PREPARATION AND PROPERTIES OF CYCLODEXTRIN INCLUSION COMPOUNDS OF ORGANOMETALLIC COMPLEXES. FERROCENE INCLUSION COMPOUNDS

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ABSTRACT: Inclusion compounds of ferrocene(FcH) and its derivatives with cyclodextrins(CDs; α-CD, β-CD, and γ-CD) were prepared. CD-ferrocene inclusion compounds were obtained in a crystalline state in high yield. β-CD and γ-CD formed 1:1 stoichiometric inclusion compounds with ferrocene and its derivatives. α-CD formed 2:1 (CD:guest) complexes with ferrocene and the monosubstituted derivatives, but did not form complexes with 1,1'-disubstituted derivatives. α-CD-FcH and β-CD-FcH complexes are thermally stable and do not liberate ferrocene on heating at 100°C in vacuo. The cyclodextrin inclusion compounds were characterized by ^{1}H-NMR, IR, UV, and CD spectra. A large positive induced Cotton effect was observed in the case of β-CD-FcH complex, while the γ-CD-FcH complex showed a negative spectrum. The binding mode is discussed. β-Cyclodextrin was found to form inclusion complexes in ethylene glycol, diethylene glycol, triethylene glycol, methyl cellosolve, ethyl cellosolve, methyl alcohol, and glycerine solutions. γ-CD also formed complexes in ethylene glycol solution. The binding of ferrocene by β-CD is stronger in ethylene glycol than in dimethyl sulfoxide and dimethyl formamide.

1. Introduction

Organotransition metal complexes have been extensively used as homogeneous catalysts in organic reactions and much effort has been paid to improve their activity and selectivity. Meanwhile, cyclodextrins(CDs) have been studied as a model of enzyme for selective catalysts. Therefore to combine the function of organometallic complexes and that of cyclodextrins, we tried to prepare cyclodextrin inclusion compounds of organometallic complexes. There are only a few reports on the interaction between organometallic complexes and cyclodextrins. Breslow et al. reported high acylation rates for β-CD using ferrocene derivatives and assumed β-CD-substrate complexes as intermediates. [1] Osa et al. reported the effect of β-CD on the electron transfer of ferrocene-carboxylic acid. [2] Maeda et al. reported the ^{59}Fe Mossbauer spectra of ferrocene derivatives enclosed in α- and β-CD molecule. [3] In a

previous communication we reported briefly the preparation of cyclo-
dextrin-ferrocene inclusion compounds as an example of CD inclusion
complexes of organotransition metal complexes. [4] We describe here the
preparation and properties of inclusion compounds of ferrocene and its
derivatives with cyclodextrins in detail. In the course of our investi-
gation on the properties of the inclusion compounds of ferrocene we
have found that cyclodextrins form inclusion compounds not only in
aqueous solution but in alcohol solutions. Until recently it was
generally believed that cyclodextrins form inclusion complexes only in
aqueous solutions. [5] Water seemed to be intimately involved in the
association process because attempts to induce precipitation of cyclo-
dextrin adducts from organic solvents have failed. [6] Recently,
however, Breslow et al. reported that inclusion complex formation also
takes place in dimethyl sulfoxide and in dimethyl formamide. [7] To our
knowledge, there are no reports of inclusion complex formation in
organic solvents other than dimethyl sulfoxide and dimethyl formamide.
Although cyclodextrins are almost insoluble in organic solvents, they
are soluble in glycols, methyl and ethyl cellosolve, and methyl alcohol.
Cyclodextrins have been found to form inclusion complexes in such alco-
hols. We describe here the complex formation in such alcohol solutions.

2. Results and Discussion

2.1. Preparation of Inclusion Compounds

    Since metallocenes are insoluble in water, co-crystallization
method from aqueous solutions, which is usually employed with water-
soluble compounds to obtain inclusion compounds, cannot be used in this
case. In an attempt to prepare CD-ferrocene inclusion compounds several
methods were tested. **Method A:** an alcohol solution of ferrocene was
added to an aqueous solution of CD with stirring and heating. **Method B:**
an aqueous alcohol solution (40% ethanol) of CD was mixed with an
aqueous alcohol solution of ferrocene (60% ethanol), then water was
added and/or ethanol was partially removed by evaporation. **Method C:**
fine crystals of ferrocene were added to a CD aqueous solution at 60° C
with stirring. The product obtained was washed thoroughly with water and
THF, and then recrystallized from water or aqueous alcohol. Among the
above three methods, method C was found to be the best and gave β-CD-
ferrocene inclusion complex quantitatively, while method A gave a lower
yield. Method B afforded high yields, but Fe content of the complex was
relatively low. (Table I) α-CD-Fc and γ-CD-Fc complexes could not be
obtained by Method A nor B, but C.
    The CD-ferrocene complexes were characterized by elemental
analysis, IR, UV, and ^{1}H-NMR spectra. Stoichiometries were determined by
elemental analysis, and especially the iron content measured by atomic
absorption analysis and from the ^{1}H-NMR spectra, which show all the
complexes obtained here are stoichiometric compounds and have definite
ratios of CD/guest depending on the combinations of host and guest.
Table I shows the results of the preparation of inclusion compounds of
CDs with ferrocene. β-CD formed 1:1 inclusion compounds with ferrocene,
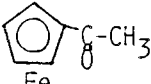
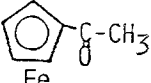Table I. Synthesis of CD -Ferrocene   inclusion complexes
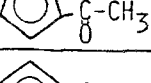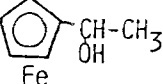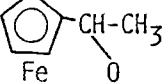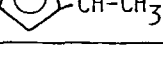
CD	Fc	molar ratio of CD/Fc charged	method[a]	product			
				yield %	Fe % Found	Fe % Calcd	CD:Fc
α		2:1	C	68	2.6	2.6	2:1
α		1:1	C	75	2.5	2.6	2:1
α		1:4	C	70	2.5	2.6	2:1
β	Fc (ferrocene)	2:1	B	85	3.9	4.2	1:1
β		1:1	A	56	4.2	4.2	1:1
β		1:4	A	36	4.4	4.2	1:1
β		1:4	C	100	4.4	4.2	1:1
γ		1:1	C	59	3.6	3.8	1:1
γ		1:5	C	67	3.6	3.8	1:1

regardless of the molar ratio of the host to the guest charged in the reaction. This result indicates that the interaction between cyclo-dextrin and ferrocene is a real inclusion phenomenon. γ-CD also formed 1:1 complexes, while α-CD formed 2:1 (α-CD:guest) complexes in high yields even if α-CD was treated with an excess of ferrocene or ferrocene derivatives. Table II shows the results on the preparation of inclusion compounds of substituted ferrocene derivatives. β-CD and γ-CD formed 1:1 complexes with both mono- and disubstituted derivatives in high yields. β-CD and γ-CD complexes with acetyl ferrocene, α-hydroxylethyl ferrocene and oxy-bis-ethylidene ferrocene, for example, were obtained almost quantitatively. However, although α-CD did not form complexes with 1,1'-disubstituted derivatives, it did form complexes with monosubstituted derivatives with a 2:1 (CD:guest) stoichiometry.

2.2. Properties of CD complexes

β-CD-FcH and γ-CD-FcH complexes are so stable that they can be recrystallized from water to give yellow crystals. α-CD-FcH and β-CD-FcH complexes are thermally stable and do not liberate ferrocene on heating at 100°C in vacuo. Figure 1 shows the results on the thermogravimetric analysis of the β-CD-FcH complex, free ferrocene , and the mixture of β-CD and ferrocene. In the case of the mixture each component behaves independently, that is, ferrocene sublimed below 80°C and β-CD melts and decomposes around 300°C. In the case of the complex there is no change around 80°C. The complex is stable up to 200°C and dissociates around the m.p. of the CD component. These results indicate that the ferrocene

TableII. Synthesis of CD -Ferrocenes inclusion complexes

CD	Fc	molar ratio of CD/Fc charged	method[a]	product			
				yield %	Fe % Found	Fe % Calcd	CD:Fc
α	Fc–C(=O)–CH$_3$ (acetylferrocene)	1:2	C	73	2.5	2.6	2:1
β		1:2	C	100	4.1	4.1	1:1
γ		1:2	C	74	4.0	3.7	1:1
α	Fc(–C(=O)–CH$_3$)$_2$ (1,1'-diacetylferrocene)	1:2	C	0	–	–	–
β		1:2	C	74	3.9	4.0	1:1
γ		1:2	C	90	3.7	3.6	1:1
α	Fc–CH(OH)–CH$_3$	1:2	C	80	2.6	2.6	2:1
β		1:2	C	100	4.5	4.1	1:1
γ		1:2	C	100	4.1	3.7	1:1
α	Fc(–CH(CH$_3$)–)$_2$O	1:2	C	0	–	–	–
β		1:2	C	100	3.7	4.0	1:1
γ		1:2	C	100	3.1	3.6	1:1
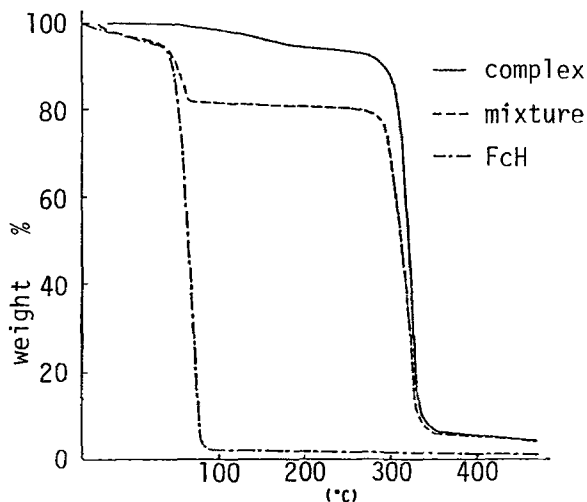
Fig.1. Thermogravimetric analysis of β-CD-FcH complex. *in vacuo.*

molecule is tightly included in the β–CD cavity.

Figure 2 shows the absorption and c.d. spectra of ferrocene in the presence of β–CD and γ–CD in solution. β–CD 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–CD caused a smaller but definite decrease in the absorption spectrum of ferrocene and showed a negative Cotton effect at about 460 nm. According to theory 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. [8] The above results indicate that the orientation of ferrocene molecule in the cavity of β–CD is different from that in γ–CD cavity.
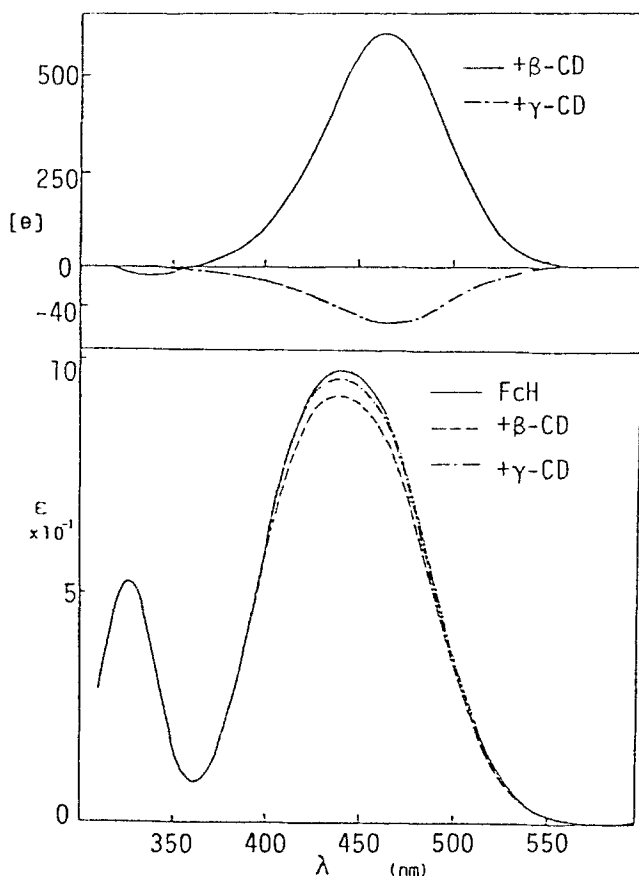
Fig.2. Absorption and c.d. spectra of ferro-cene(FcH) in the presence of β-CD and γ-CD in ethylene glycol. [CD]=[FcH]=10⁻² M

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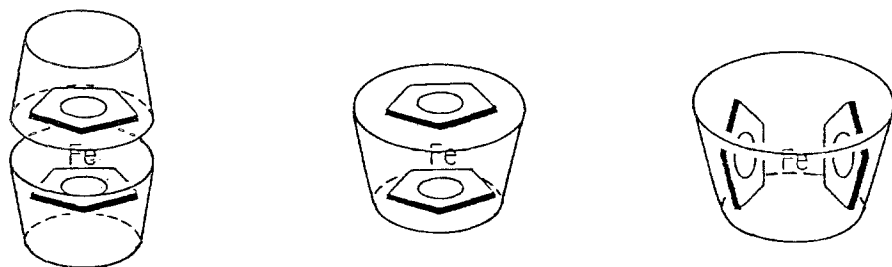

Figure 3   a   b   c

            α-CD—FcH   β-CD—FcH   γ-CD—FcH
            2:1 complex   1:1 complex   1:1 complex

The change of absorption and c.d. spectra of ferrocene on addition of β-CD was observed in ethylene glycol, diethylene glycol, triethylene glycol, methyl cellosolve, ethylcellosolve, and glycerine solutions. These results indicate that β-CD forms inclusion complexes in such alcohol solutions. Plots of the UV absorption change at 440 nm and increase in the c.d. spectra at 460 nm as functions of the β-CD concentration gave saturation curves indicating that the spectral changes were due to complex formation. The dissociation constants of the complexes were obtained by Benesi Hildebrand plots. Table III summarizes the dissociation constants of the β-CD-substrate complexes in ethylene glycol and methyl cellosolve. The dissociation constants were confirmed by plotting the change in optical rotation of 0.5 mM β-CD solution as a function of the concentration of added substrate. The dissociation constants obtained by these three methods were in good agreement. The binding of ferrocene by β-CD is stronger in ethylene glycol than in dimethyl sulfoxide, but the dissociation constants in methyl cellosolve and dimethyl sulfoxide are similar. β-CD was found to solubilize ferrocene in ethylene glycol. The ferrocene-β-CD complex was so stable that it could be recrystallized from ethylene glycol. Ferrocene also bound to β-CD in methyl alcohol solution with a dissociation constant of 8mM. Bromobenzene, chlorobenzene, and trichrene were shown by measurement of the optical rotation change of β-CD to be bound with β-CD. γ-CD was also found to form complexes in ethylene glycol.

Table III. Dissociation constants of β-CD-substrate complexes

substrate	Kd (mM)		
	in ethylene glycol	in methyl cellosolve	in DMSO
ferrocene	12[a]	25[c]	21[d]
	13[b]		
	12[c]		
toluene	60[c]	400[c]	444[d]
anisole	66[c]	–	400[d]

a) determined from c. d. spectrum
b) determined from uv spectrum
c) determined from optical rotation
d) reference 3)

3. Experimental

Cyclodextrins (α-CD, β-CD, and γ-CD) 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 diacetylferrocene were prepared from ferrocene and acetic anhydride by a procedure similar to that described previously. [9] α-Hydroxyethyl ferrocene was prepared by the procedure described previously. [10]

Preparation of CD-Ferrocene inclusion complexes

β-CD-FcH complex was prepared by adding finely ground crystals of ferrocene (0.372 g, 2.0 mmol) to an aqueous solution of β-CD (10H$_2$O adduct, 0.657 g, 0.5 mmol) at 60° C with stirring. The product was washed with water to remove remaining CD, and dried in vacuum. 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 is 100%. The crude product was recrystallized from water or aqueous alcohol to give yellow crystal. mp 285-295° C (decomposed); IR 1100 cm^{-1}; ^{1}H-NMR (DMSO, 100MHz) δ 4.3 (s 10H) Anal. Calcd. for C$_{52}$H$_{80}$O$_{62}$Fe: C,47.27; H,6.10. Found: C,47.00; H,6.35.

The other inclusion compounds were prepared in a similar way.

Instrumentation

Infrared spectra were taken on a Hitachi 295 spectrometer and UV spectra were recorded on a Shimadzu UV-202 spectrophotometer. ^{1}H-NMR spectra were run on a JEOL FX100 spectrometer. CD spectra were recorded on a JASCO J-205 spectropolarimeter. Thermogravimetric analysis was made using Shimadzu thermal analyzer DT-30. Atomic absorption analysis was made using a Shimadzu A-610S atomic absorption/flame spectrophotometer.

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