DETERMINATION OF SOME PHYSICAL CONSTANTS OF CYCLODEXTRIN COMPLEXES BY ELECTROCHEMICAL METHODS

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Abstract. The characterization of cyclodextrin(CD) systems by electrochemical methods, mainly by cyclic voltammetry, is discussed. The addition of CD to the electrolyte solution causes a decrease in the peak current and also a shift in the apparent half-wave potential in cyclic voltammetry. Quantitative analysis in the both phenomena affords the formation constants of CD complexes. The formation or dissociation rate constants can be evaluated from the cyclic voltammetric data at high scan rates. Adsorption of CD on the electrode surface is also mentioned.

1. Introduction

Cyclodextrin(CD) is the most widely studied host compound among a variety of hosts which are capable of forming inclusion complexes. Recent studies using various types of techniques to explore the mysteries of CD have led a conclusion that in many cases a major driving force for the inclusion reaction is the hydrophobic interaction [1] between non-polar CD interior and guest molecule created on accommodation of the guest component in the cavity from polar environment outside CD. The most interesting aspect in CD chemistry is that it has an ability for recognizing guest molecules mainly by their molecular sizes[1]. The interesting character of CD has, thus, prompted many scientists to use it for artificial enzymes. CD exhibits enzyme-like abilities for many chemical reactions, e.g., ester and amide hydrolyses [2], decarboxylation[3], chlorination[4], etc. On performing CD chemistry, of extreme importance is chracterization of CD systems in order to understand quantitatively the role of CD. Much effort has been made to clarify the molecular dynamics of CD systems mainly using spectrophotometric techniques. Now we have considerably wide knowlegde on kinetic and thermodynamic properties of CD systems. However, little is known on the electrochemical behaviours of CD systems. Inclusion phenomena do influence the electrochemistry of an electroactive guest molecule. How and why does CD affect the electrochemical course of the guest compound? Can we obtain any useful information from the electro-

chemical measurements? We did not have quantitative answer for these questions. Undoubtly the measurement of electrochemical response of electroactive guest compounds is essential if CD acts as a catalyst or inhibitor for energy transfer reactions (including electron transfer). CD system may be used in the field of electronics since increasing interest is focused onto bio- or molecular-switches as a new-type elctronic material. CD is a strong potential candidate as a component of such systems. Although the investigation of electrochemical property of CD systems is extremely important not only in such case but in those where the guest compounds are electoactive, this field in CD chemistry is probably the least studied. In this review, we will describe the recent development of CD electrochemistry; mainly emphasizing how we can characterize a CD system by electrochemical methods.

Inclusion phenomena of CD systems are usually characterized by the formation constant of the complex (equilibrium constant) and the formation (or dissociation) rate constant. Among various methods proposed to determine these constants, the spectrophotometric techniques, using nmr[5], UV-vis absorption[6], circular dichroism[7], etc, are the most popular. When the guest molecule is electroactive, an electrochemical method is applicable for the purpose and sometimes this method is superior to other methods because information not only on the substrate but on the electrogenerated species formed after electron transfer reaction can concurrently be obtained by this method. The electrochemical reaction in the presence of CD is represented by a square mechanism shown in Scheme 1, where R and O are the reduced and oxidized species, respectively. If the substrate undergoes other chemical reactions, e.g., protonation, deprotonation, cleavage, etc, the electochemical mechanism becomes much more complicated. Let us consider the square mechanism without any complexed chemical reactions and the oxidized species (O) be the substrate (or starting material). The following arguments are mainly concentrated on the electrochemical response from cyclic voltammetry (CV).

$$O \ + \ CD \ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \ O\text{--}CD \qquad K_1 = \frac{k_1}{k_{-1}}$$

$$E^{\circ}_f, \ k_s \qquad ne \ \big\Updownarrow \ -ne \qquad\qquad ne \ \big\Updownarrow \ -ne \quad E^{\circ}_c$$

$$R \ + \ CD \ \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \ R\text{--}CD \qquad K_2 = \frac{k_2}{k_{-2}}$$

E°_c, E°_f; Formal potential.

Scheme 1 k_s; Standard electron transfer rate.

2. Determination of Formation Constant (Simple Case)

When the concentration of CD is much higher than that of substrate (at least 20 times higher), the formation constant of the CD complex can easily be determined by the quantitative analysis of the dependence

of peak current (CV) or diffusion current (polarography) on the concentration of CD in solution.

Fig. 1 shows typical cyclic voltammogr ams with and without large excess of CD. The shape of the voltammogram is sensitive to the heterogeneous electron transfer rate[8] between the substrate and electrode, and also to the dissociation and formation rates. If the electron transfer is reversible, i.e., the concentrations of the electroactive species at the electrode surface are determined by the Nernst equation, and if the relative contribution of the latter factor is small, the cyclic voltammogram shows a typical shape[8] with reversible electron transfer and no chemical reaction. In this case, the electrochemical response is purely controlled by the diffusion process of the substrate, CD and the complex. The peak separation in this case is 57 mV at 25°C, which is not affected by addition of CD to the electrolyte solution. This situation is usually attained by the use of slow scan rates[9] in CV. Since complexation reaction can be assumed to remain at equilibrium everywhere in the diffusion layer in the present circumstance, the apparent diffusion coefficient, D_{app}, from the voltammogram in the presence of CD is written as

$$D_{app} = xD_c + (1-x)D_f \qquad (1)$$

where D_c, D_f, and x represent the diffusion coefficient of the inclusion complex, that of the free substrate and fraction of the complex formed, respectively[9]. The value of x is correlated with the formation constant and concentration of CD;

$$K_1 = \frac{x}{C*(1-x)} \qquad (2)$$

where C* is the bulk concentration of CD. In general, the molecular sizes of guest compounds for CD are small as compared with that of CD. The diffusion coefficient is well-known to depend on the molecular size (or weight). This means that the diffusion coefficient of the complex is usually smaller than that of free substrate. Therefore, the addition of CD to the electrolyte solution causes a decrease in the peak current, since the peak current is proportional to the sqare root of the diffusion coefficient. Thus relatively simple relationship[10] can be derived from eqs (1) and (2),

$$\left(\frac{i_p}{i_{p,o}}\right)^2 = \frac{1}{K_1 C*}\left[1 - \left(\frac{i_p}{i_{p,o}}\right)^2\right] + \frac{D_c}{D_f} \qquad (3)$$

where i_p and $i_{p,o}$ are the peak currents with and without CD, respectively. This equation indicates that quantitative treatment of the dependence of the relative peak current, $(i_p/i_{p,o})$, on the concentration of CD will provide the value of formation constant and relative diffusion coefficient, D_c/D_f. In this treatment the absolute value of the diffusion coefficient of the substrate is not necessary to know for the determination. This equation is still valid in polarography (the
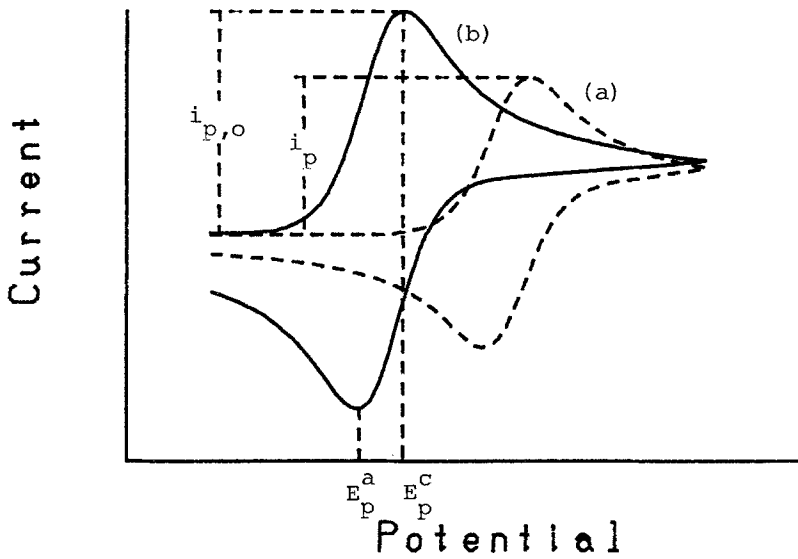
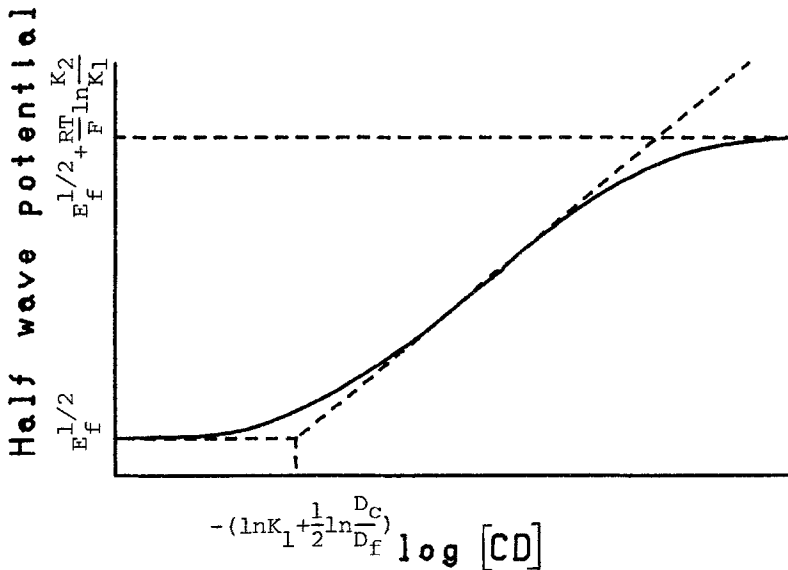Figure 1. Typical cyclic voltammograms with (a) and without (b) CD.

Figure 2. Relationship between the apparent half-wave potential and the concentration of CD.

diffusion current instead of peak current should be used). This method is applicable to any electroactive guest compound-CD systems in which the use of spectrophotometric method is difficult due to small spectral changes induced by addition of CD.

The variation of the apparent formal potential also reflects the formation constants. In contrast with the above method, the quantitative analysis of the shift in the apparent half-wave potential may give information on the complexation reaction between CD and the electro-generated species after electron transfer reaction as well as on the substrate-CD complex. The apparent formal potential of a substrate, E°_{app}, in the presence of CD in the electrolyte solution is given by eq. (4),

$$E^\circ_{app} = E^\circ_f + \frac{RT}{nF} \ln \frac{1 + K_2 C^*}{1 + K_1 C^*} \tag{4}$$

where E°_f is the formal redox potential of the substrate in the absence of CD. One may find that it is more convenient to use apparent half-wave potentials, since they can be determined directly from experimental voltammograms. Assuming that the diffusion coefficients of the substrate and electrogenerated species are equal, the following equation is derived from eq. (4) in terms of the apparent half-wave potential[11];

$$E^{1/2}_{app} = E^{1/2}_f + \frac{RT}{2nF} \ln \frac{1 + K_2 C^*}{1 + K_1 C^*} + \frac{RT}{2nF} \ln \frac{D_f + K_2 C^* D_c}{D_f + K_1 C^* D_c} \tag{5}$$

When $C^* \rightarrow \infty$

$$E^{1/2}_{app} \longrightarrow E^{1/2}_f + \frac{RT}{nF} \ln \frac{K_2}{K_1} \tag{6}$$

This situation is drawn in Fig. 2. Therefore, a detail analysis of the dependence of apparent half-wave potential on the concentration of CD would provide the formation constants of the CD complexes for the substrate.

3. Determination of Rate Constants

The determination of formation (or dissociation) rate constants by electrochemical method is somewhat complicated since the electrochemical response depends greatly on the nature of individual CD systems. Let us consider a simple case where the formal potential of the complexed species is less negative than that of free substrate (or electron transfer rate to/from the complex is very slow as compared with that of free substrate). In addition, CD exists in large excess over the substrate, for simplicity, so that all substrate is incorporated in CD before measurements. Under this circumstance, the electrochemical reaction of CD system can be reduced to a simple EC mechanism. Among various electrochemical techniques applicable to this simple system, cyclic voltammetry or chronoamperometry may be the most convenient way.

If the electrochemical reaction is totally controlled by pure kinetics, the cyclic voltammogram has no peak and the shape resembles a polarogram [12]. The kinetic current in this case is independent of the scan rates. The current observed in chronoamperometry also shows a constant value, independent of time. The kinetic current, i , observed from both techniques is exactly the same and expressed by the following equation assuming C*>>1;

$$i_k = nFAC*_o(D_f k_{-1})^{1/2}(C*K_1)^{-1/2} \qquad\qquad (7)$$

where A is the electrode area and C_o^* represents the total concentration of substrate. This means that the kinetic current is governed purely by the chemical rate of conversion of CD-O to O. Thus the dissociation rate constant of the inclusion equilibrium can be determined from this relationship.

When the electrochemical reaction is partly controlled by diffusion process, the situation becomes slightly difficult. However, the use of working curves from literature [8] makes it possible to determine these rate constants.

4. Complicated Case

The above argument is effective only when the concentration of CD in solution is much higher than the total concentration of substrate. Under this condition, the concentration of CD is essentially constant over the diffusion layer; thus the effect of CD on the peak current and peak potential takes on particularly simple forms as described above. This is sometimes impractical because of the limited solubiity of CD and the difficulty of performing quantitative electrochemical measurements. When the above simplyfing assumption is not applicable, the concentration of CD in the diffusion region varies with both time and position. The exact analytical solution for such complicated case has not been derived sofar. However, digital simulation[13] will give a theoretical electrochemical behaviour. This technique is extremely powerful for handling such a complex diffusion problem. By using digital simulation, the formation constants for ferrocenecarboxylic acid- β-CD complex has been determined to be 2200 M^{-1} at 20°C. No binding of the oxidized ferrocene by β-CD could be detected. Quantitative evaluation at high scan rates (50-200 V/s) in CV gave 2.1×10^4 s^{-1} for the dissociation rate constant[13].

5. Adsorption of CD on Electrode

Adsorption of CD is an important subject in CD electrochemistry. Since electrode reaction is essentially heterogeneous reaction with electron transfer occuring at electrode-solution interface, adsorption of organic material on electrode surface has sometimes a critical influence on the total reaction. The adsorption phenomena of CD on a mercury electrode were investigated by means of CV in a phosphate

buffer. α-CD and β-CD gave two characteristic capacitive peaks on a cyclic voltammogram which correspond to the adsorption and desorption processes of CD[15]. The treatment for Langmuir isotherm of the peak heights afforded the equilibrium constants for adsorption of CD on a mercury electrode. The value determined for β-CD was about eight times larger than that for α-CD. This might be related with the fact that β-CD is about eight times less soluble in water than α-CD, because the adsorptivity of organic compounds in aqueous system usually increases as the solubility decreases. This property could be used for the determination of samll amount of CD dissolved in water.

6. Concluding Remarks

As described above, useful information is available from electro-chemical measurements of CD systems. Since CD is a large macrocyclic compound, incorporation of small guest molecule in the bulky CD makes the apparent diffusivity of guest lower. Taking adsvantage of this phenomenon the formation constant of inclusion complex can be easily determined by quantitative treatment of the variation of peak current (CV) or diffusion current (polarography) on the CD concentration in the electrolyte solution.

The shift in apparent half-wave potential also provides the formation constants of CD complexes. It is worth noting that one may be able to evaluate concurrently the chemical property of the electro-generated species from the substrate.

The formation (or dissociation) rate of CD complexes can also be determined by using various electrochemical techniques, conveniently CV or chronoamperometry.

The unique property of CD provides many selective organic reactions. Among these reactions, CD can also be used for selective organic electrosyntheses[16]. The major advantages of electrochemical synthesis over ordinary organic reaction is easiness to control the reaction by adjusting the applied potential or current. Thus electrolysis provides a higher possibility for selective reaction which would be impossible in ordinary organic chemistry. A combination of CD and electrochemistry will give much sophisticated reaction with very high selectivity. There are many biological electron transfer systems in nature. CD is one of the strongest candidate as a component in constructing an artificial analog to mimic and understand nature. In such case the use of electrochemical technique to investigate the system is unavoidable. Undoubtly CD chemistry with electrochemical techniques will develop rapidly in near future.

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$$E^{1/2} = E° + \frac{RT}{nF} \ln \left(\frac{D_R}{D_O} \right)^{1/2}$$

In many cases, including the present case, the molecular sizes of the reduced and oxidized species are, in general, equal, resulting in

$$E^{1/2} \simeq E°$$

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