

Selected Papers

Complex Formation of Cyclodextrins with a Dumbbell Molecule Bearing Two Ferrocene Moieties at the Ends

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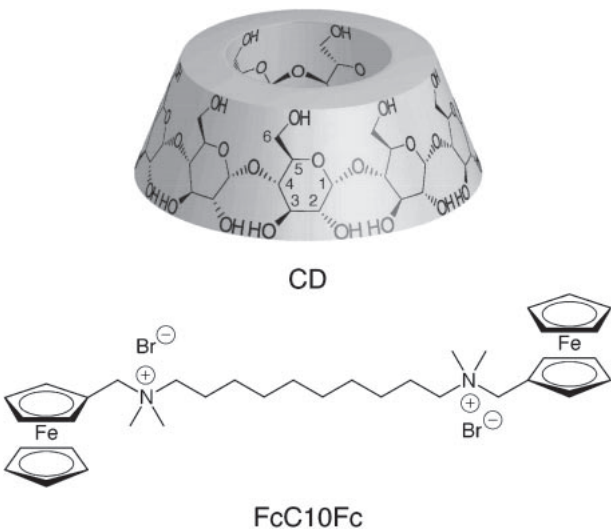
The complexation behavior of cyclodextrins (CDs) with a dumbbell molecule possessing ferrocene (Fc) moieties at both the ends (FcC10Fc) was investigated by ^{1}H NMR, two-dimensional rotating frame Overhauser spectroscopy, circular dichroism spectroscopy, and cyclic voltammetry. α-CD includes the cyclopentadienyl rings of the Fc moiety shallowly from the wider side but not the decamethylene (C10) moiety, whereas β-CD and γ-CD include not only the Fc moiety but also the C10 moiety. These observations indicate that the Fc moiety can pass through β-CD and γ-CD cavities but not the α-CD cavity.

Biological systems maintain their living activities using supramolecular assemblies responsive to external stimuli, which are responsible for various functions.[1–3] These biological stimuli-responsive supramolecular assemblies have inspired a number of research groups to devote their efforts to construction of artificial supramolecular assemblies responsive to external stimuli, e.g., temperature, pH, chemicals, and light.[4–22] Compared to thermo-, pH-, chemical-, and photo-responsive supramolecular assemblies, redox-responsive ones have been an underexamined subject of investigation, although redox stimulus is promising because it can be provided not only chemically by adding oxidants or reductants but also electrochemically by applying a potential.[23–25]

Cyclodextrins (CDs) are cyclic oligomers of D-(+)-glucopyranose units linked through an α-1,4-glycoside bond (Scheme 1). CDs of 6, 7, and 8 glucopyranose units are called α-CD, β-CD, and γ-CD, respectively. CDs are toroidal with narrower primary hydroxy and wider secondary hydroxy sides. The most important features of CDs are their hydrophilic exterior and hydrophobic cavity, and thus CDs recognize hydrophobic compounds of size and shape matching their cavity to form inclusion complexes in aqueous media. Since CDs are soluble in water and nontoxic, they are investigated widely as a building block for supramolecular assemblies.[26–34] A number of examples of CD-based supramolecular assemblies responsive to external stimuli have been also reported.[27–31,33,34]

It is known that CDs and ferrocene are a molecular recognition pair responsive to redox stimulus: CDs interact with the reduced form, ferrocene, to form inclusion complexes, but not with the oxidized form, ferrocenium.[35–54] Using pairs of CDs and ferrocene moieties, redox-responsive hydrogel,[55] controlled release,[56] and vesicle[53] have been realized. In order to construct more sophisticated redox-responsive supramolecular assemblies, e.g., Janus [2]rotaxanes and molecular shuttles, it is necessary to obtain fundamental data including not only how strong they interact (i.e., association constants) but also whether or not a ferrocene moiety can pass through the cavity of CDs. To the best of our knowledge however, there has been no research clarifying the latter point. To obtain experimental evidence for whether or not a certain moiety can pass through the cavity of CDs, the behavior of complex formation of CDs with a dumbbell molecule possessing the moieties at both ends should be investigated.[57] Thus, this study deals with the



Scheme 1. Molecular structures of CD and the dumbbell molecule, FcC10Fc.

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complex formation of CDs with a dumbbell molecule bearing ferrocene moieties at both ends, FcC10Fc (Scheme 1).

Experimental

^{1}H NMR spectra were recorded on a JEOL ECA500 spectrometer at 30 °C. Chemical shifts were referenced to the solvent value (4.7 ppm for D_2O). Two-dimensional rotating frame Overhauser spectroscopy (2D ROESY) NMR data were obtained on a VARIAN VNMR600 spectrometer at 30 °C. In the 2D ROESY NMR, the mixing time before the acquisition of free induction decay was fixed at 200 ms for all the samples. UV–vis absorption spectra were recorded on a JASCO V-650 spectrometer at 30 °C with 1 cm quartz cells. Circular dichroism spectra were recorded on a JASCO J-820 polarimeter in water at 30 °C with a 0.1 cm quartz cell. All electrochemical measurements were performed with a workstation equipped ALS/[H] CH Instruments Electrochemical Analyzer Model 611A. A platinum working electrode (0.018 cm^2), a platinum counter electrode, and a silver chloride reference electrode in saturated potassium chloride were fitted to a 20 mL electrochemical cell. The platinum electrodes were polished with a 0.05 μm alumina/water slurry on an abradant pad before measurements. Cyclic voltammograms were obtained in 0.1 M NaBr at 25 °C in the potential range from 0.0 to 0.7 V vs. Ag/AgCl. Scan rate was fixed at 100 mV s^{-1}.

Diethyl ether and tetrahydrofuran (THF) were obtained from Kanto Chemical Co., Inc. (*N*,*N*-Dimethylaminomethyl)-ferrocene and 1,10-dibromodecane were obtained from Tokyo Chemical Industry Co., Ltd. α-Cyclodextrin (α-CD), β-cyclodextrin (β-CD), and γ-cyclodextrin (γ-CD) were purchased from Junsei Chemical Co., Ltd., and purified by recrystallization from water. D_2O used as solvents for NMR was obtained from Merck Ltd. Other reagents were used without further purification.

The dumbbell molecule, FcC10Fc, was prepared by quarternization of (*N*,*N*-dimethylaminomethyl)ferrocene with 1,10-dibromodecane as follows. (*N*,*N*-Dimethylaminomethyl)-ferrocene (500 mg, 2.53 mmol) was dissolved in THF (2 mL), and cooled to 0 °C. 1,10-Dibromodecane (183 mg, 0.61 mmol) was dissolved in diethyl ether (1 mL), and added dropwise to the solution of (*N*,*N*-dimethylaminomethyl)ferrocene at 0 °C. After the mixture was stirred for 30 min, the mixture was allowed to warm to room temperature and stirred for 3 days. The precipitate was filtered and washed with diethyl ether to give FcC10Fc as a brown solid. Yield 653 mg, 83%. ^{1}H NMR (D_2O, 500 MHz, 30 °C): δ 4.51 (t, $J = 1.83$ Hz, 4H, 2-position of cyclopentadienyl), 4.45 (t, $J = 1.79$ Hz, 4H, 3-position of cyclopentadienyl), 4.39 (s, 4H, methylene in the vicinity of cyclopentadienyl), 4.30 (s, 10H, cyclopentadienyl), 3.11 (m, 4H, α-methylene in the vicinity of quaternary amine), 2.90 (s, 12H, methyl of quaternary amine), 1.75 (m, 4H, β-methylene in decamethylene in the vicinity of quaternary amine), 1.32–1.30 (m, 12H, methylene in decamethylene). ^{13}C NMR (D_2O, 125.77 MHz, 30 °C): δ 77.9, 76.5, 75.6, 71.9, 70.6, 59.7, 53.3, 42.7, 42.5, 40.5, 37.5. Found: C, 51.05; H, 7.03; N, 3.36%. Calcd for $C_{36}H_{54}N_2Fe_2Br_2 \cdot 3.5H_2O$: C, 50.91; H, 7.24; N, 3.30%.

In a similar manner, FcC10Fc possessing iodide (I^-) as counter anion {FcC10Fc(I^-)} was prepared from (*N*,*N*-dimethylaminomethyl)ferrocene (486 mg, 2.0 mmol) and 1,10-diiododecane (200 mg, 0.51 mmol). FcC10Fc(I^-) was obtained as brown solid. Yield 248 mg, 83%. FcC10Fc(I^-) (20 mg, 23 μmol) and NH_4PF_6 (770 mg, 4.7 mmol) were dissolved in acetone (1.6 mL). After filtration of the solution, water (4 mL) was added to the filtrate to form precipitate. The precipitate was dissolved in a solution of NH_4PF_6 in acetone (4.72 M, 1 mL). The solution was poured into excess water to obtain crude FcC10Fc possessing hexafluorophosphate (PF_6^-) as counter anion {FcC10Fc(PF_6^-)}. FcC10Fc(PF_6^-) was purified by recrystallization from acetone. Yield 20 mg, 95%.

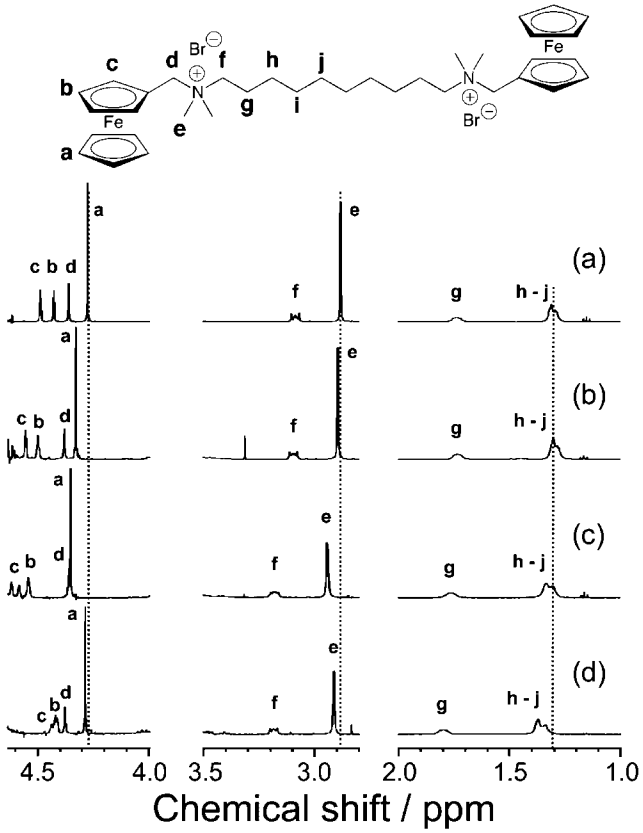

Figure 1. ^{1}H NMR spectra for 1.0 mM FcC10Fc in the absence (a) and presence of 10 mM α-CD (b), β-CD (c), and γ-CD (d).

FcC10Fc was oxidized electrochemically and chemically. A solution of FcC10Fc in 0.1 M NaBr (1 mM) was purged with argon for 10 min. FcC10Fc was oxidized using the electrochemical analyzer at 0.7 V for 7 h. An aqueous solution of sodium hypochlorite (ca. 2 mM, 300 μL) was added to an aqueous solution of FcC10Fc (1 mM, 300 μL). The solution immediately turned from yellow to green. After ca. 10 s, however, the reaction mixture became yellow brown, and then brown precipitate was formed.

Results and Discussion

The complexation behavior was first examined by ^{1}H NMR. Figure 1 demonstrates a typical example of ^{1}H NMR spectra for 1.0 mM FcC10Fc in the absence and presence of 10 mM α-CD, β-CD, and γ-CD. The spectrum in the presence of 10 mM α-CD exhibits downfield shifts of the signals ascribable to **a**, **b**, and **c** protons in the Fc moieties but no shifts of the

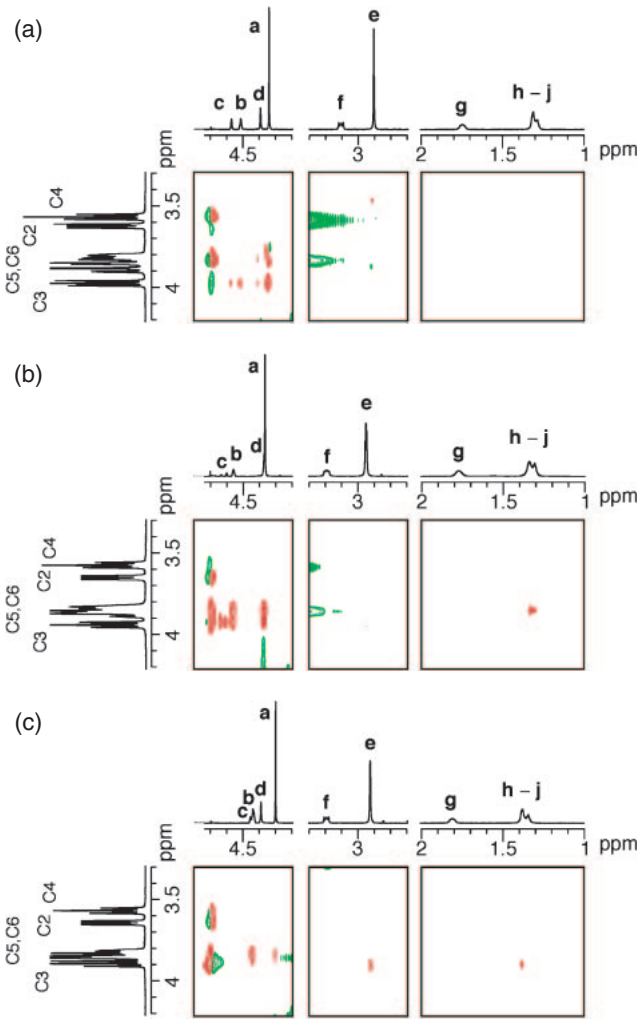

Figure 2. 2D ROESY NMR spectra for mixtures of 1.0 mM FcC10Fc with 10 mM α-CD (a), β-CD (b), and γ-CD (c).

signals ascribable to the decamethylene (C10) moiety. These observations indicate that α-CD includes the Fc moieties but not the C10 moiety. The spectra in the presence of β-CD and γ-CD indicate downfield shifted signals ascribable to **a**, **b**, and **c** protons in the Fc moieties and to **g** and **h**–**j** protons in the C10 moiety, indicating that β-CD and γ-CD include not only the Fc moieties but also the C10 moiety. It should be noted here that the spectrum in the presence of β-CD exhibits separated signals assignable to **c** protons in the Fc moiety, suggestive of strong interaction of β-CD with FcC10Fc.

The structures of the complexes of CDs with FcC10Fc were investigated by 2D ROESY and circular dichroism spectroscopy. Figure 2 demonstrates 2D ROESY data for mixtures of 10 mM CDs with 1.0 mM FcC10Fc. The spectrum for the α-CD/FcC10Fc mixture exhibits ROE correlation signals (red signals) between signals ascribable to the C3 protons in α-CD and **a**, **b**, and **c** protons in the Fc moiety but not any significant correlation signals between signals due to α-CD and the C10 moiety (Figure 2a). This spectrum indicates that two α-CD molecules include shallowly the cyclopentadienyl (Cp) rings of the Fc moiety from the wider side[35–37] and confirms that α-CD does not include the C10 moiety. The spectrum for the β-CD/FcC10Fc mixture contains ROE correlation signals between

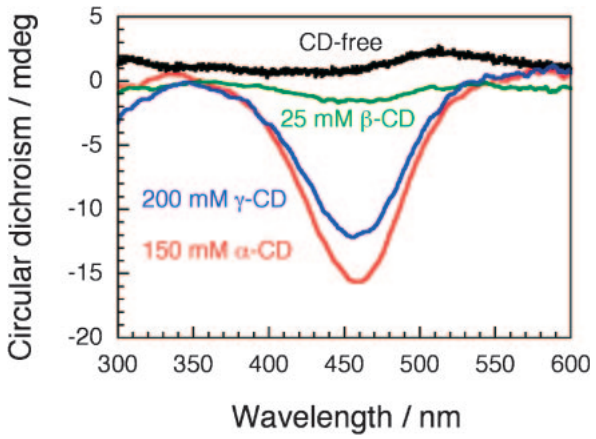

Figure 3. Circular dichroism spectra for 12.5 mM FcC10Fc in the absence (black) and presence of 150 mM α-CD (red), 25 mM β-CD (green), and 200 mM γ-CD (blue). These spectra were measured for solutions of concentrated FcC10Fc because of weak icd signals.

signals due to β-CD and the Fc moiety (**a**–**c** protons) and between signals due to β-CD and the C10 moiety (**h**–**j** protons), indicating that β-CD includes both the Fc and C10 moieties (Figure 2b). It should be noted here that signals of the **c** proton in the Fc moiety show ROE correlation signals only with the C3 protons in β-CD, indicating that β-CD includes the Fc moiety rather deeply from the wider side. The spectrum for the γ-CD/FcC10Fc mixture also indicates ROE correlation signals not only between signals due to γ-CD and the Fc moiety (**a**–**c** protons) but also between signals due to γ-CD and the C10 moiety (**h**–**j** protons), indicating that γ-CD also includes both the Fc and C10 moieties. The **b** and **c** protons in the Fc moiety indicate ROE correlation signals only with the C5 and C6 protons in γ-CD, indicative of the Fc moiety deeply included by γ-CD from the narrower side. As can be seen in Figure 3, the circular dichroism spectra for the α-CD/FcC10Fc and γ-CD/FcC10Fc mixtures indicate a strong negative induced circular dichroism (icd) band ascribable to the d–d transition moment of the Fc moiety, indicative of the complexation of CDs with the Fc moiety. Since α-CD includes shallowly the Cp rings of the Fc moiety, the negative icd band indicates that the rotational axis and the d–d transition moment of the Fc moiety, which is parallel to the Cp rings,[58–60] are close to perpendicular.[61–63] On the other hand, since γ-CD includes deeply the Fc moiety, the negative icd band indicates that the rotational axis of γ-CD and the transition moment are close to parallel.[64] The spectrum for the β-CD/FcC10Fc mixture shows only a weak negative icd band. This spectrum indicates that the rotational axis of β-CD and the transition moment of the Fc moiety make an angle close to 54.7° in the β-CD/FcC10Fc inclusion complex.[65] Figure 4 demonstrates proposed structures for the complexes of CDs with FcC10Fc based on the characterization data described above.

To understand details of equilibria of the complexation of CDs with FcC10Fc, ^{1}H NMR spectra were recorded at a constant FcC10Fc concentration (1.0 mM) at varying concentrations of CD ($[CD]_t$). Using the spectra, the peak shifts for the Fc (**a** proton) and C10 (**h**–**j** protons) moieties ($\Delta\delta_{Fc}$ and $\Delta\delta_{C10}$, respectively) were calculated and plotted in Figure 5 as a

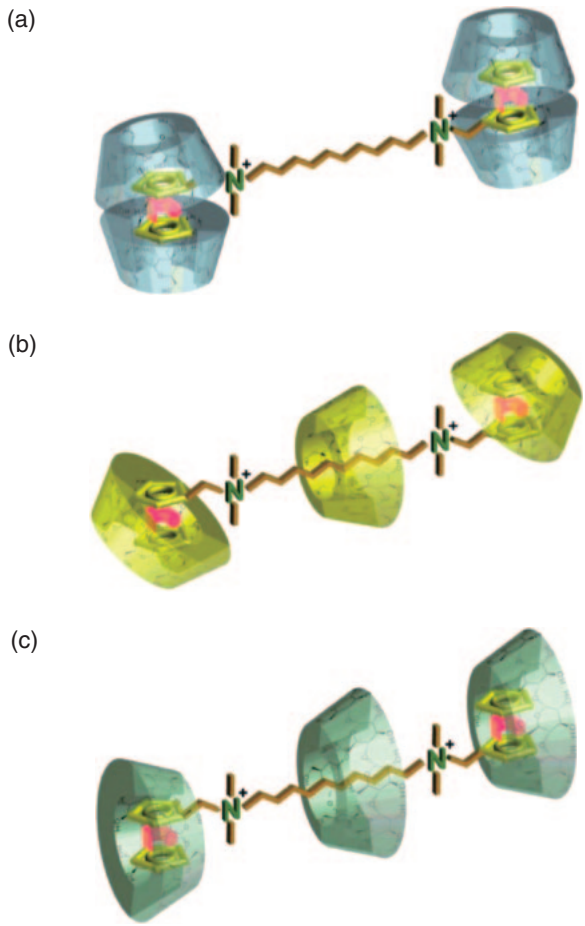

Figure 4. Proposed structures of the complexes of FcC10Fc with α-CD (a), β-CD (b), and γ-CD (c).

function of $[CD]_t$. On the basis of the structures of complexes (Figure 4), we propose simplified schemes for equilibria of the complexations of CDs with FcC10Fc (Scheme 2). As described in Appendix, $\Delta\delta_{Fc}$ and $\Delta\delta_{C10}$ can be calculated as eqs A16, A32, and A33. Fitting data using these equations (see Figure 5 and Appendix), we roughly estimated the first and second association constants (K_1 and K_2, respectively) for the α-CD/FcC10Fc systems and the association constant for the CD/Fc complexation (K_{Fc}) and the equilibrium constant between complexed Fc and C10 moieties (K_{Fc-C10}) for the β-CD/FcC10Fc and γ-CD/FcC10Fc systems, as listed in Table 1.[66,67] The K_1 and K_2 values (3×10^2 and $5 \times 10^2\ M^{-1}$, respectively) for the α-CD/FcC10Fc systems are indicative of weak

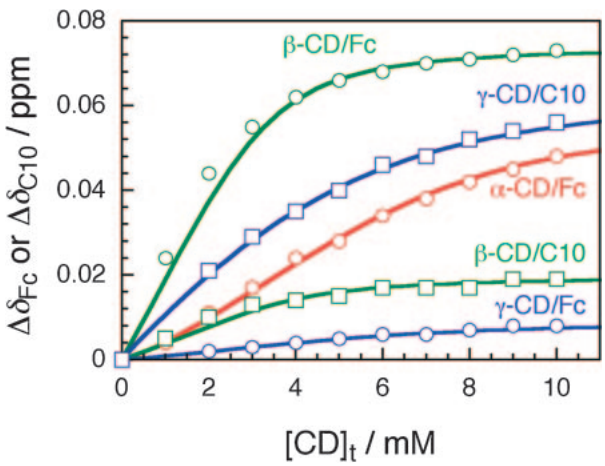

Figure 5. Peak shifts ($\Delta\delta_{Fc}$ and $\Delta\delta_{C10}$) for the signals due to the ferrocene (circle) and decamethylene (square) moieities in FcC10Fc as a function of the total CD concentration ($[CD]_t$): α-CD (red), β-CD (green), and γ-CD (blue). The best fitted curves using eqs A16, A32, and A33 are also drawn (see Supporting Information).

(a)

$$\mathrm{FcC10Fc + CD} \overset{K_1}{\rightleftharpoons} \mathrm{\underline{Fc}C10Fc} \qquad \mathrm{\underline{Fc}C10Fc + CD} \overset{K_2}{\rightleftharpoons} \mathrm{\underline{\underline{Fc}}C10Fc}$$

$$\mathrm{\underline{Fc}C10Fc + CD} \overset{K_1}{\rightleftharpoons} \mathrm{\underline{Fc}C10\underline{Fc}} \qquad \mathrm{\underline{Fc}C10\underline{Fc} + CD} \overset{K_2}{\rightleftharpoons} \mathrm{\underline{\underline{Fc}}C10\underline{Fc}}$$

$$\mathrm{\underline{\underline{Fc}}C10Fc + CD} \overset{K_1}{\rightleftharpoons} \mathrm{\underline{Fc}C10\underline{Fc}} \qquad \mathrm{\underline{Fc}C10\underline{Fc} + CD} \overset{K_2}{\rightleftharpoons} \mathrm{\underline{\underline{Fc}}C10\underline{\underline{Fc}}}$$

(b)

$$\mathrm{FcC10Fc + CD} \overset{K_{Fc}}{\rightleftharpoons} \mathrm{\underline{Fc}C10Fc} \qquad \mathrm{\underline{Fc}C10Fc} \overset{K_{Fc\text{-}C10}}{\rightleftharpoons} \mathrm{Fc\underline{C10}Fc}$$

$$\mathrm{\underline{Fc}C10Fc + CD} \overset{K_{Fc}}{\rightleftharpoons} \mathrm{\underline{Fc}C10\underline{Fc}} \qquad \mathrm{\underline{Fc}C10\underline{Fc}} \overset{K_{Fc\text{-}C10}}{\rightleftharpoons} \mathrm{\underline{Fc}\underline{C10}Fc}$$

$$\mathrm{Fc\underline{C10}Fc + CD} \overset{K_{Fc}}{\rightleftharpoons} \mathrm{\underline{Fc}\underline{C10}Fc}$$

$$\mathrm{\underline{Fc}\underline{C10}Fc + CD} \overset{K_{Fc}}{\rightleftharpoons} \mathrm{\underline{Fc}\underline{C10}\underline{Fc}}$$

Scheme 2. Schemes for equilibria for the complexations of α-CD (a) and β- or γ-CD (b) with FcC10Fc.

cooperativity for the complexation of α-CD with the Fc moiety. The K_{Fc} value for β-CD ($2.5 \times 10^3\,M^{-1}$) is larger than that for γ-CD ($3.5 \times 10^2\,M^{-1}$), indicating that β-CD includes the Fc moiety more strongly than does γ-CD. The K_{Fc-C10} values (0.8 and 2.5 for β-CD and γ-CD, respectively) demonstrate that β-CD includes the Fc moiety more strongly than the C10 moiety whereas γ-CD prefers the C10 moiety to the Fc moiety.

The redox behavior of FcC10Fc was investigated by cyclic voltammetry (CV) in the absence and presence of 10 mM α-CD, β-CD, or γ-CD, as can be seen in Figure 6. From these voltammograms, the potentials of oxidation and reduction peaks (E_{pa} and E_{pc}, respectively) and the peak currents at oxidation and reduction (i_{pa} and i_{pc}, respectively) were determined as listed in Table 2. In the absence of CD, the cyclic voltammogram for FcC10Fc shows a single redox wave in the potential range of 0–0.7 V vs. Ag/AgCl. Separate CV experiments for FcC10Fc(PF_6^-) in acetonitrile also exhibited a single redox wave in the potential range of 0–1.0 V vs. Ag/AgCl (data not shown).[68] These observations indicate that the Fc moieties in FcC10Fc undergo the redox reaction independently presumably because of the relative longer decamethylene linker. In the presence of α-CD, β-CD, and γ-CD, the cyclic voltammograms also indicate a single redox wave in the potential range of 0–0.7 V vs. Ag/AgCl (Figures 6b, 6c, and 6d). The values of E_{pa} and E_{pc} in the presence of α-CD, β-CD, and γ-CD are larger than those in their absence, indicating that the oxidation of FcC10Fc requires a higher potential in the presence of CDs. The values of i_{pa} and i_{pc} in the presence of α-CD, β-CD, and γ-CD are smaller than those in their absence, indicating that CDs retard redox reaction on the electrode surface. In addition, the differences between E_{pa} and E_{pc} are larger than 0.057 V, which is the theoretical value in the case where redox reactions are determined by diffusion, for all the voltammograms. These observations indicate that the redox reaction of FcC10Fc is not diffusion-controlled under the present conditions. It is noteworthy that β-CD causes larger differences in the cyclic voltammogram for FcC10Fc than do α-CD and γ-CD, indicating that β-CD interacts most strongly with FcC10Fc.

Since CDs do not interact significantly with ferrocene derivatives in their oxidized state,[38,41–43] α-CD may not interact with FcC10Fc of its oxidized form, and β-CD or γ-CD may form a *pseudo*-rotaxane, in which β-CD or γ-CD includes the C10 moiety. To investigate the interaction of CDs with FcC10Fc in its oxidized state, we attempted to prepare oxidized FcC10Fc by electrochemical and chemical methods. FcC10Fc

Table 1. Equilibrium Constants for the Comlexation of CDs with FcC10Fc

CD	K_1/M^{-1}	K_2/M^{-1}	K_{Fc}/M^{-1}	K_{Fc-C10}/M^{-1}
α-CD	3×10^2	5×10^2		
β-CD			2.5×10^3	0.8
γ-CD			3.5×10^2	2.5

Table 2. Results of CV Measurements for 1 mM FcC10Fc in the Absence and Presence of 10 mM α-CD, β-CD, or γ-CD[a)]

CD	E_{pa}/V[b)]	E_{pc}/V[b)]	$i_{pa}/\mu A$	$i_{pc}/\mu A$
—	0.477	0.409	6.34	−5.38
α-CD	0.516	0.412	3.86	−2.50
β-CD	0.584	0.461	2.07	−1.13
γ-CD	0.496	0.431	5.29	−4.33

a) Measured in 0.1 M NaBr at 298 K. b) vs. Ag/AgCl.

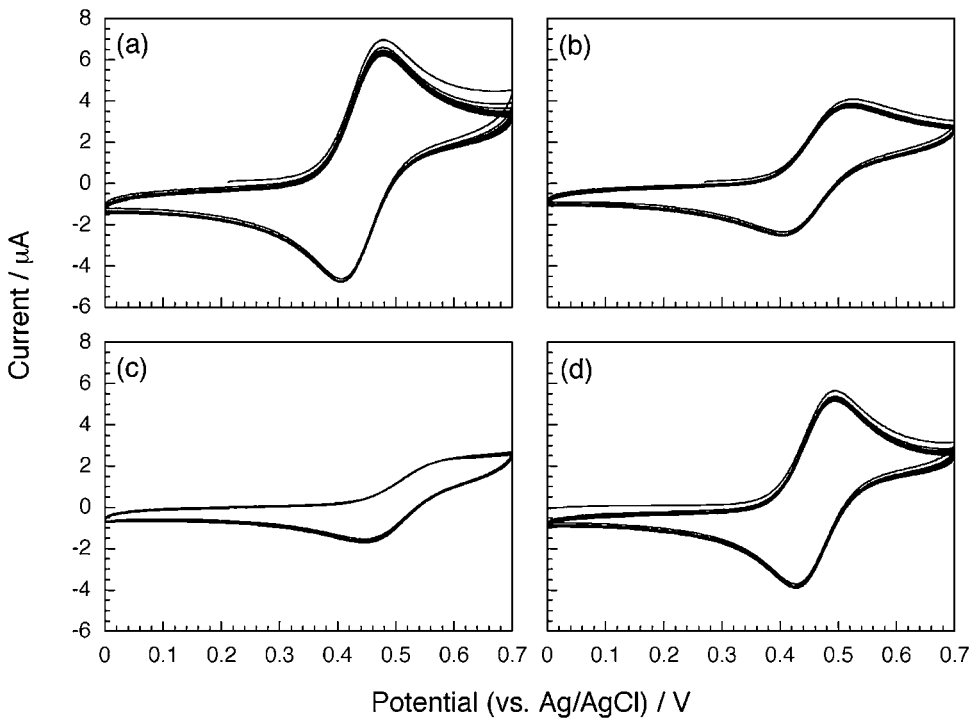

Figure 6. Cyclic voltammograms for 1.0 mM FcC10Fc in the absence (a) and presence of 10 mM α-CD (b), β-CD (c), and γ-CD (d) in 0.1 M NaBr at 298 K. Scan rate was fixed at 100 mV s^{-1}.

was oxidized at a constant potential of 0.7 V vs. Ag/AgCl using the electrochemical analyzer. Absorption spectra indicated that the intensity of the absorption band around 630 nm ascribable to the ferrocenium moiety increased with time and leveled off after 3 h, indicative of oxidation of the Fc moieties in FcC10Fc. At 7 h, however, the absorption band ascribable to the Fc in the reduced state around 440 nm still remained. These observations indicate that the complete oxidation of FcC10Fc is difficult under these conditions. FcC10Fc was also oxidized using sodium hypochlorite as an oxidant. When ca. 2 equivalents of sodium hypochlorite was added to a solution of FcC10Fc, the color of the solution immediately turned from yellow to green. After ca. 10 s, however, the reaction mixture became yellow-brown, and then brown precipitate was formed. This observation implies that FcC10Fc is not stable in its oxidized state. We observed that decomposition of FcC10Fc of the reduced form at the ammonium moiety upon heating at 60 °C. It is likely that the ammonium moiety is less stable in the oxidized state presumably because of electrostatic repulsion.

Conclusion

The complexation behavior of CDs with FcC10Fc was investigated by ^{1}H NMR, 2D ROESY, circular dichroism spectroscopy, and CV. α-CD includes the Cp rings of the Fc moiety shallowly from the wider side but not the C10 moiety because of the smaller cavity. On the other hand, β-CD and γ-CD include not only the Fc moiety but also the C10 moiety. β-CD prefers the Fc moiety to the C10 moiety whereas γ-CD prefers the C10 moiety to the Fc moiety. On the basis of these results, the construction of redox-responsive supramolecular assemblies is in progress.

Appendix

Equilibria of the Complexations of CDs with FcC10Fc α-CD/FcC10Fc System. A simplified scheme for the equilibrium of the complexation of α-CD with FcC10Fc is proposed in Scheme 2a, where **Fc** and **Fc** denote Fc moieties complexed with an α-CD molecule and with two α-CD molecules, respectively. When the first and second association constants for α-CD with Fc moiety are defined as K_1 and K_2, respectively. K_1 and K_2 are written as

$$K_1 = \frac{[\underline{\mathbf{Fc}}\mathrm{C10Fc}]}{[\mathrm{FcC10Fc}][\mathrm{CD}]} = \frac{[\underline{\mathbf{Fc}}\mathrm{C10}\underline{\mathbf{Fc}}]}{[\underline{\mathbf{Fc}}\mathrm{C10Fc}][\mathrm{CD}]} = \frac{[\underline{\underline{\mathbf{Fc}}}\mathrm{C10}\underline{\mathbf{Fc}}]}{[\underline{\underline{\mathbf{Fc}}}\mathrm{C10Fc}][\mathrm{CD}]} \quad \text{(A1)}$$

$$K_2 = \frac{[\underline{\underline{\mathbf{Fc}}}\mathrm{C10Fc}]}{[\underline{\mathbf{Fc}}\mathrm{C10Fc}][\mathrm{CD}]} = \frac{[\underline{\underline{\mathbf{Fc}}}\mathrm{C10}\underline{\mathbf{Fc}}]}{[\underline{\mathbf{Fc}}\mathrm{C10}\underline{\mathbf{Fc}}][\mathrm{CD}]} = \frac{[\underline{\underline{\mathbf{Fc}}}\mathrm{C10}\underline{\underline{\mathbf{Fc}}}]}{[\underline{\underline{\mathbf{Fc}}}\mathrm{C10}\underline{\mathbf{Fc}}][\mathrm{CD}]} \quad \text{(A2)}$$

The concentrations of all the species complexed are represented as

$$[\underline{\mathbf{Fc}}\mathrm{C10Fc}] = K_1[\mathrm{CD}][\mathrm{FcC10Fc}] - \frac{[\underline{\mathbf{Fc}}\mathrm{C10}\underline{\mathbf{Fc}}]}{K_1[\mathrm{CD}]} - \frac{[\underline{\underline{\mathbf{Fc}}}\mathrm{C10Fc}]}{K_2[\mathrm{CD}]} \quad \text{(A3)}$$

$$[\underline{\mathbf{Fc}}\mathrm{C10}\underline{\mathbf{Fc}}] = K_1[\mathrm{CD}][\underline{\mathbf{Fc}}\mathrm{C10Fc}] - \frac{[\underline{\underline{\mathbf{Fc}}}\mathrm{C10}\underline{\mathbf{Fc}}]}{K_2[\mathrm{CD}]} \quad \text{(A4)}$$

$$[\underline{\underline{\mathbf{Fc}}}\mathrm{C10Fc}] = K_2[\mathrm{CD}][\underline{\mathbf{Fc}}\mathrm{C10Fc}] - \frac{[\underline{\underline{\mathbf{Fc}}}\mathrm{C10}\underline{\mathbf{Fc}}]}{K_1[\mathrm{CD}]} \quad \text{(A5)}$$

$$[\underline{\underline{\mathbf{Fc}}}\mathrm{C10}\underline{\mathbf{Fc}}] = K_1[\mathrm{CD}][\underline{\underline{\mathbf{Fc}}}\mathrm{C10Fc}] + K_2[\underline{\mathbf{Fc}}\mathrm{C10}\underline{\mathbf{Fc}}] - \frac{[\underline{\underline{\mathbf{Fc}}}\mathrm{C10}\underline{\underline{\mathbf{Fc}}}]}{K_2[\mathrm{CD}]} \quad \text{(A6)}$$

$$[\underline{\underline{\mathbf{Fc}}}\mathrm{C10}\underline{\underline{\mathbf{Fc}}}] = K_2[\mathrm{CD}][\underline{\underline{\mathbf{Fc}}}\mathrm{C10}\underline{\mathbf{Fc}}] \quad \text{(A7)}$$

where [CD] denotes the concentration of free α-CD. From the conservation of mass,

$$[\mathrm{FcC10Fc}]_\mathrm{t} = [\mathrm{FcC10Fc}] + [\underline{\mathbf{Fc}}\mathrm{C10Fc}] + [\underline{\mathbf{Fc}}\mathrm{C10}\underline{\mathbf{Fc}}] + [\underline{\underline{\mathbf{Fc}}}\mathrm{C10Fc}] + [\underline{\underline{\mathbf{Fc}}}\mathrm{C10}\underline{\mathbf{Fc}}] + [\underline{\underline{\mathbf{Fc}}}\mathrm{C10}\underline{\underline{\mathbf{Fc}}}] \quad \text{(A8)}$$

$$[\mathrm{CD}]_\mathrm{t} = [\mathrm{CD}] + [\underline{\mathbf{Fc}}\mathrm{C10Fc}] + 2[\underline{\mathbf{Fc}}\mathrm{C10}\underline{\mathbf{Fc}}] + 2[\underline{\underline{\mathbf{Fc}}}\mathrm{C10Fc}] + 3[\underline{\underline{\mathbf{Fc}}}\mathrm{C10}\underline{\mathbf{Fc}}] + 4[\underline{\underline{\mathbf{Fc}}}\mathrm{C10}\underline{\underline{\mathbf{Fc}}}] \quad \text{(A9)}$$

Here [FcC10Fc] is the concentration of free FcC10Fc, and $[\mathrm{FcC10Fc}]_\mathrm{t}$ and $[\mathrm{CD}]_\mathrm{t}$ denote the total concentrations of FcC10Fc and α-CD, respectively. Solving eqs A3–A7 as a set of simultaneous equations,

$$[\underline{\mathbf{Fc}}\mathrm{C10Fc}] = \frac{1}{2}K_1[\mathrm{CD}][\mathrm{FcC10Fc}] \quad \text{(A10)}$$

$$[\underline{\mathbf{Fc}}\mathrm{C10}\underline{\mathbf{Fc}}] = \frac{1}{4}K_1{}^2[\mathrm{CD}]^2[\mathrm{FcC10Fc}] \quad \text{(A11)}$$

$$[\underline{\underline{\mathbf{Fc}}}\mathrm{C10Fc}] = \frac{1}{4}K_1K_2[\mathrm{CD}]^2[\mathrm{FcC10Fc}] \quad \text{(A12)}$$

$$[\underline{\underline{\mathbf{Fc}}}\mathrm{C10}\underline{\mathbf{Fc}}] = \frac{1}{4}K_1{}^2K_2[\mathrm{CD}]^3[\mathrm{FcC10Fc}] \quad \text{(A13)}$$

$$[\underline{\underline{\mathbf{Fc}}}\mathrm{C10}\underline{\underline{\mathbf{Fc}}}] = \frac{1}{4}K_1{}^2K_2{}^2[\mathrm{CD}]^4[\mathrm{FcC10Fc}] \quad \text{(A14)}$$

Substituting eqs A10–A14 into eq A8, it can be solved for [FcC10Fc] as

$$[\mathrm{FcC10Fc}] = \frac{[\mathrm{FcC10Fc}]_\mathrm{t}}{1 + \frac{1}{2}K_1[\mathrm{CD}] + \frac{1}{4}K_1{}^2[\mathrm{CD}]^2 + \frac{1}{4}K_1K_2[\mathrm{CD}]^2 + \frac{1}{4}K_1{}^2K_2[\mathrm{CD}]^3 + \frac{1}{4}K_1{}^2K_2{}^2[\mathrm{CD}]^4} \quad \text{(A15)}$$

When K_1, K_2, [CD], and $[\mathrm{FcC10Fc}]_\mathrm{t}$ are given, the concentrations of all the species can be calculated by substituting eq A15 into eqs A10–A14.

The peak shift, $\Delta\delta_\mathrm{Fc}$, can be also calculated as

$$\Delta\delta_\mathrm{Fc} = \frac{\Delta\delta_{\mathrm{Fc1,max}}\{[\underline{\mathbf{Fc}}\mathrm{C10Fc}] + 2[\underline{\mathbf{Fc}}\mathrm{C10}\underline{\mathbf{Fc}}] + [\underline{\underline{\mathbf{Fc}}}\mathrm{C10}\underline{\mathbf{Fc}}]\} + \Delta\delta_{\mathrm{Fc2,max}}\{[\underline{\mathbf{Fc}}\mathrm{C10Fc}] + [\underline{\mathbf{Fc}}\mathrm{C10}\underline{\mathbf{Fc}}] + 2[\underline{\underline{\mathbf{Fc}}}\mathrm{C10}\underline{\mathbf{Fc}}]\}}{2[\mathrm{FcC10Fc}]_\mathrm{t}} \quad \text{(A16)}$$

where $\Delta\delta_{\mathrm{Fc1,max}}$ and $\Delta\delta_{\mathrm{Fc2,max}}$ are the peak shifts for the Fc moieties complexed with an α-CD molecule and two α-CD molecules, respectively. The free CD concentration ([CD]) is necessary for these calculations, but only $[\mathrm{CD}]_\mathrm{t}$ is known in

experiments. Thus, upon the fitting procedure, $[CD]_t$ values calculated numerically with eq A9 were used.

β-CD/FcC10Fc and γ-CD/FcC10Fc Systems. A simplified scheme for the equilibrium of the complexation of β-CD or γ-CD with FcC10Fc is proposed in Scheme 2b, where **Fc** and **C10** in bold and underlined type denote Fc and C10 moieties included in the CD cavity, respectively. When the association constant for CD with Fc moiety and the equilibrium constant between **Fc** and **C10** are defined as K_{Fc} and $K_{Fc\text{–}C10}$, respectively. K_{Fc} and $K_{Fc\text{–}C10}$ are written as

$$K_{Fc} = \frac{[\underline{\mathbf{Fc}}C10Fc]}{[FcC10Fc][CD]} = \frac{[\underline{\mathbf{Fc}}C10\underline{\mathbf{Fc}}]}{[\underline{\mathbf{Fc}}C10Fc][CD]} = \frac{[Fc\underline{\mathbf{C10}}Fc]}{[Fc\underline{\mathbf{C10}}Fc][CD]} = \frac{[\underline{\mathbf{FcC10Fc}}]}{[\underline{\mathbf{FcC10}}Fc][CD]} \quad \text{(A17)}$$

$$K_{Fc\text{–}C10} = \frac{[Fc\underline{\mathbf{C10}}Fc]}{[\underline{\mathbf{Fc}}C10Fc]} = \frac{[\underline{\mathbf{FcC10}}Fc]}{[\underline{\mathbf{Fc}}C10\underline{\mathbf{Fc}}]} \quad \text{(A18)}$$

The concentrations of all the species complexed are represented as

$$[\underline{\mathbf{Fc}}C10Fc] = K_{Fc}[CD][FcC10Fc] - \frac{[\underline{\mathbf{Fc}}C10\underline{\mathbf{Fc}}]}{K_{Fc}[CD]} - \frac{[Fc\underline{\mathbf{C10}}Fc]}{K_{Fc\text{–}C10}} \quad \text{(A19)}$$

$$[Fc\underline{\mathbf{C10}}Fc] = K_{Fc\text{–}C10}[\underline{\mathbf{Fc}}C10Fc] - \frac{[\underline{\mathbf{FcC10}}Fc]}{K_{Fc}[CD]} \quad \text{(A20)}$$

$$[\underline{\mathbf{Fc}}C10\underline{\mathbf{Fc}}] = K_{Fc}[CD][\underline{\mathbf{Fc}}C10Fc] - \frac{[\underline{\mathbf{FcC10}}Fc]}{K_{Fc\text{–}C10}} \quad \text{(A21)}$$

$$[\underline{\mathbf{FcC10}}Fc] = K_{Fc}[CD][Fc\underline{\mathbf{C10}}Fc] + K_{Fc\text{–}C10}[\underline{\mathbf{Fc}}C10\underline{\mathbf{Fc}}] - \frac{[\underline{\mathbf{FcC10Fc}}]}{K_{Fc}[CD]} \quad \text{(A22)}$$

$$[\underline{\mathbf{FcC10Fc}}] = K_{Fc}[CD][\underline{\mathbf{FcC10}}Fc] \quad \text{(A23)}$$

From the conservation of mass,

$$[FcC10Fc]_t = [FcC10Fc] + [\underline{\mathbf{Fc}}C10Fc] + [Fc\underline{\mathbf{C10}}Fc] + [\underline{\mathbf{Fc}}C10\underline{\mathbf{Fc}}] + [\underline{\mathbf{FcC10}}Fc] + [\underline{\mathbf{FcC10Fc}}] \quad \text{(A24)}$$

$$[CD]_t = [CD] + [\underline{\mathbf{Fc}}C10Fc] + [Fc\underline{\mathbf{C10}}Fc] + 2[\underline{\mathbf{Fc}}C10\underline{\mathbf{Fc}}] + 2[\underline{\mathbf{FcC10}}Fc] + 3[\underline{\mathbf{FcC10Fc}}] \quad \text{(A25)}$$

Solving eqs A19–A23 as a set of simultaneous equations,

$$[\underline{\mathbf{Fc}}C10Fc] = \frac{1}{2}K_{Fc}[CD][FcC10Fc] \quad \text{(A26)}$$

$$[Fc\underline{\mathbf{C10}}Fc] = \frac{1}{4}K_{Fc}K_{Fc\text{–}C10}[CD][FcC10Fc] \quad \text{(A27)}$$

$$[\underline{\mathbf{Fc}}C10\underline{\mathbf{Fc}}] = \frac{1}{4}K_{Fc}{}^2[CD]^2[FcC10Fc] \quad \text{(A28)}$$

$$[\underline{\mathbf{FcC10}}Fc] = \frac{1}{4}K_{Fc}{}^2K_{Fc\text{–}C10}[CD]^2[FcC10Fc] \quad \text{(A29)}$$

$$[\underline{\mathbf{FcC10Fc}}] = \frac{1}{4}K_{Fc}{}^3K_{Fc\text{–}C10}[CD]^3[FcC10Fc] \quad \text{(A30)}$$

Substituting eqs A26–A30 into eq A24, it can be solved for [FcC10Fc] as

$$[FcC10Fc] = \frac{[FcC10Fc]_t}{1 + K_{Fc}[CD]\left(\frac{1}{2} + \frac{K_{Fc\text{–}C10}}{4}\right) + K_{Fc}{}^2[CD]^2\left(\frac{1}{4} + \frac{K_{Fc\text{–}C10}}{4}\right) + \frac{K_{Fc}{}^3K_{Fc\text{–}C10}[CD]^3}{4}} \quad \text{(A31)}$$

When K_{Fc}, $K_{Fc\text{–}C10}$, [CD], and $[FcC10Fc]_t$ are given, the concentrations of all the species can be calculated by substituting eq A31 into eqs A26–A30.

The peak shifts, $\Delta\delta_{Fc}$ and $\Delta\delta_{C10}$, can be also calculated as

$$\Delta\delta_{Fc} = \frac{\Delta\delta_{Fc,max}\{[\underline{\mathbf{Fc}}C10Fc] + 2[\underline{\mathbf{Fc}}C10\underline{\mathbf{Fc}}] + [\underline{\mathbf{FcC10}}Fc] + 2[\underline{\mathbf{FcC10Fc}}]\}}{2[FcC10Fc]_t} \quad \text{(A32)}$$

$$\Delta\delta_{C10} = \frac{\Delta\delta_{C10,max}\{[Fc\underline{\mathbf{C10}}Fc] + [\underline{\mathbf{FcC10}}Fc] + [\underline{\mathbf{FcC10Fc}}]\}}{[FcC10Fc]_t} \quad \text{(A33)}$$

where $\Delta\delta_{Fc,max}$ and $\Delta\delta_{C10,max}$ are the peak shifts for the complexed Fc and C10 moieties. The free CD concentration ([CD]) is necessary for these calculations, but only $[CD]_t$ is known in experiments. Thus, upon the fitting procedure, $[CD]_t$ values calculated numerically with eq A25 were used.

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References

1 D. Voet, J. G. Voet, *Biochemistry*, 3rd ed., John Wiley & Sons, Inc., New York, **2004**.

2 J. Berg, J. L. Tymoczko, L. Stryer, *Biochemistry*, 6th ed., W. H. Freeman, New York, **2007**.

3 B. Alberts, A. Johnson, J. Lewis, M. Raff, K. Roberts, P. Walter, *Molecular Biology of the Cell*, 5th ed., Garland Science, New York, **2008**.

4 *Supramolecular Polymers*, 2nd ed., ed. by A. Ciferri, CRC Press, Boca Raton, FL, **2005**.

5 T. Ishi-i, S. Shinkai, *Supermolecular Dye Chemistry* in *Topics in Current Chemistry*, ed. by F. Würthner, Springer, Berlin, **2005**, Vol. 258, pp. 119–160. doi:10.1007/b135554.

6 T. Nagasaki, S. Shinkai, *J. Inclusion Phenom. Macrocyclic Chem.* **2007**, *58*, 205.

7 J. M. J. Paulusse, R. P. Sijbesma, *Angew. Chem., Int. Ed.* **2006**, *45*, 2334.

8 H. S. Choi, N. Yui, *Prog. Polym. Sci.* **2006**, *31*, 121.

9 M. J. Serpe, S. L. Craig, *Langmuir* **2007**, *23*, 1626.

10 L. Bouteiller, *Hydrogen Bonded Polymers* in *Advances in Polymer Science*, ed. by W. Binder, Springer, Berlin, **2007**, Vol. 207, pp. 79–112. doi:10.1007/12_2006_110.

11 S. Rieth, C. Baddeley, J. D. Badjić, *Soft Matter* **2007**, *3*, 137.

12 P. Y. W. Dankers, E. W. Meijer, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 2047.

13 B. Champin, P. Mobian, J.-P. Sauvage, *Chem. Soc. Rev.*

2007, *36*, 358.
14 R. Hoogenboom, D. Fournier, U. S. Schubert, *Chem. Commun.* **2008**, 155.
15 S. Yagai, A. Kitamura, *Chem. Soc. Rev.* **2008**, *37*, 1520.
16 K. K. Cotí, M. E. Belowich, M. Liong, M. W. Ambrogio, Y. A. Lau, H. A. Khatib, J. I. Zink, N. M. Khashab, J. F. Stoddart, *Nanoscale* **2009**, *1*, 16.
17 K. C.-F. Leung, C.-P. Chak, C.-M. Lo, W.-Y. Wong, S. Xuan, C. H. K. Cheng, *Chem.—Asian J.* **2009**, *4*, 364.
18 H.-J. Schneider, R. M. Strongin, *Acc. Chem. Res.* **2009**, *42*, 1489.
19 J. D. Fox, S. J. Rowan, *Macromolecules* **2009**, *42*, 6823.
20 F. van de Manakker, T. Vermonden, C. F. van Nostrum, W. E. Hennink, *Biomacromolecules* **2009**, *10*, 3157.
21 A. O. Moughton, R. K. O'Reilly, *Macromol. Rapid Commun.* **2010**, *31*, 37.
22 C. Tsitsilianis, *Soft Matter* **2010**, *6*, 2372.
23 M. W. Ambrogio, T. A. Pecorelli, K. Patel, N. M. Khashab, A. Trabolsi, H. A. Khatib, Y. Y. Botros, J. I. Zink, J. F. Stoddart, *Org. Lett.* **2010**, *12*, 3304.
24 C. J. Bowerman, B. L. Nilsson, *J. Am. Chem. Soc.* **2010**, *132*, 9526.
25 D.-S. Guo, S. Chen, H. Qian, H.-Q. Zhang, Y. Liu, *Chem. Commun.* **2010**, *46*, 2620.
26 G. Wenz, B.-H. Han, A. Müller, *Chem. Rev.* **2006**, *106*, 782.
27 A. Hashidzume, I. Tomatsu, A. Harada, *Polymer* **2006**, *47*, 6011.
28 A. Harada, A. Hashidzume, Y. Takashima, *Supramolecular Polymers Polymeric Betains Oligomers* in *Advances in Polymer Science*, Springer, Berlin, **2006**, Vol. 201, pp. 1–43. doi:10.1007/12_056.
29 A. Harada, Y. Takashima, H. Yamaguchi, *Chem. Soc. Rev.* **2009**, *38*, 875.
30 A. Harada, A. Hashidzume, H. Yamaguchi, Y. Takashima, *Chem. Rev.* **2009**, *109*, 5974.
31 A. Harada, A. Hashidzume, *Aust. J. Chem.* **2010**, *63*, 599.
32 J. Zhou, H. Ritter, *Polym. Chem.* **2010**, *1*, 1552.
33 F. Yuen, K. C. Tam, *Soft Matter* **2010**, *6*, 4613.
34 G. Chen, M. Jiang, *Chem. Soc. Rev.* **2011**, *40*, 2254.
35 A. Harada, S. Takahashi, *J. Chem. Soc., Chem. Commun.* **1984**, 645.
36 A. Harada, S. Takahashi, *J. Inclusion Phenom. Microcyclic Chem.* **1984**, *2*, 791.
37 A. Harada, Y. Hu, S. Yamamoto, S. Takahashi, *J. Chem. Soc., Dalton Trans.* **1988**, 729.
38 T. Matsue, D. H. Evans, T. Osa, N. Kobayashi, *J. Am. Chem. Soc.* **1985**, *107*, 3411.
39 V. V. Strelets, I. A. Mamedjarova, M. N. Nefedova, N. I. Pysnograeva, V. I. Sokolov, L. Pospísil, J. Hanzlík, *J. Electroanal. Chem. Interfacial Electrochem.* **1991**, *310*, 179.
40 S. McCormack, N. R. Russell, J. F. Cassidy, *Electrochim. Acta* **1992**, *37*, 1939.
41 W. Kutner, K. Doblhofer, *J. Electroanal. Chem.* **1992**, *326*, 139.
42 I. Suzuki, Q. Chen, Y. Kashiwagi, T. Osa, A. Ueno, *Chem. Lett.* **1993**, 1719.
43 R. M. Nielson, L. A. Lyon, J. T. Hupp, *Inorg. Chem.* **1996**, *35*, 970.
44 R. Castro, I. Cuadrado, B. Alonso, C. M. Casado, M. Morán, A. E. Kaifer, *J. Am. Chem. Soc.* **1997**, *119*, 5760.
45 E. Coutouli-Argyropoulou, A. Kelaidopoulou, C. Sideris, G. Kokkinidis, *J. Electroanal. Chem.* **1999**, *477*, 130.
46 D. Osella, A. Carretta, C. Nervi, M. Ravera, R. Gobetto, *Organometallics* **2000**, *19*, 2791.
47 J. Liu, R. Castro, K. A. Abboud, A. E. Kaifer, *J. Org. Chem.* **2000**, *65*, 6973.
48 J. Liu, J. Alvarez, W. Ong, E. Román, A. E. Kaifer, *J. Am. Chem. Soc.* **2001**, *123*, 11148.
49 B. González, I. Cuadrado, B. Alonso, C. M. Casado, M. Morán, A. E. Kaifer, *Organometallics* **2002**, *21*, 3544.
50 S. Mendoza, E. Castaño, Y. Meas, L. A. Godínez, A. E. Kaifer, *Electroanalysis* **2004**, *16*, 1469.
51 F. Hapiot, S. Tilloy, E. Monflier, *Chem. Rev.* **2006**, *106*, 767.
52 J. Casas-Solvas, E. Ortiz-Salmerón, I. Fernández, L. García-Fuentes, F. Santoyo-González, A. Vargas-Berenguel, *Chem.—Eur. J.* **2009**, *15*, 8146.
53 Q. Yan, J. Yuan, Z. Cai, Y. Xin, Y. Kang, Y. Yin, *J. Am. Chem. Soc.* **2010**, *132*, 9268.
54 L. Zhu, D. Zhang, D. Qu, Q. Wang, X. Ma, H. Tian, *Chem. Commun.* **2010**, *46*, 2587.
55 I. Tomatsu, A. Hashidzume, A. Harada, *Macromol. Rapid Commun.* **2006**, *27*, 238.
56 N. M. Khashab, A. Trabolsi, Y. A. Lau, M. W. Ambrogio, D. C. Friedman, H. A. Khatib, J. I. Zink, J. F. Stoddart, *Eur. J. Org. Chem.* **2009**, 1669.
57 A. Miyawaki, P. Kuad, Y. Takashima, H. Yamaguchi, A. Harada, *J. Am. Chem. Soc.* **2008**, *130*, 17062.
58 D. R. Scott, R. S. Becker, *J. Chem. Phys.* **1961**, *35*, 516.
59 H. B. Gray, Y. S. Sohn, N. Hendrickson, *J. Am. Chem. Soc.* **1971**, *93*, 3603.
60 D. Nielson, D. Boone, H. Eyring, *J. Phys. Chem.* **1972**, *76*, 511.
61 M. Kodaka, T. Fukaya, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1154.
62 M. Kodaka, *J. Phys. Chem.* **1991**, *95*, 2110.
63 M. Kodaka, *J. Am. Chem. Soc.* **1993**, *115*, 3702.
64 K. Harata, H. Uedaira, *Bull. Chem. Soc. Jpn.* **1975**, *48*, 375.
65 M. Kodaka, *J. Phys. Chem. A* **1998**, *102*, 8101.
66 In the present study, it is very difficult to describe the precision of the equilibrium constants because there are six fitting parameters.
67 In the case of β-CD, fitting is not good at lower $[CD]_t$, indicating that the model proposed in this study is over-simplified for the complexation of β-CD with FcC10Fc.
68 Since Br^- undergoes redox reactions in the potential range of 0–1.0 V vs. Ag/AgCl, the counter anion of FcC10Fc was converted to PF_6^-, which is redox inactive in the potential range, for the CV measurements in acetonitrile.