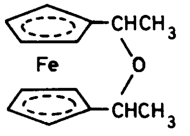
Since the discovery of ferrocene a great number of organometallic complexes have been synthesized and found to have unique structures and properties.[1] Meanwhile, molecular complexes, in which two or more molecules are weakly bound by noncovalent bonds, have received much attention because of their characteristic chemical and physical properties and in relation to the function of biologically important substances.[2] Although there have been many reports on molecular complexes with both organic and inorganic compounds, few concern the molecular complexes with organometallic complexes. Intercalation compounds of organometallic complexes, for example, have been prepared to improve their catalytic and conductive properties.[3] Recently, inclusion compounds of organotransition-metal complexes with crown ethers[4] and cryptands[5] have been reported.

Cyclodextrins, which are naturally occurring macrocyclic glucose polymers containing a minimum of six D(+)-glucopyranose units, attached by α-(1,4) linkages, are well known host molecules and have been studied as an enzyme model for selective catalysts.[6] Although cyclodextrins (α-, β-, and γ-) form inclusion compounds with various compounds, ranging from organic molecules to small ions, and even rare gases, there have been few reports on the interaction between organometallic complexes and cyclodextrins. Breslow *et al.*[7] reported high acylation rates for β-cyclodextrin using ferrocene derivatives and assumed the formation of intermediate β-cyclodextrin–substrate complexes. Osa and co-workers[8] reported the effect of β-cyclodextrin on the electron transfer of ferrocenecarboxylic acid. Adducts of α-cyclodextrin with rhodium complexes have recently been reported.[9]

In a previous communication we reported briefly on the preparation of cyclodextrin–ferrocene inclusion compounds as an example of cyclodextrin inclusion complexes of organotransition-metal complexes.[10] We describe here the preparation and properties of inclusion compounds of ferrocene and its derivatives with cyclodextrins in detail and discuss the binding mode especially on the basis of the circular dichroism spectra.



(1) $R = R' = H$
(2) $R = COCH_3$, $R' = H$
(3) $R = R' = COCH_3$
(4) $R = CH(OH)CH_3$, $R' = H$
(5) $R = COCH_2CH_3$, $R' = H$
(6) $R = CH(OH)CH_2CH_3$, $R' = H$
(7) $R = CO(CH_2)_2CH_3$, $R' = H$
(8) $R = CH(OH)(CH_2)_2CH_3$, $R' = H$



(9)

Results and Discussion

Preparation of Inclusion Compounds.—Ferrocene (1) and its derivatives (2)—(9) are almost insoluble in water. So a cocrystallization method from aqueous solution, as is usually used with water-soluble compounds to obtain inclusion compounds, cannot be employed in this case. In an attempt to prepare cyclodextrin–ferrocene inclusion compounds several methods were tested. In method A an aqueous solution of cyclodextrin was added to an alcohol solution of ferrocene with stirring and heating; in method B an aqueous alcohol solution (40% ethanol) of cyclodextrin was mixed with an aqueous alcohol solution of ferrocene (60% ethanol), then water was added and/or ethanol was partially removed by evaporation; in method C fine crystals of ferrocene were added to an aqueous solution of cyclodextrin at 60 °C with stirring. The product obtained was washed thoroughly with water to remove remaining cyclodextrin and with tetrahydrofuran (thf) to remove unincluded molecules, and then recrystallized from water or aqueous alcohol. Of these three methods, C was found to be the best and gave β-cyclodextrin–ferrocene inclusion compounds quantitatively, while method A gave a lower yield. Method B afforded higher yields, but the iron content of the complex was relatively low (Table 1). The complexes of ferrocene with α- and γ-cyclodextrin could not be obtained by method A or B, only C.

The inclusion compounds of ferrocene with cyclodextrin were characterized by elemental analyses, i.r., u.v., and ^{1}H n.m.r. spectroscopy. Stoicheiometries were determined by elemental analyses, including atomic absorption analysis of the iron contents, and from the ^{1}H n.m.r. and the absorption spectra. These results show that all the complexes obtained are stoicheiometric compounds and have definite ratios of cyclodextrin : guest depending on the combinations of host and guest. Table 1 shows results on the preparation of inclusion compounds of cyclodextrins with ferrocene. β-Cyclodextrin formed 1 : 1 inclusion compounds with ferrocene, regardless of

Table 1. Synthesis of inclusion compounds of ferrocene with cyclodextrins

Cyclodextrin	Cyclodextrin : ferrocene molar ratio	Method	Yield (%)	Product % Fe Found	Product % Fe Calc.	Product Molar ratio
α	2:1	C	68	2.6	2.6	2:1
α	1:1	C	75	2.5	2.6	2:1
α	1:4	C	70	2.5	2.6	2:1
β	2:1	B	85	3.9	4.2	1:1
β	1:1	A	56	4.2	4.2	1:1
β	1:4	A	36	4.4	4.2	1:1
β	1:4	C	100	4.4	4.2	1:1
γ	1:1	C	59	3.6	3.8	1:1
γ	1:5	C	67	3.6	3.8	1:1

Table 2. Synthesis of inclusion compounds of ferrocene derivatives with cyclodextrins

Cyclodextrin	Guest	Cyclodextrin : guest molar ratio	Yield (%)	Product %Fe Found	Product %Fe Calc.	Product Molar ratio
α	**(2)**	1:2	73	2.5	2.6	2:1
β	**(2)**	1:2	100	4.1	4.1	1:1
γ	**(2)**	1:2	74	4.0	3.7	1:1
α	**(3)**	1:2	0	—	—	—
β	**(3)**	1:2	74	3.9	4.0	1:1
γ	**(3)**	1:2	90	3.7	3.6	1:1
α	**(4)**	1:2	80	2.6	2.6	2:1
β	**(4)**	1:2	100	4.5	4.1	1:1
γ	**(4)**	1:2	100	4.1	3.7	1:1
α	**(5)**	1:2	72	2.8	2.6	2:1
β	**(5)**	1:2	100	3.5	4.0	1:1
γ	**(5)**	1:2	98	3.5	3.6	1:1
α	**(6)**	1:2	46	3.5	2.6	2:1
β	**(6)**	1:2	100	3.6	4.0	1:1
γ	**(6)**	1:2	100	2.8	3.6	1:1
α	**(7)**	1:2	18	2.7	2.5	2:1
β	**(7)**	1:2	100	3.6	4.0	1:1
γ	**(7)**	1:2	100	3.6	3.6	1:1
α	**(8)**	1:2	67	2.8	2.5	2:1
β	**(8)**	1:2	100	3.5	4.0	1:1
γ	**(8)**	1:2	100	2.9	3.6	1:1
α	**(9)**	1:2	0	—	—	—
β	**(9)**	1:2	100	3.7	4.0	1:1
γ	**(9)**	1:2	100	3.1	3.6	1:1

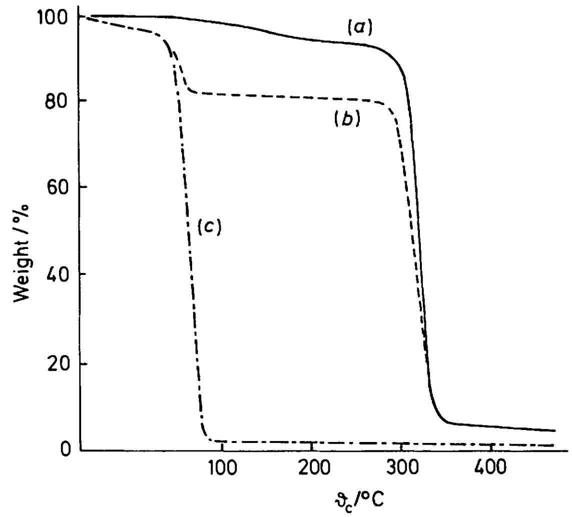


Figure 1. Thermogravimetric analysis *in vacuo* of (*a*) β-cyclodextrin–ferrocene complex, (*b*) a mixture of the cyclodextrin and ferrocene, and (*c*) ferrocene

the molar ratio of the host to guest in the reaction. This result indicates that the interaction between cyclodextrin and ferrocene is a real inclusion phenomenon. γ-Cyclodextrin also formed 1:1 complexes, while α-cyclodextrin formed 2:1 [α-cyclodextrin:**(1)**] complexes in high yields even when it was treated with an excess of ferrocene. Table 2 shows the results on the preparation of inclusion compounds of substituted ferrocene derivatives. The β- and γ-cyclodextrins formed 1:1 complexes with both mono- and di-substituted derivatives in high yields. For example, the complexes with α-hydroxyalkylferrocene and oxydiethylideneferrocene were obtained almost quantitatively. However, although α-cyclodextrin did not form complexes with 1,1′-disubstituted derivatives, it did form complexes with monosubstituted derivatives with a 2:1 (host:guest) stoicheiometry. The selective inclusion by cyclodextrin can be applied to the separation of ferrocene derivatives. Mono- and 1,1′-di-α-hydroxyethylferrocene, for example, could be successfully separated by complex formation with α-cyclodextrin. The monosubstituted ferrocene can be extracted from the inclusion compounds of α-cyclodextrin and the disubstituted derivative which is not included can be obtained by extraction from the residue.

Properties of Cyclodextrin Complexes.—Inclusion compounds of ferrocene with β- and γ-cyclodextrin are so stable that they can be recrystallized from water to give yellow crystals. The complexes of ferrocene with α- and β-cyclodextrin are thermally stable and do not liberate ferrocene on heating at 100 °C *in vacuo*. Figure 1 shows the results of the thermogravimetric analysis of the complex of ferrocene with β-cyclodextrin, free ferrocene, and a mixture of β-cyclodextrin and ferrocene. In the case of the mixture each component behaves independently, that is, ferrocene sublimes below 80 °C and β-cyclodextrin melts and decomposes around 300 °C. In the case of the complex there is no change around 80 °C. It is stable up to 200 °C and dissociates around the m.p. of the cyclodextrin component. These results indicate that the ferrocene molecule is tightly included in the β-cyclodextrin cavity.

Figure 2 shows the absorption and circular dichroism spectra of ferrocene in the presence of β- and γ-cyclodextrin in solution.

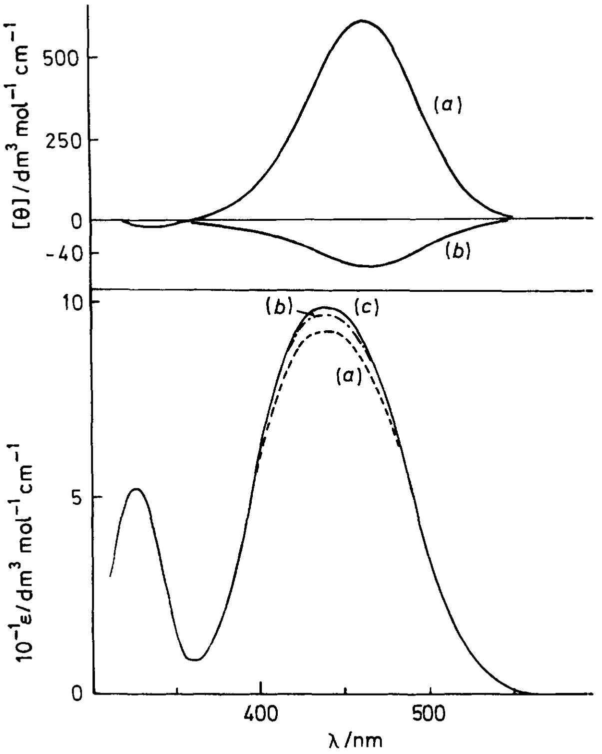


Figure 2. Absorption and c.d. spectra of ferrocene in the presence of β-cyclodextrin (*a*) and γ-cyclodextrin (*b*), [cyclodextrin] = [ferrocene] = 10^{-2} mol dm^{-3}, and (*c*) in the absence of cyclodextrin

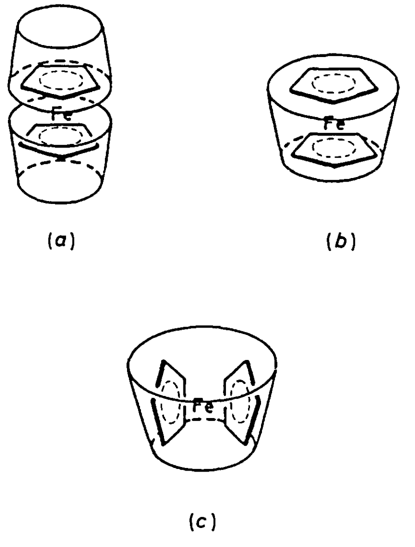


Figure 3. Proposed structures for (*a*) the 2:1 complex of α-cyclodextrin and ferrocene, (*b*) the 1:1 complex of β-cyclodextrin and ferrocene, and (*c*) the 1:1 complex of γ-cyclodextrin and ferrocene

Table 3. Characterization of inclusion compounds (cyd = cyclodextrin)

Complex	Analysis (%)[a] C	H	M.p.[b] (°C)	I.r. (cm^{-1})	^{1}H N.m.r. (δ/p.p.m.)
2α-cyd–(**1**)–$2H_2O$	45.45 (45.15)	6.25 (6.50)	300	1 100	4.2 (s, 10 H)
2α-cyd–(**2**)–$2H_2O$	46.00 (45.25)	6.25 (6.55)	270	1 660	2.3 (s, 3 H)
2α-cyd–(**4**)–$2H_2O$	45.95 (45.30)	6.35 (6.75)	275		1.4 (d, 3 H)
β-cyd–(**2**)	47.60 (47.40)	6.05 (6.30)	280	1 660	2.3 (s, 3 H) 4.2 (s, 5 H)
β-cyd–(**3**)–$2H_2O$	46.65 (45.90)	6.15 (6.70)	270	1 660	
β-cyd–(**4**)–$2H_2O$	46.30 (46.65)	6.20 (6.50)	265		2.3 (s, 6 H)
β-cyd–(**9**)	47.10 (46.40)	6.35 (6.70)	260		1.4 (q, 6 H)
γ-cyd–(**1**)–$2H_2O$	45.85 (45.90)	6.25 (6.65)	275	1 100	4.2 (s, 10 H)
γ-(cyd–(**2**)–$2H_2O$	46.65 (46.40)	6.25 (6.60)	265	1 660	2.3 (s, 3 H) 4.2 (s, 5 H)
γ-cyd–(**3**)–$2H_2O$	46.90 (45.75)	6.20 (6.35)	250	1 660	2.3 (s, 6 H)
γ-cyd–(**4**)	47.20 (47.35)	6.20 (6.40)	265		1.4 (d, 3 H) 4.2 (s, 5 H)
γ-cyd–(**9**)	47.95 (47.25)	6.20 (6.45)	240		1.4 (q, 6 H)
2α-cyd–(**5**)	46.65 (46.25)	6.15 (6.75)	268	1 660	1.2 (t, 3 H)
β-cyd–(**5**)	47.95 (48.25)	6.15 (6.45)	270	1 660	1.2 (t, 3 H)
γ-cyd–(**5**)	47.60 (47.30)	6.15 (6.40)	269	1 660	1.2 (t, 3 H)
2α-cyd–(**6**)	46.60 (46.60)	6.25 (6.55)	256	1 100	1.2 (t, 3 H)
β-cyd–(**6**)–$2H_2O$	46.70 (46.60)	6.40 (6.55)	264	1 100	1.2 (t, 3 H)
γ-cyd–(**6**)	47.55 (47.50)	6.25 (6.50)	241	1 100	1.2 (t, 3 H)
2α-cyd–(**7**)	46.90 (46.25)	6.20 (6.90)	270	1 660	0.9 (t, 3 H) 2.7 (t, 2 H)
β-cyd–(**7**)	46.90 (47.00)	6.20 (6.50)	270	1 680	0.9 (t, 3 H) 2.7 (t, 2 H)
γ-cyd–(**7**)	47.10 (46.55)	6.35 (7.05)	270	1 660	0.9 (t, 3 H) 2.7 (t, 2 H)
2α-cyd–(**8**)	46.85 (46.70)	6.30 (6.60)	270	1 150	0.9 (t, 3 H) 3.3 (s, 1 H)
β-cyd–(**8**)–$2H_2O$	47.35 (46.80)	6.35 (7.01)	270	1 160	0.9 (t, 3 H) 3.3 (s, 1 H)
γ-cyd–(**8**)–$2H_2O$	48.40 (48.85)	6.35 (7.00)	270	1 160	0.9 (t, 3 H) 3.3 (t, 1 H)

[a] Required values are given in parentheses. [b] With decomposition.

β-Cyclodextrin caused a marked decrease in the absorption spectrum of ferrocene at about 440 nm and showed a large positive Cotton effect at about 460 nm with a small negative Cotton effect at about 340 nm. γ-Cyclodextrin caused a smaller but definite decrease in the absorption spectrum of ferrocene and showed a negative Cotton effect at about 460 nm. According to calculation, an electric dipole moment on the axis of the cyclodextrin ring gives a positive Cotton effect, whereas one perpendicular to the axis gives a negative one.[11] The above results indicate that the orientation of the ferrocene molecule in the cavity of β-cyclodextrin is different from that in the cavity of γ-cyclodextrin.

Molecular models of the cyclodextrins and ferrocene indicate that a ferrocene molecule could fit well into a β-cyclodextrin cavity by axial inclusion, while a γ-cyclodextrin cavity is large enough to accommodate a ferrocene molecule equatorially. A consideration of the molecular dimensions of α-cyclodextrin and ferrocene implies that the ferrocene molecule is too large to be completely included in a single cavity of this cyclodextrin, which can accommodate only one cyclopentadienyl ring, but appears to fit well into the cavity formed by two such molecules. Proposed structures for the complexes are shown in Figure 3.

Experimental

Materials.—Cyclodextrins (α-, β-, and γ-) were obtained from Hayashibara Biochemical Laboratories Inc. Their purities were checked by elemental analysis and optical rotation. Ferrocene was purchased from Aldrich Chemical Co. Acetylferrocene and 1,1′-diacetylferrocene were prepared from ferrocene and acetic anhydride by a procedure similar to that described previously.[12] α-Hydroxyethylferrocene was prepared by the procedure described previously.[13] Propionylferrocene and 1-ferrocenylbutanone were prepared in similar manner to that of acetylferrocene. α-Hydroxypropyl-and α-hydroxybutyl-ferrocene were prepared similarly to α-hydroxyethylferrocene. 1,1′-Di-α-hydroxyethylferrocene was prepared from 1,1′-diacetylferrocene as described in the literature.[14]

Preparation of Cyclodextrin–Ferrocene Inclusion Complexes.—Finely ground crystals of ferrocene (0.372 g, 2.0 mmol) were added to an aqueous solution of β-cyclodextrin (10H$_2$O adduct; 0.657 g, 0.5 mmol) at 60 °C with stirring. The product was washed with water to remove the remaining cyclodextrin and dried *in vacuo*. Uncomplexed ferrocene was removed by washing the residue with tetrahydrofuran. During this process the included guest was not liberated from the cyclodextrin cavity. The yield of the crude product was quantitative. The crude product was recrystallized from water or aqueous alcohol to give yellow crystals: m.p. 285—295 °C (decomp.); i.r. 1 100 cm^{-1}; ^{1}H n.m.r. (Me$_2$SO, 100 MHz) δ 4.3 (10 H, s) (Found: C, 47.00; H, 6.35. Calc. for C$_{52}$H$_{80}$FeO$_{62}$: C, 47.25; H, 6.10%).

The other inclusion compounds were prepared in a similar way and their characterization data are summarized in Table 3.

Separation of Mono- and 1,1′-*Di-α-hydroxyethylferrocene.*—A 1:1 mixture of mono- and 1,1′-di-α-hydroxyethylferrocene (0.5 mmol each) was added to an aqueous solution of α-cyclodextrin (2 mmol in 12 cm^3 water). The solution was stirred at 60 °C for 12 h. The product was filtered off and dried. Mono-α-hydroxyethylferrocene was recovered from the inclusion compounds in 78% yield by extraction with CHCl$_3$. 1,1′-Di-α-hydroxyethylferrocene was obtained in 80% yield from the mother-liquor by extraction with CH$_2$Cl$_2$.

Measurements.—Infrared spectra were recorded on a Hitachi 295 spectrometer, u.v. spectra on a Shimadzu UV-202 spectrophotometer, ^{1}H n.m.r. spectra on a JEOL FX100 spectrometer, and circular dichroism spectra on a JASCO J-205 spectropolarimeter. Thermogravimetric analysis was made using a Shimadzu DT-30 thermal analyzer. Atomic absorption analysis was performed using a Shimadzu A-610S atomic absorption–flame spectrophotometer.

References

1 F. G. Stone, G. Wilkinson, and E. W. Abel, 'Comprehensive Organometallic Chemistry,' Pergamon Press, Oxford, 1982.

2 F. Vögtle, 'Host Guest Complex Chemistry I,' Springer, Berlin, 1981.

3 M. S. Whittington and A. J. Jacobson, 'Intercalation Chemistry,' Academic Press, New York, 1982; T. J. Pinnavia, *Science*, 1983, **220**, 365.

4 H. M. Colquhoun, J. F. Stoddart, and D. J. Williams, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 487.

5 D. R. Alston, A. M. Z. Slain, J. F. Stoddart, and D. J. Williams, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 821.

6 M. L. Bender and M. Komiyama, 'Cyclodextrin Chemistry,' Springer, New York, 1977; J. Szejtli, 'Cyclodextrin and Their Inclusion Complexes,' Akademiai Kiado, Budapest, 1982; W. Saenger, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 344.

7 R. Breslow, G. Trainor, and A. Ueno, *J. Am. Chem. Soc.*, 1983, **105**, 2739.

8 T. Matsue, N. Kobayashi, and T. Osa, *Nippon Kagaku Kaishi*, 1983, 303.

9 D. R. Alston, A. M. Z. Slawin, J. F. Stoddart, and D. J. Williams, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 786.

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

11 K. Harata and H. Uedaira, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 375.

12 Y. Nagai, J. Hooz, and R. A. Benkeser, *Bull. Chem. Soc. Jpn.*, 1964, **37**, 53.

13 F. S. Arimoto and A. C. Haven, jun., *J. Am. Chem. Soc.*, 1955, **77**, 6295.

14 P. J. Graham, R. V. Lindsey, G. W. Parshall, M. L. Peterson, and G. M. Whitman, *J. Am. Chem. Soc.*, 1957, **79**, 3416.

Received 28*th April* 1987; *Paper* 7/758