

These acids were converted to *O*-acetyl derivatives (acetyl chloride) and then treated with thionyl chloride. The resulting acid chlorides were subjected to aminolysis with appropriate amine. Hydrolysis (sodium hydroxide-methanol) of the products gave the *N*-substituted β -hydroxycarboxamides.

β -Amino alcohols prepared by reduction of the corresponding amino acid ethyl ester,¹⁴ hydroxynitrile,¹⁵ or hydroxy ketoxime¹⁶ were acylated with benzoyl chloride. Hydrolysis (sodium hydroxide-methanol) of the *O,N*-dibenzoyl products gave *N*-benzoyl- β -amino alcohols.

Benzoin was purchased from Tokyo Kasei. 2-Hydroxy-1-phenyl-1-propanone were prepared by the procedure given in the literature.¹⁷ α -Hydroxy ketone was treated with hydroxylamine to give a diastereomeric mixture of α -hydroxy ketoximes, which were separated into two

isomers by preparative silica gel column.

α -Amino acid derivatives,¹⁸ β -hydroxy ketones,¹⁹ and 1,2-diols²⁰ were prepared according to literature procedures.

All derivatives were identified by their ¹H NMR, IR, and MS spectra. Bi- β -naphthol was kindly supplied by Dr. Takaya and Prof. Nohira.

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Electron-Transfer Reactions Associated with Host-Guest Complexation. Oxidation of Ferrocenecarboxylic Acid in the Presence of β -Cyclodextrin

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Abstract: The oxidation of ferrocenecarboxylic acid in the presence of β -cyclodextrin (β -CD) has been investigated by cyclic voltammetry in pH 9.2 aqueous solution in which the ferrocene is present as the anion, FCA⁻. Binding of FCA⁻ by β -CD is indicated by changes in the UV-vis absorption spectrum and the appearance of induced circular dichroism. The latter data also show that FCA⁻ is complexed by β -CD in a configuration with the Cp-Fe-Cp axis parallel to the axis of the β -CD cavity. In slow scan rate cyclic voltammetry, β -CD causes a decrease in the peak current and a positive shift in the peak potential for FCA⁻ oxidation. Each of these effects was quantitatively evaluated, giving a formation constant for FCA⁻- β -CD of 2200 M⁻¹ at 20 °C and $\Delta H = -2.8$ kcal/mol, $\Delta S = 5$ cal/(K·mol). No binding of the oxidized form of FCA⁻ by β -CD could be detected. Fast scan rate studies revealed that the inclusion complex is oxidized via a CE scheme in which the complex first dissociates to FCA⁻ and β -CD followed by oxidation of the free FCA⁻. Quantitative evaluation of the data gave 2.1×10^4 s⁻¹ for the dissociation rate constant, and variable temperature studies yielded an activation enthalpy for dissociation of 15 kcal/mol. Significantly, no direct oxidation of FCA⁻- β -CD at the electrode could be detected. Possible explanations are discussed, and the significance of the present results to earlier electrochemical synthetic studies with cyclodextrins is highlighted.

The cyclodextrins (CDs) are among the most important and widely studied examples of host molecules which are capable of forming inclusion complexes with a variety of guests by incorporating them within the relatively nonpolar cavity of these cyclic oligosaccharides.² The CDs have very interesting catalytic properties, and they have been used as models of hydrolytic enzymes. Previous studies have not emphasized the effect of CDs on the oxidation-reduction reactions of guest molecules, but there has been an increasing interest in their use as modifiers of organic electrode reactions.³ It has been found that CDs, either added to solution or bound to the electrode surface, can cause substantial beneficial changes in the selectivity of electroorganic synthesis.

A commonly proposed mechanism for this improved selectivity involves electron transfer to/from the electrode from/to the guest molecule in the inclusion complex forming a reactive intermediate (e.g., an anion radical) which is held within the CD cavity. The reactivity of this intermediate will differ from that of the uncomplexed intermediate leading to the change in selectivity which is observed in the presence of the CD.

Almost nothing is known about the details of electron-transfer reactions of guest molecules in the presence of hosts such as CDs so we set out to investigate a suitable model system, ferrocenecarboxylic acid (FCAH) and β -cyclodextrin (β -CD), the CD containing seven glucose units in its cyclic structure. Ferrocenes exhibit simple electrochemical behavior which is favorable to this study. Oxidation to the ferricinium ion is reversible and uncomplicated by associated chemical reactions. Addition of the carboxylic acid function gives excellent solubility in water, and other ferrocenes are known to be good guest compounds for CDs.⁴ The formation constant of the ferrocene- β -CD complex has been determined by polarography.^{4b} In the present study, the FCAH/ β -CD system in pH 9.2 aqueous buffer has been inves-

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tigated thoroughly by cyclic voltammetry and the following significant results were obtained: the formation constant for the guest-host complex was evaluated by two methods, one based on the diminution of the peak current and the other on the shift in peak potential; the oxidation of ferrocenecarboxylic acid proceeds by prior dissociation of the complex followed by electron transfer from the free ferrocene; fast cyclic voltammetry has permitted evaluation of the rate constant for dissociation of the complex; within the accessible range of potentials, no direct electron transfer from the complexed ferrocene could be detected.

Experimental Section

FCAH (Aldrich) was recrystallized from ethanol/water, and β -CD (Kodak) was used as received. The solvent was triply distilled water containing 0.20 M Na_2HPO_4 (pH 9.2). The cell design and means of temperature control were the same as used previously.⁵ The working electrode was a 0.60 cm diameter glassy carbon disk (Fluorocarbon, Anaheim, CA) mounted in a Teflon sheath and polished to a mirror finish with alumina (Buehler). The final polishing was done with 0.05 μm alumina and was followed by a thorough rinse with water in an ultrasonic cleaning bath (Branson Model B12). All potentials are reported vs. a saturated calomel reference electrode (SCE) which was at room temperature, ca. 20 $^\circ\text{C}$.

The electrochemical instrumentation, data acquisition, resistance compensation, and background correction have been described.⁵ With the electrode used in this work, the amount of solution resistance which was compensated was 16.2, 14.6, 14.4, and 11.1 Ω for 10, 20, 27, and 34 $^\circ\text{C}$, respectively. These numbers may be compared to 17.5, 13.8, 11.9, and 10.5 Ω calculated for the solution resistance between a 0.60 cm diameter disk working electrode and a distant reference electrode⁶ with resistivities of 0.20 M Na_2HPO_4 found by interpolation and extrapolation of literature values.⁷ Thus, the error in compensation of resistance should not have exceeded about $\pm 2 \Omega$ which, for example, would lead to an error of $\pm 4 \text{ mV}$ at the anodic peak in Figure 5, and still less at other points on the voltammogram.

The normal explicit finite difference digital simulation technique⁸ was used for high scan rates (50–200 V/s) where the currents were governed in part by the dissociation rate of the complex. For the simulation of slow scan rates where the complexation reaction is assumed to remain at equilibrium, the normal program requires long computation times. We have used a modified program in which the concentrations at the electrode surface as well as those in all volume elements are maintained at equilibrium. If electron transfer is reversible, it is possible to write the following set of flux equations for the reaction shown in Scheme I. (Each species is numbered as in the scheme. FCAH is ionized under the experimental conditions and is present as FCA^- .) $\theta = C_{2,0}/C_{1,0} = \exp(-((F/RT)(E - E_f^0))$; $f_{1,0} + f_{3,0} = -(f_{2,0} + f_{4,0})$; $f_{5,0} = -(f_{3,0} + f_{4,0})$; $C_{3,0} = K_1 C_{1,0} C_{5,0}$; $C_{4,0} = K_2 C_{2,0} C_{5,0}$; $f_{1,0} = 2D_1(C_{1,1} - C_{1,0})$; $f_{2,0} = 2D_2(C_{2,1} - C_{2,0})$; $f_{3,0} = 2D_3(C_{3,1} - C_{3,0})$; $f_{4,0} = 2D_4(C_{4,1} - C_{4,0})$; $f_{5,0} = 2D_5(C_{5,1} - C_{5,0})$ where $f_{i,0}$ is the surface flux of species i , D_i is its diffusion coefficient, and $C_{i,0}$ and $C_{i,1}$ are the concentrations at the electrode surface and in the first volume element, respectively. If it is assumed that $D_1 = D_2$ and $D_3 = D_4 = D_5$, the above ten equations can be combined to give the following equation of which $f_{1,0}$ is taken as the physically meaningful root. Once

$$(1 + \theta)(K_1 + K_2\theta)f_{1,0}^2 - \{2D_1K_2(1 + \theta)(\theta C_{1,1} - C_{2,1}) + 2D_1(1 + \theta)(K_1 C_{1,1} + K_2 C_{2,1}) + 2D_1(K_1 + K_2\theta)(\theta C_{1,1} - C_{2,1}) + 2D_3C_{5,1}(K_1 + K_2\theta) + 2D_1(1 + \theta)\}f_{1,0} + 2D_1(\theta C_{1,1} - C_{2,1}) \times \{2D_1K_2(\theta C_{1,1} - C_{2,1}) + 2D_1(K_1 C_{1,1} + K_2 C_{2,1}) + 2D_3C_{5,1}K_2 + 2D_1\} = 0$$

$f_{1,0}$ has been calculated, the fluxes of the other four species may be obtained by substitution into the earlier equations. Throughout this work it has been assumed that the diffusion coefficients of β -CD, FCA^- - β -CD and FCA - β -CD are equal as are those of FCA^- and FCA . The common value of the former is designated D_c and that of the latter D_f .

The circular dichroism spectrum was obtained with a JASCO CD-400X instrument with 0.20 M Na_2HPO_4 aqueous solutions at about 20 $^\circ\text{C}$.

Results

Induced Circular Dichroism and UV-vis Absorption Spectra. Evidence for complexation of ferrocenecarboxylic acid by β -CD

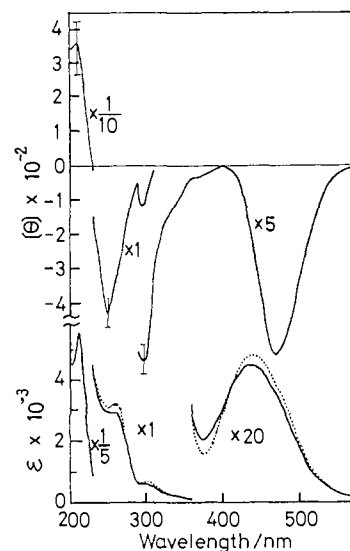
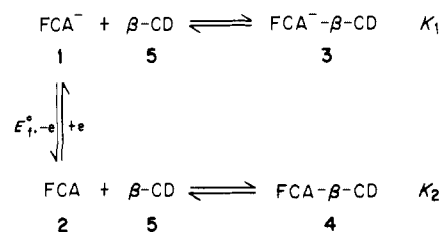


Figure 1. Induced circular dichroism (ICD) spectrum (top) and optical absorption spectrum (bottom) of FCA^- in the absence (---) and presence (—) of β -CD (2.9 mM FCA^- , 10.0 mM β -CD).

Scheme I



was found in the UV-vis absorption and induced circular dichroism (ICD) spectra (Figure 1). Small but significant changes in the absorption spectrum were observed upon addition of β -CD to a solution of FCA^- . Because β -CD is a chiral host molecule, circular dichroism will be induced in the spectral region where complexed guest molecules absorb. The observation of ICD proves that complexation occurs and can also indicate the orientation of FCA^- within the cavity of β -CD. FCA^- is roughly spherical with a protruding carboxylic acid function, and a variety of orientations are possible. Both theory⁹ and the accumulation of data¹⁰ support the conclusion that electronic transitions of a complexed aromatic molecule which are polarized parallel to the axis of the CD cavity produce a circular dichroism of positive sign and those polarized along an axis normal to the above give a negative sign. Since the d-d transitions (400–550 nm) of ferrocene are known¹¹ to be polarized along the axis parallel to the cyclopentadienyl rings, the ICD spectrum supports an orientation of FCA^- in β -CD in which the Cp-Fe-Cp axis is parallel to the central axis of the cavity. In addition to ICD,¹⁰ ^1H NMR spectroscopy has also been effectively employed to characterize CD inclusion complexes.^{3f}

Determination of Formation Constant and Diffusion Coefficients. As do other ferrocene derivatives, FCAH undergoes a reversible oxidation to the ferrocinium ion.¹² The $\text{p}K_a$ of FCAH is^{12a} 4.20

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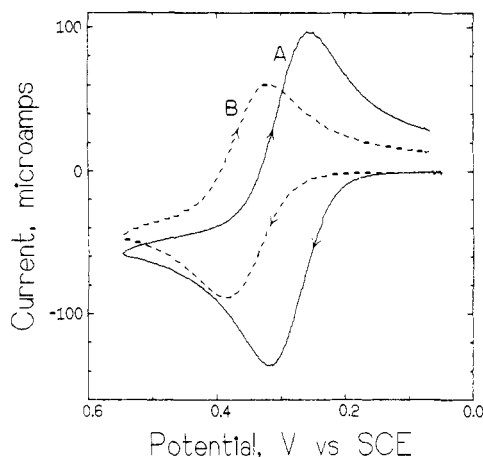


Figure 2. Cyclic voltammograms of FCA^- in the absence (—) and presence (---) of $\beta\text{-CD}$ (10.08 mM) (2.12 mM FCA^- , 0.100 V/s, 20 °C).

so it exists as the carboxylate anion, FCA^- , in our experiments which were conducted at pH 9.2. Therefore, the electrochemical oxidation proceeds from the anion to the (overall) neutral ferricinium product, FCA (Figure 2A). The ferricinium will not be protonated at the carboxylate as its $\text{p}K_a$ is^{12a} 1.35.

The effects of complexation of FCA^- by $\beta\text{-CD}$ are clearly evident in Figure 2B where 10.08 mM $\beta\text{-CD}$ has been added to the solution used in Figure 2A. The peaks retain their reversible shape but have been shifted to a more positive potential. FCA^- is more difficult to oxidize in the presence of $\beta\text{-CD}$ because it is more strongly bound than is the oxidized form, FCA .

A substantial reduction of the peak currents is also observed upon addition of $\beta\text{-CD}$ (Figure 2B). This decrease is caused by the fact that much of the FCA^- exists as the more slowly diffusing inclusion complex.¹³ The current could also be diminished if the $\beta\text{-CD}$ caused an increase in the solution viscosity with a corresponding decrease in the diffusion coefficients. However, no change in solution viscosity could be detected over the range of 0–10 mM $\beta\text{-CD}$.

The shift in the peak potential and the decrease in peak current as the concentration of $\beta\text{-CD}$ is increased can be used to evaluate the formation constant if the electrode reaction is reversible and if the formation and dissociation of the inclusion complex are fast enough to maintain equilibrium on the time scale of the experiment. The first requirement is met by the $\text{FCA}^-/\beta\text{-CD}$ system as shown by the approximately 60 mV peak separation observed both with and without $\beta\text{-CD}$ at 0.100 V/s (Figure 2). Concerning the second requirement, the formation and dissociation reactions are quite fast (see below) and application of theoretical criteria¹⁴ shows that the system remains close to equilibrium at a scan rate of 0.100 V/s. As we will see, the dissociation of the complex becomes rate limiting at rapid scan rates which affords an excellent means for evaluating the rate constants.

Determination of the formation constant for the $\text{FCA}^-/\beta\text{-CD}$ inclusion complex will be illustrated by data obtained with 3.37 mM FCA^- . Voltammograms were recorded at 0.100 V/s for a series of solutions containing 0.5 to 13 mM $\beta\text{-CD}$, and the anodic peak currents, i_p , and apparent half-wave potential, $(E_{1/2})_{\text{app}}$, were measured. The latter was taken as the mean of the anodic and cathodic peak potentials in both experiments and simulations.

The ratio of the anodic peak current to its value in the absence of $\beta\text{-CD}$, $i_p/i_{p,0}$, is plotted in Figure 3. A detectable decrease in peak current occurs even at the lowest $\beta\text{-CD}$ concentration, and it continues to decrease with increasing $\beta\text{-CD}$ concentration, slowly approaching a limiting value around 0.6. As stated earlier, the decrease is caused by incorporation of more and more of the FCA^- into the slowly diffusing inclusion complex. At concentrations of $\beta\text{-CD}$ near 0.01 M, most of the FCA^- has been bound and the

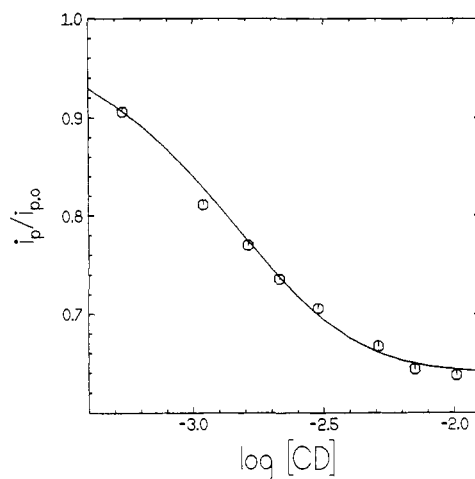


Figure 3. Ratio of anodic peak current for FCA^- oxidation in the presence of $\beta\text{-CD}$ (i_p) to anodic peak current in the absence of $\beta\text{-CD}$ ($i_{p,0}$) as a function of the total concentration of $\beta\text{-CD}$. Data: 3.37 mM $\beta\text{-CD}$, 0.100 V/s, 20 °C. Curve: theoretical based on $K_1 = 2200 \text{ M}^{-1}$, $K_2 = 0$, $D_c/D_f = 0.41$.

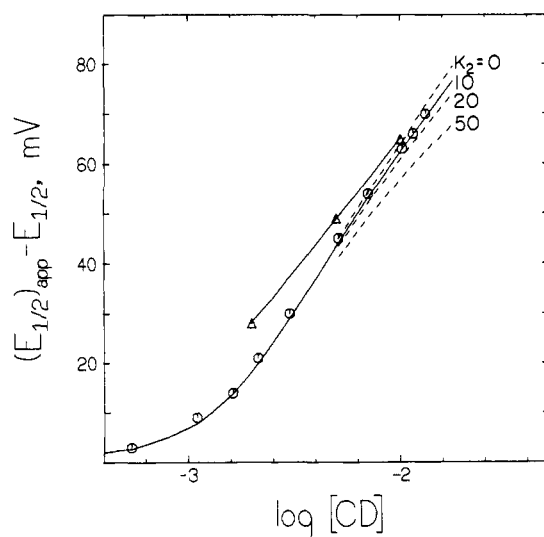
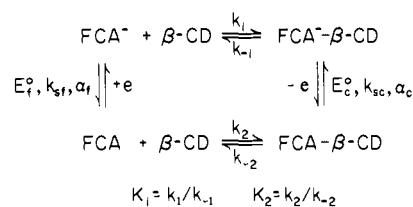


Figure 4. Half-wave potential of FCA^- in the presence of $\beta\text{-CD}$ ($(E_{1/2})_{\text{app}}$) with respect to half-wave potential in the absence of $\beta\text{-CD}$ ($E_{1/2}$) as a function of the total concentration of $\beta\text{-CD}$. Data: \circ , 3.37 mM FCA^- ; Δ , 1.21 mM FCA^- ; \square , 0.100 V/s; 20 °C. Theoretical: (—) $K_1 = 2200 \text{ M}^{-1}$, $K_2 = 10 \text{ M}^{-1}$; (---) $K_1 = 2200 \text{ M}^{-1}$, K_2 as indicated; (···) eq 1 with $K_1 = 2200 \text{ M}^{-1}$, $D_c/D_f = 0.41$.

Scheme II



peak current approaches a level governed by diffusion of the complex.

At intermediate values of the concentration of $\beta\text{-CD}$, the peak current is sensitive to the magnitude of the formation constant, K_1 (see Scheme II), as well as the ratio of diffusion coefficients of FCA^- and $\text{FCA}^- \cdot \beta\text{-CD}$, D_f and D_c , respectively. The smooth curve in Figure 3 is based on digital simulations using $K_1 = 2200 \text{ M}^{-1}$ and $D_c/D_f = 0.41$. It has been assumed that FCA is not complexed ($K_2 = 0$), a point which will be addressed later.

D_f was determined from the anodic peak currents for FCA^- obtained in the absence of $\beta\text{-CD}$ and at slow scan rates where the reaction is essentially reversible. The results were 3.7, 5.4, 6.4,

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and 8.3×10^{-6} cm²/s at 10, 20, 27, and 34 °C, respectively. The value at 20 °C, $D_f = 5.4 \times 10^{-6}$ cm²/s, and $D_c/D_f = 0.41$ found in Figure 3 give $D_c = 2.2 \times 10^{-6}$ cm²/s, in reasonable agreement with values for other CD inclusion complexes found by polarography.¹³ $D_c/D_f = 0.41$ was used throughout this work.

The relationship between $(E_{1/2})_{app}$ and the total concentration of β -CD is given in Figure 4, where it is apparent that, up to the limit of the solubility of β -CD, $(E_{1/2})_{app}$ continues to shift to more positive potentials as the β -CD concentration is increased. The half-wave potential obtained in the absence of β -CD is designated as $E_{1/2}$.

In the case where the concentration of β -CD is always much larger than the total concentration of FCA⁻, a rather simple relationship between $(E_{1/2})_{app}$ and [CD] pertains¹⁵ in the range where the inclusion complex is prevalent (eq 1). Due to the

$$(F/RT)((E_{1/2})_{app} - E_{1/2}) = \ln(1 + K_1[CD]) + \ln(D_c/D_f)^{1/2} \quad (1)$$

limited solubility of β -CD and the difficulty of making quantitative measurements by cyclic voltammetry at submillimolar concentrations of FCA⁻, it was not possible to conduct the experiments with a large excess of β -CD. Thus the digital simulation technique was essential to take into account properly the fact that a significant fraction of the β -CD was in the form of the inclusion complex and, furthermore, that this fraction is different in different parts of the diffusion layer.

In Figure 4 the smooth curve connecting the data for 3.37 mM FCA⁻ (octagons) was obtained by using $K_1 = 2200$ M⁻¹, exactly the same as that found from the peak current measurements. For comparison, the dotted curve represents eq 1 with $K_1 = 2200$ M⁻¹. The data and simulations show smaller shifts in $(E_{1/2})_{app}$ compared to eq 1, due largely to the fact that the actual concentration of free β -CD is smaller than the total concentration because some has complexed FCA⁻. Of course, if a lower concentration of FCA⁻ is used, we more closely approach the case where β -CD is always present in great excess. This expectation was confirmed for 1.21 mM FCA⁻ (triangles) where the simulation line, also based on $K_1 = 2200$ M⁻¹, falls closer to the curve given by eq 1.

Analyses of both the peak currents and values of $(E_{1/2})_{app}$ have given the same value of K_1 . So far, we have assumed that the oxidized form, FCA, is not bound by β -CD, i.e., $K_2 = 0$ (see Scheme II). If K_2 is not zero, one expects the $(E_{1/2})_{app} - E_{1/2}$ vs. $\log[CD]$ plot to rise less steeply at high concentrations of β -CD where a significant fraction of oxidized form, FCA, would be bound. At very high concentrations, a limiting value would be approached (eq 2) where the overall electrode process can be

$$(E_{1/2})_{app} - E_{1/2} = (RT/F) \ln(K_1/K_2) \quad (2)$$

described as $FCA-\beta-CD \rightleftharpoons FCA-\beta-CD + e$. Of course, the present data are far from this limiting behavior, and it is difficult to determine whether K_2 is significantly greater than zero. The fact that the points for the three highest β -CD concentrations fall below the $K_2 = 0$ curve (Figure 4) could indicate some inclusion of FCA by β -CD, but the effect is too small to provide a reliable determination of K_2 . The most that can be said is that $K_2 \lesssim 20$ M⁻¹.

Returning to the inclusion complex of FCA⁻, it should be noted that some species are known to form a ternary complex containing two cyclodextrins and one guest molecule.^{3f} Were this to occur with FCA⁻, the plot of $(E_{1/2})_{app} - E_{1/2}$ vs. $\log[CD]$ would become steeper at β -CD concentrations where significant ternary complex exists, approaching a slope twice that shown in Figure 4. The data indicate that a ternary complex does not form in the available range of β -CD concentrations.

A unit containing two β -CD and two ethyl cinnamate molecules occurs in the solid state.^{3h} However, the formation of significant amounts of $(FCA-\beta-CD)_2$ in solution is not consistent with the data in Figure 4. If $(FCA-\beta-CD)_2$ were the predominant form

Table I. Formation Constant of the FCA⁻- β -CD Inclusion Complex and Standard Potential of the FCA/FCA⁻ Couple

temp, °C	K_1 , M ⁻¹	E_f° , V vs. SCE
10	2500 ± 100	0.300
20	2200 ± 100	0.288
27	1900 ± 100	0.283
34	1700 ± 100	0.276

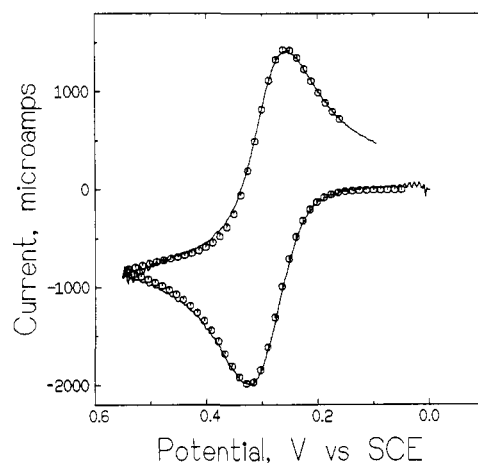


Figure 5. Cyclic voltammogram of 0.97 mM FCA⁻ at 100 V/s, 20 °C. Curve, experimental; points; digital simulation with $E_f^\circ = 0.288$ V; $k_s/D_1^{1/2} = 150$ s^{-1/2}.

of the inclusion complex, the $(E_{1/2})_{app} - E_{1/2}$ vs. $\log[CD]$ data at any given FCA⁻ concentration could be fit by ignoring $(FCA-\beta-CD)_2$ but the data at another FCA⁻ concentration would require a change in K_1 to obtain agreement. The fact that the data from two FCA⁻ concentrations were adequately described by using the same K_1 rules out $(FCA-\beta-CD)_2$ as the predominant form of the inclusion complex.

An interesting feature of the voltammograms obtained in the midrange of β -CD concentrations (1–3 mM) is that the difference between anodic and cathodic peak potentials slightly exceeded the 57-mV value expected¹⁶ for a simple reversible reaction. This was not an indication of sluggish electron-transfer kinetics. The observed peak potential separations were reproduced faithfully by the simulations which assumed reversible electron transfer. The origin must reside in the complex pattern of diffusion which exists when the solution contains significant mole fractions of rapidly diffusing FCA⁻ and slowly diffusing FCA⁻- β -CD, fractions which depend both on position in the diffusion layer and potential (i.e., time).

Data were obtained at other temperatures, and the $(E_{1/2})_{app}$ data were analyzed as above. Values of K_1 are summarized with other data in Table I. The temperature dependence of K_1 gives $\Delta H = -2.8$ kcal/mol (-12 kJ/mol) and $\Delta S = 5$ cal/(K·mol) (20 J/(K·mol)) for the binding reaction which fall in the range of reported values for other β -CD inclusion complexes.¹⁷

Characterization of the Reversibility of the FCA⁻/FCA Couple. Because the measurement of the dissociation rate of the FCA⁻- β -CD complex will require fast scan rates where electron-transfer kinetics can influence the data, we studied the oxidation of FCA⁻ in the absence of β -CD to determine the extent of reversibility of the reaction.

A voltammogram at 100 V/s is shown in Figure 5 along with the best fit digital simulation based on $k_s = 0.55$ cm/s. Care was taken to be certain that solution resistance was properly compensated (see Experimental Section), but the observed peak separation (ca. 70 mV) is so close to that expected for the reversible limit (57 mV¹⁶) that one cannot say that the difference is not due entirely to residual uncompensated resistance. Thus, 0.5 cm/s

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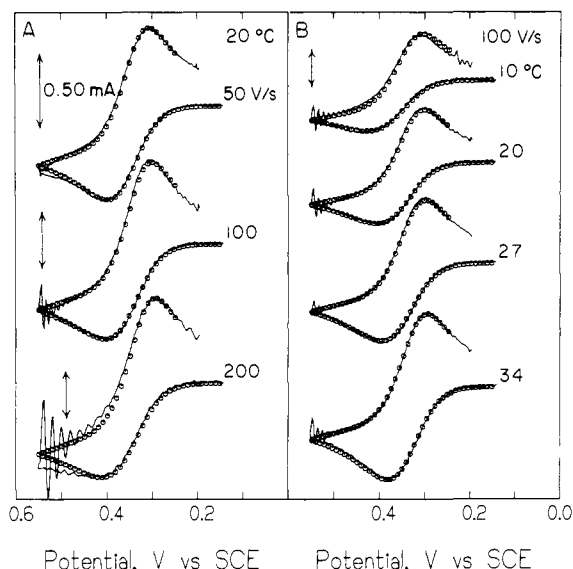


Figure 6. Fast scan rate cyclic voltammograms of 0.97 mM FCA⁻ in the presence of 10.00 mM β -CD showing the effect of the preceding dissociation reaction. Curves, experimental; points, digital simulation based on $k_{-1} = 0.9, 2.1, 4.1,$ and $8.3 \times 10^4 \text{ s}^{-1}$ for 10, 20, 27, and 34 °C, respectively. Other parameters from Table I and text ($k_s/D_f^{1/2}$).

should be regarded only as a lower limit for k_s . The reaction exhibits a high degree of reversibility which facilitates the interpretation of the kinetic results (see below).

As is often observed with solid electrodes, the apparent electron-transfer rate constant depends upon the treatment of the electrode surface.¹⁸ For glassy carbon electrodes, a common method involves polishing with alumina followed by ultrasonic rinsing.¹⁹ This procedure gave reproducible results as long as only a few cyclic voltammograms were recorded between successive polishings. Continued cycling resulted in less reversible behavior. The same phenomenon has been observed with the ferri/ferrocyanide system²⁰ where it is thought that slightly soluble species formed under the influence of the electric field cover the electrode surface. FCA has been reported^{12a} to undergo decomposition in aqueous solution so a similar phenomenon may be occurring in the present work. In any case, a high degree of reversibility was maintained by restricting data acquisition to the first few cycles after polishing the electrode. The reaction was very reversible at all temperatures used. The minimum values of $k_s/D_f^{1/2}$ for 10, 20, 27, and 34 °C were 90, 150, 180, and 240 $\text{s}^{-1/2}$, respectively.

Determination of the Dissociation Rate Constant of the FCA⁻ β -CD Complex. The slow scan rate experiments described earlier provided information of a thermodynamic nature concerning the initial and final states of the overall electrode reaction. It was determined that FCA⁻ was bound to β -CD with formation constant K_1 and that the oxidized form, FCA, was not bound in the available range of β -CD concentrations. These experiments gave no information concerning the mechanism of the reaction. At least three possibilities need to be considered: (1) electron transfer from the FCA⁻ β -CD complex to the electrode followed by dissociation to FCA and β -CD, (2) dissociation of the FCA⁻ β -CD complex followed by oxidation of FCA⁻ to FCA and, perhaps least likely, (3) concurrent electron transfer from and dissociation of FCA⁻ β -CD, giving FCA and β -CD directly.²¹

Mechanism 2 differs from 1 and 3 in a way which permits a simple experimental discrimination. In 1 and 3 the first (or only) step is an electron-transfer reaction so the observed current must approach the mass transport limited value at sufficiently positive polarizations. In mechanism 2, however, a chemical reaction precedes the electron transfer, and in sufficiently fast experiments the current can be limited partially or totally by the rate of the preceding chemical reaction.

Results obtained at fast scan rates for the oxidation of FCA⁻ in the presence of β -CD are shown in Figure 6. The qualitative shape of the voltammograms does not differ much from that seen for the oxidation of FCA⁻ in the absence of β -CD (Figure 5), but one feature points directly to mechanism 2 (a CE scheme²²), viz., the noticeable flattening of the anodic peak seen at fast scan rates (Figure 6A) or low temperatures (Figure 6B). In a CE scheme under pure kinetic control, the current on the forward scan exhibits a plateau rather than a peak.¹⁷ Quantitative examination of the data also suggests that the current is controlled in part by a preceding chemical reaction. The anodic peak currents in Figure 6A are only 47, 42, and 36% of the values obtained in the absence of β -CD for 50, 100, and 200 V/s, respectively. Of course, even if the preceding chemical reaction were not partially rate limiting, the current would be only 64% as large as in the absence of β -CD due to the smaller diffusion coefficient of the complex (cf. Figure 3). However, the observed peak currents are still lower because the chemical reaction is partially rate limiting.

A quantitative test of the validity of mechanism 2 was carried out by generating the entire voltammogram and comparing the result with experiment and, as can be seen in Figure 6, the agreement was excellent. It is fortunate that almost all of the parameters needed in the simulation had been measured in other experiments ($E_{1/2}$, K_1 , D_f , D_c , $k_s/D_f^{1/2}$) leaving only one parameter, k_{-1} , which could be adjusted. Significantly, the same value of k_{-1} ($2.1 \times 10^4 \text{ s}^{-1}$) produced excellent fits at all three scan rates in Figure 6A. Equally good fits were found at other temperatures by using only k_{-1} as an adjustable parameter (Figure 6B).

The model used to account for the results does not include oxidation of the FCA⁻ β -CD complex. The sequence of processes in the model is as follows: the inclusion complex (95% of the FCA⁻ is complexed under the conditions of Figure 6A) diffuses to the vicinity of the electrode where it dissociates with rate constant k_{-1} forming FCA⁻ which diffuses to the electrode surface and is oxidized, giving the current which is observed. In the range of potentials used, no current due to direct oxidation of FCA⁻ β -CD was detected.

There can be two reasons for this observation: either the standard potential for the FCA⁻ β -CD/FCA⁻ β -CD couple is so positive or the heterogeneous electron transfer rate constant for the reaction is so small that no significant oxidation of the complex occurs in the range of potentials studied.

At 200 V/s in Figure 6A there appears to be a small excess of current between 0.45 and 0.55 V. At this scan rate the current is much less than the diffusion-controlled level so a significant amount of complex remains near the electrode and is available for oxidation. The potential range of the fast scan voltammogram was extended to +1.0 V, but no peak for direct oxidation of the complex could be detected. Accurate correction for the background current is difficult at more positive potentials because the backgrounds obtained in separate experiments using only the supporting electrolyte are not very reproducible. This factor may account for the excess current apparently present between 0.45 and 0.55 V.

The determination of the formation constant described earlier permits a calculation of a lower limit for the standard potential for the complex, E_c° . Because $K_1 = 2200 \text{ M}^{-1}$ and K_2 cannot exceed 20 M^{-1} , E_c° must be at least 0.12 V positive of E_f° (cf. eq 2), i.e., assuming $E_f^\circ = E_{1/2} = 0.288 \text{ V}$ at 20 °C, E_c° must be more positive than +0.41 V. Unfortunately, we cannot now

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(21) Of course, dissociation and electron transfer cannot be simultaneous because electron motion is much faster than nuclear motion. What is meant here is that electron transfer could occur from the complex in a configuration where FCA⁻ was partially removed from the β -CD.

(22) In this system of classification, the sequence of steps in a reaction scheme is indicated by a sequence of letters. C indicates a chemical reaction and E a heterogeneous electron-transfer reaction.

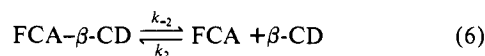
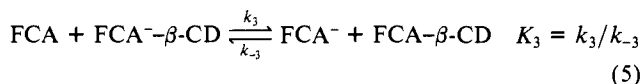
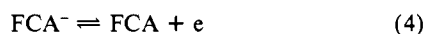
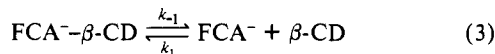
Table II. Experimental $i_p/i_{p,0}$ Values and Corresponding Values of k_{-1} ^a

concn, mM		v , V/s	10 °C		20 °C		27 °C		34 °C	
FCA ⁻	β -CD		$i_p/i_{p,0}$	k_{-1}	$i_p/i_{p,0}$	k_{-1}	$i_p/i_{p,0}$	k_{-1}	$i_p/i_{p,0}$	k_{-1}
0.97	10.00	50	0.42	1.0 ± 0.2	0.47	2.1 ± 0.6	0.50	2.7 ± 0.4		
		100	0.35	0.9 ± 0.2	0.42	2.1 ± 0.3	0.48	4.0 ± 0.7	0.53	8.7 ± 1.9
		200	0.29	0.9 ± 0.2	0.36	1.8 ± 0.2	0.42	3.3 ± 0.5	0.49	7.8 ± 1.2
1.21	10.04	50			0.46	1.8 ± 0.4				
		100			0.42	2.0 ± 0.4				
2.12	10.08	50			0.49	2.7 ± 0.7				
		100			0.43	2.1 ± 0.5				
3.36	10.08	100	0.35	0.7 ± 0.3	0.44	2.3 ± 0.6	0.49	4.1 ± 1.1	0.54	9.7 ± 2.5
		200	0.32	1.0 ± 0.3	0.39	2.2 ± 0.6	0.47	6.2 ± 1.3	0.48	5.8 ± 1.2
0.97	5.00	100			0.50	2.3 ± 0.4				
1.21	5.04	100			0.51	2.7 ± 0.5				
2.12	5.05	100			0.50	1.8 ± 0.5				
			av 0.9 ± 0.3		2.1 ± 0.5		4.1 ± 0.9		8.0 ± 1.2	

^a k_{-1} , s⁻¹ × 10⁻⁴.

say whether the failure to observe oxidation of the complex is due to unfavorable thermodynamics, kinetics, or both.

Returning to our analysis of mechanism 2, there is an additional reaction pathway which should be considered. Homogeneous electron-transfer reaction 5 could occur, giving the oxidized form of the complex, FCA- β -CD, which would rapidly dissociate by reaction 6. Reaction 5 is energetically unfavorable. Its equilibrium constant, K_3 is given by the ratio of K_2 to K_1 so it must be less than 9×10^{-3} .



The value of k_3 may be entirely negligible particularly if K_3 is significantly smaller than 9×10^{-3} . At the other extreme, the largest possible value of k_3 will arise when k_{-3} is at the diffusion-controlled limit, k_{diff} , and K_3 is equal to the maximum possible value, 9×10^{-3} . The Smoluchowski equation²³ can be used to calculate k_{diff} from D , the average value of the diffusion coefficients

$$k_{\text{diff}} = 4\pi Dd \quad (7)$$

of the reactants, and d , the average distance between the reactant centers at the time of reaction. Using $D_f = 5 \times 10^{-6}$ and $D_c = 2 \times 10^{-6}$ cm²/s and estimating d to be 10 Å (β -CD is roughly cylindrical with a radius of 8 Å and a height of 8 Å^{2a}), we obtain $k_{\text{diff}} = 2 \times 10^9$ M⁻¹ s⁻¹. In view of the cyclodextrin walls surrounding the FCA, not all collisions will be equally effective in allowing electron transfer so the above value was multiplied by about one-third to obtain the estimate $k_{\text{diff}} = 7 \times 10^8$ M⁻¹ s⁻¹. Using $K_3 = k_3/k_{-3} = k_3/k_{\text{diff}}$, we calculate the maximum value of k_3 to be about 6×10^6 M⁻¹ s⁻¹.

In order to determine the importance of reactions 5 and 6 in the reaction scheme, simulations which included these reactions were carried out and compared with those in which they had been ignored. A typical result is given in Figure 7 where the ratio of the anodic peak current in the presence of β -CD to that in its absence, $i_p/i_{p,0}$, is plotted vs. $\log(RTk_{-1}/Fv)$. Also included was the effect of k_3 of the FCA/FCA⁻ couple which was set at the lower limit estimated in this work (0.5 cm/s) and at the reversible limit. It can be seen in Figure 7 that the inclusion of reactions 5 and 6 and uncertainty in reversibility cause small but significant changes in the predicted $i_p/i_{p,0}$ for a given value of k_{-1} .

In the simulations where k_3 was taken as 6×10^6 M⁻¹ s⁻¹, k_{-2} was arbitrarily set equal to k_{-1} . The fact that k_3 was rate limiting was established by increasing k_{-2} a factor of ten which caused

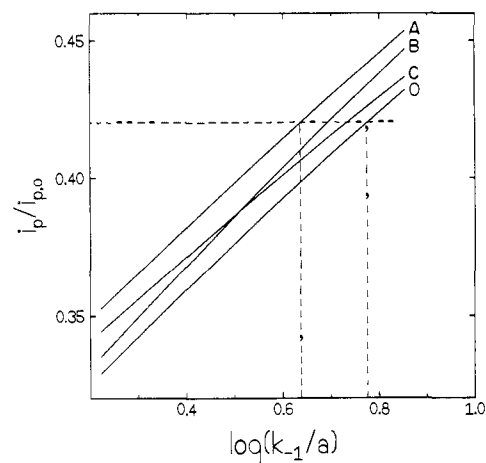


Figure 7. Theoretical values of $i_p/i_{p,0}$ as a function of k_{-1}/a ($a = Fv/RT$ where v is the scan rate) for the following conditions: 0.97 mM FCA⁻, 10.00 mM β -CD, 20 °C. (A) Reversible electron transfer, $k_3 = 6 \times 10^6$ L/(mol-s); (B) reversible electron transfer, $k_3 = 0$; (C) $k_3/D_f^{1/2} = 150$ s^{-1/2}, $k_3 = 6 \times 10^6$ L/(mol-s); (D) $k_3/D_f^{1/2} = 150$ s^{-1/2}, $k_3 = 0$. (---) Data for 50 V/s showing the range of possible k_{-1} .

a barely perceptible increase in $i_p/i_{p,0}$, <0.5%.

Experimental values of $i_p/i_{p,0}$ were obtained under a variety of conditions and are summarized in Table II. From each $i_p/i_{p,0}$ and the appropriate theoretical plot analogous to Figure 7, a range of values of k_{-1} was obtained. The process is illustrated in Figure 7 for the 20 °C, 50 V/s data obtained with 0.97 mM FCA⁻, 10.00 mM β -CD. The mean values of k_{-1} so obtained are also listed in Table II.

These values of k_{-1} are satisfactorily constant for a range of conditions including various sweep rates, FCA⁻ concentrations, and two different β -CD concentrations. Analysis of the temperature dependence of the k_{-1} data yields an activation enthalpy for dissociation of FCA⁻- β -CD of 15 kcal/mol (63 kJ/mol).

Discussion

In order to characterize the electron-transfer reactions associated with this guest-host relationship, it was first necessary to interpret two effects seen upon addition of β -CD to a solution of FCA⁻. These were the suppression of the peak current and the shift in the peak potential observed at slow scan rate where the complexation reaction could remain close to equilibrium.

The present system differs from those studied earlier¹³ because it was not practical to conduct our experiments under conditions where β -CD is present in great excess over FCA⁻ and FCA⁻- β -CD owing to the limited solubility of β -CD (ca. 15 mM at 20 °C) and the difficulty of performing quantitative cyclic voltammetry below about mM FCA⁻. Thus it was not possible to make the simplifying assumption that the concentration of β -CD remains essentially constant throughout the diffusion layer. When this assumption can be made, the effect of β -CD on both peak current and peak potential takes on a particularly simple form.

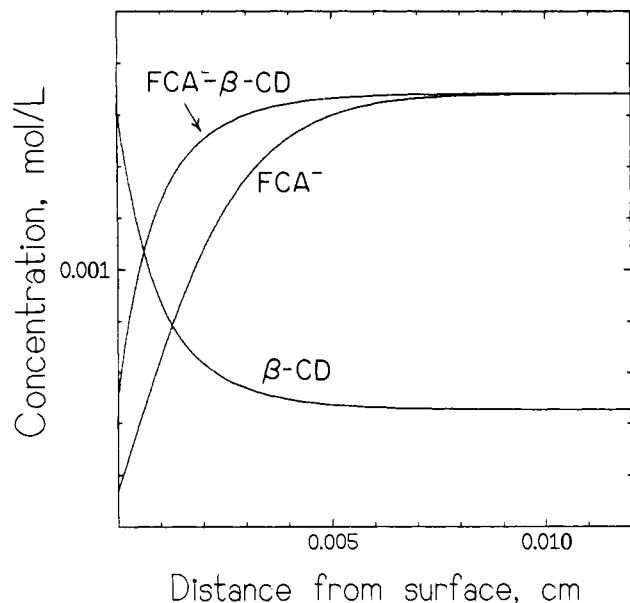


Figure 8. Concentration profiles by digital simulation. Total concentrations: 3.37 mM FCA^- , 2.14 mM $\beta\text{-CD}$; 0.100 V/s, $D_e = 1.8 \times 10^{-6}$ cm^2/s , $D_f = 4.3 \times 10^{-6}$ cm^2/s , $K_1 = 2200 \text{ M}^{-1}$. Profiles correspond to anodic peak potential, 0.344 V vs. SCE.

In contrast, the concentration of $\beta\text{-CD}$ in the present experiments varies with both time and position within the diffusion layer. The technique of digital simulation is extremely powerful for handling such complex diffusion problems as illustrated by the successful analysis of the data in Figures 3 and 4. Concentration profiles generated by digital simulation are shown in Figure 8 for the condition where exactly half of the FCA^- is complexed in the bulk of solution. The profiles were calculated at the anodic peak potential for a slow scan rate. It is clear that the concentration of $\beta\text{-CD}$ in the diffusion layer significantly exceeds its value in the bulk of solution which leads, through the complexation equilibrium, to a larger fraction of FCA^- being complexed in the diffusion layer than in the bulk. It is also interesting to note the larger effective diffusion layer thickness for the more rapidly diffusing FCA^- as compared to $\text{FCA}^- \text{-}\beta\text{-CD}$ and $\beta\text{-CD}$.

The present results provide the first information about the relative binding by a cyclodextrin of the oxidized and reduced forms of a half reaction. We have found that FCA^- has a formation constant with $\beta\text{-CD}$ which is at least 100 times that of the oxidized form, FCA. The latter, with its positive ferricinium center and negative carboxylate, will be strongly dipolar if not

zwitterionic, but it is not clear what factors are most important in preventing its complexation by $\beta\text{-CD}$. For Brønsted acid-base pairs, the anion is likewise more strongly bound than the neutral form in nitrophenols,²⁴ but the opposite holds for benzoic acid.²⁵

It has been clearly shown that oxidation of the $\text{FCA}^- \text{-}\beta\text{-CD}$ inclusion complex must proceed by prior dissociation to form free FCA^- which then transfers an electron to the electrode. While this is not a predictable result, it is entirely reasonable in view of the stabilization of FCA^- by inclusion which makes it thermodynamically more difficult to oxidize than free FCA^- . It is also likely that electron transfer from the FCA^- surrounded by the $\beta\text{-CD}$ molecule may be kinetically inhibited. Unfortunately, it is not possible with the present data to determine which of these factors is the more important.

In the light of the present results, it is of interest to examine some of the reported effects of CDs in electroorganic synthesis. Both the reduction of benzaldehyde in the presence of $\alpha\text{-CD}$ ^{3e} and the reduction of ethyl cinnamate in the presence of $\beta\text{-CD}$ ^{3f} were found to give considerably less dimeric product than when the electrolyses were conducted in the absence of the CD. The explanation offered was that dimerization of the radical intermediates was impeded by their inclusion within the CD.

In view of the rapid dissociation reactions of the CD inclusion complexes, as exemplified by $\text{FCA}^- \text{-}\beta\text{-CD}$, it seems probable that dissociation can occur prior to reduction of the substrate, giving radical anion intermediates which are not complexed. The observed suppression of dimerization reactions may arise from the somewhat lower steady-state concentration of radicals produced in the presence of CD or it may turn out that the anionic or neutral radicals are more strongly bound than the starting material causing the subsequent reactions to occur with complexed radical intermediates. If such were the case, E_c° would be positive of E_f° for the substrate/radical couple and direct reduction of the substrate-CD complex would be thermodynamically favored though, of course, there may be a significant kinetic barrier for electron transfer to the complex. A full kinetic characterization of the reduction of benzaldehyde or ethyl cinnamate in the presence of CD would be quite enlightening though the occurrence of fast and irreversible reactions of the radical intermediates will make the task difficult.

Acknowledgment. This research was supported by the National Science Foundation and by a Grant-in-Aid for Scientific Research from the Ministry of Education of Japan (No. 59350052).

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