The Formation and Structure of Copper(II) Complexes with Cyclodextrins in an Alkaline Solution

Yoshihisa MATSUI, Toyoaki KURITA, Masao YAGI, Tetsuo OKAYAMA, Kazuo MOCHIDA, and Yoshio DATE

Department of Agricultural Chemistry, Shimane University, Nishikawazu, Matsue 690

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Copper(II) forms a 2: 1 complex with cyclodextrin in an alkaline solution. The complexes with α- and β-cyclodextrins were isolated from solutions by the addition of ethanol. They are labile, and, upon heating, the Cu(II) is reduced to Cu(0). The role of the hydroxide ion was examined by means of potentiometric and conductometric titrations; it was found that the reaction of 1 mol of α-cyclodextrin with 2 mol of $Cu(OH)_2$ consumes 2 mol of the hydroxide ion, whereas 3 mol of the hydroxide ion are consumed for the reaction of β-cyclodextrin. Polarimetric measurements showed that the optical rotation of cyclodextrin changes from dextrorotatory to levorotatory upon the formation of the Cu(II)–cyclodextrin complex. It was suggested, with a molecular model, that the two pairs of C_2 and C_3' secondary hydroxyl groups of contiguous glucose units are cross-linked by the $Cu(OH^-)_2Cu$ ion bridge in the α-cyclodextrin complex and by $Cu(OH^-)(O^{2-})Cu$ ion bridge in the β-cyclodextrin complex. Furthermore, the circular ring of cyclodextrin may be distorted to the ellipsoidal form by the complex formation, causing a pronounced change in the optical rotation.

Cyclodextrins are cyclic oligomers composed of six or more α-D-glucopyranose units linked 1→4 as in amylose. The molecular shape of cyclodextrin is schematically depicted as a torus.[1] One side of the torus is hemmed round by the C_2 and C_3 secondary hydroxyl groups of the glucopyranoses. Even the smallest one of the cyclodextrins, α-cyclodextrin, has 12 hydroxyl groups arranged side by side around one edge of the torus. The analogy with the structure of porphyrin, which has four amino groups in the vicinity of one another in a molecule, suggests the possibility that cyclodextrins are good ligands for metallic cations. Although the hydroxyl group has a poor ability for coordinating to metallic cations, some diol compounds can form complexes with copper(II).[2] Therefore, copper(II) was selected for the study of the formation of cyclodextrin complexes with metallic cations. Some preliminary results have previously been reported.[3]

Experimental

Materials. The α-, β-, and γ-cyclodextrins were prepared by the method of Lane and Pirt.[4] They were separated and purified according to the directions of Cramer and Henglein.[5] The $CuSO_4 \cdot 5H_2O$ was purified by recrystallization from water. The EDTA, murexide (ammonium purpurate), methyl α-D-glucopyranoside, and potassium chloride, all of a reagent grade, were used without further purification.

Methods and Procedures. *The solubilization of $Cu(OH)_2$ in an alkaline solution containing cyclodextrin*: Two aqueous solutions, 0.2 to 2.0 M NaOH and 0.02 M $CuSO_4$, of an equal volume were mixed. The precipitate of $Cu(OH)_2$ was formed immediately. The supernatant was virtually colorless. Solid cyclodextrin was then added to the mixture. The mixture was stirred well and then allowed to stand at 25 °C for about 1 hr. The supernatant thus became blue. The concentration of the dissolved Cu(II) was titrimetrically determined by the use of EDTA and murexide, as a titrant and an indicator respectively, after the neutralization of the supernatant by aqueous HCl and the addition of a few drops of 30% NH_4OH.

Isolation of Cu(II)–Cyclodextrin Complexes: To 10 ml of 0.5 M NaOH containing 0.02 M cyclodextrin, we added 15 ml of 0.04 M $CuSO_4$. The Cu(II) thus precipitated was filtered off, and 25 ml of ethanol was added to the filtrate. A blue precipitate appeared; this was then filtered off, washed with aqueous ethanol, and air-dried at room temperature. The Cu(II) content in the isolated complex was titrimetrically determined with EDTA as has been described above. The Cu(I) content was spectrophotometrically determined by the use of ammonium molybdate(VI)[6] after the complex had been dissolved in water. The Cu(0) content was determined by subtracting the Cu(II) and Cu(I) contents from the total Cu content, which was titrimetrically determined with EDTA after the complex had been oxidized by heating in concentrated HNO_3. The cyclodextrin content was determined by the measurement of the optical rotation of an aqueous solution of the complex buffered at pH *ca.* 7, where the complex dissociates into Cu(II) and cyclodextrin. In this determination, the specific rotations of the α- and β-cyclodextrins were taken to be 150.5 and 162.5 ° respectively.[7]

The potentiometric titration was carried out by the use of a Toa Electronics pH meter, Model HM-5A, with an indicator electrode for a high alkaline solution, Model HG-4005, and a reference electrode, Model HC-205. To a 50-ml beaker, we added 25 ml of 0.02 M $CuSO_4$ in 2.5 M KCl containing 0.01 M cyclodextrin or 0.02 M methyl α-D-glucopyranoside. The solution was then stirred and degassed with N_2 for 30 min. An indicator electrode and a reference electrode were immersed in the solution, to which, then, 2.28 M KOH was added, drop by drop with a syringe, at room temperature.

The polarograms of the Cu(II)–cyclodextrin complexes were measured by means of a Yanagimoto polarograph, Model P-8. The saturated calomel electrode, used as a reference electrode, was connected with the cell solution by means of a KCl-agar bridge. The cell solution was degassed and thermostated at 25 °C. The dropping mercury electrode had the following characteristics in 1 M NaOH: m=2.314 mg/s, t=3.53 s.

The polarimetric measurements were carried out at room temperature with an automatic polarimeter of the Japan Spectroscopic Co., Model DIP-SL. A Hitachi spectrophotometer, Model 124, was used for the colorimetric determination of Cu(I).

Results and Discussion

Copper(II) hydroxide is practically insoluble in aqueous NaOH. However, upon the addition of cyclodextrins, the Cu(II) ion does dissolve to form a blue solution.[3] Figure 1 shows the plots of the concentrations of the dissolved Cu(II) *vs.* those of cyclodextrins added in alkaline solutions. Each plot was linear, with a slope of about 2.0. The solubilization of $Cu(OH)_2$ in an alkaline solution also took place on the addition of methyl α-D-glucopyranoside. However, the slope of the similar plot in this case was not 2.0, but 1.0.

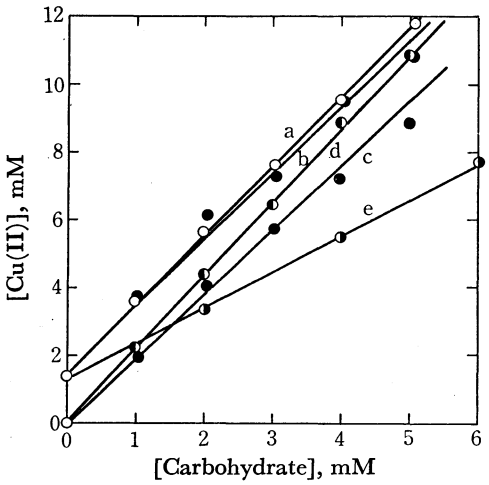

Fig. 1. Plots of the concentration of the dissolved Cu(II) *vs.* those of carbohydrates added.
a, α-cyclodextrin in 1.0 M NaOH; b, β-cyclodextrin in 1.0 M NaOH; c, β-cyclodextrin in 0.2 M NaOH; d, γ-cyclodextrin in 0.2 M NaOH; e, methyl α-D-glucopyranoside in 1.0 M NaOH.

The complexes of Cu(II) with α- and β-cyclodextrins were isolated as has been described in the Experimental section. The isolated complexes were not very stable. Thus, when the complexes were allowed to stand at room temperature for a week or were heated at 110 °C *in vacuo* for a few hours, the color of the complexes changed from blue to green. The contents of Cu(II), Cu(I), Cu(0), and cyclodextrin in the air-dried and heated samples were determined (Table 1). The results clearly show the formation of 2:1 complexes between Cu(II) and cyclodextrins. However, upon heating, the Cu(II) in the complexes is reduced in part to Cu(0). It is not yet obvious which of the substances–cyclodextrin and ethanol used as a precipitant–acts as a reductant.

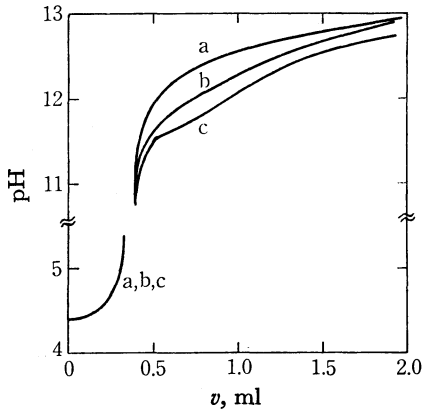

Fig. 2. Potentiometric titration of 0.02 M $CuSO_4$ in 2.5 M KCl with 2.28 M KOH in the absence (a) and in the presence of 0.01 M α- and β-cyclodextrins (b and c, respectively).

Potentiometric Titration. Cyclodextrins form complexes with Cu(II) only in an alkaline solution. In order to examine the role of the hydroxide ion, the potentiometric titration of $CuSO_4$ was carried out in the absence and in the presence of cyclodextrins, using aqueous KOH as a titrant. The ionic strength of the Cu(II) solution was kept at about 2.5 M with 2.5 M KCl. The reproducibility of the experiments was very good when an indicator electrode for high alkaline solutions was used (Fig. 2). In the absence of cyclodextrin, $Cu(OH)_2$ was precipitated by the addition of a drop of a KOH solution and did not dissolved even at a high alkaline pH. In the presence of α-cyclodextrin, on the other hand, the $Cu(OH)_2$ precipitated in the acidic pH region was re-dissolved at alkaline pH. A blue transparent solution was obtained at pH 12.4. Curves a and b in Fig. 2 are the potentiometric titration curves for $CuSO_4$ solutions in the absence and in the presence of α-cyclodextrin respectively. The pH value for the latter was always lower than that for the former at every volume of the titrant over the whole alkaline pH region. This fact suggests that the hydroxide ion is consumed in the formation of the Cu(II)–cyclodextrin complex. Curve c in Fig. 2 shows the potentiometric titration curve for a $CuSO_4$ solution containing β-cyclodextrin. The $Cu(OH)_2$ precipitated in the acidic pH region was re-dissolved at pH 12.2 to form a bluish transparent solution. The pH value at every volume of the titrant throughout the alkaline region was not only lower than that for a solution containing no

TABLE 1. THE CONTENTS OF COPPERS AND CYCLODEXTRINS IN THE ISOLATED COMPLEXES

		Content, mmol/l				mole ratio	
		Cu(0)	Cu(I)	Cu(II)	CD[a]	Cu(II)/CD	Cu[b]/CD
α-CD	air-dried	0.00	0.00	0.82	0.42	1.95	1.95
α-CD	heated to 110 °C	0.15	0.00	0.90	0.53	1.69	1.98
β-CD	air-dried	0.00	0.00	0.73	0.36	2.03	2.03
β-CD	heated to 110 °C	0.16	0.00	0.73	0.45	1.62	1.98

a) CD: Cyclodextrin. b) Cu=Cu(O)+Cu(I)+Cu(II).

cyclodextrin, but also lower than that for a solution containing α-cyclodextrin. On the other hand, the potentiometric titration curve for a $CuSO_4$ solution containing methyl α-D-glucopyranoside was virtually identical with that for a solution containing no carbohydrate. The $Cu(OH)_2$ precipitated in the acidic pH region did not completely dissolve until the pH value reached 13.1.

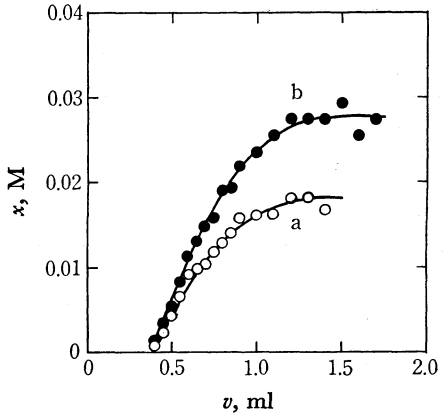

Fig. 3. Plots of the amount (x) of the hydroxide ion consumed for the formation of the complexes between 0.02 M $Cu(OH)_2$ and 0.01 M α- and β-cyclodextrins (a and b, respectively) *vs.* the volume (v) of 2.28 M KOH added.

Figure 3 shows the plots of the amount (x) of the hydroxide ion consumed for the complex formation *vs.* the volume (v) of the titrant. The x value was calculated from the difference of pH at each volume of the titrant on the assumption that the activity coefficient of the proton equals unity.[8] The x values for the reaction of 0.97 mmol of $Cu(OH)_2$ with cyclodextrin were 0.90 and 1.37 mmol for α- and β-cyclodextrins respectively. This fact suggests that, to form one mol of the Cu(II)–α-cyclodextrin and Cu(II)-β-cyclodextrin complexes, two and three mol respectively of the hydroxide ion are consumed. The reaction may be represented as follows:

$$2Cu(OH)_2 + AH_4 \rightleftarrows \underset{\mathbf{A}}{[Cu_2(AH_2^{2-})(OH^-)_2]} + 2H_2O$$

$$\mathbf{A} + OH^- \rightleftarrows \underset{\mathbf{B}}{[Cu_2(AH^{3-})(OH^-)_2]^-} + H_2O \qquad (1)$$

$$\mathbf{B} + OH^- \rightleftarrows \underset{\mathbf{C}}{[Cu_2(A^{4-})(OH^-)_2]^{2-}} + H_2O$$

$$\mathbf{C} + OH^- \rightleftarrows [Cu_2(A^{4-})(OH^-)(O^{2-})]^{3-} + H_2O$$

where AH_4 means cyclodextrin. Among these complexes, the $[Cu_2(A^{4-})(OH^-)_2]^{2-}$ complex may be the most stable one for α-cyclodextrin, whereas the $[Cu_2(A^{4-})(OH^-)(O^{2-})]^{3-}$ complex may be the most stable for β-cyclodextrin.

Conductometric Titration. The role of the hydroxide ion in the Cu(II)–cyclodextrin complex formation was also examined by means of conductometric titration. In Eq. (1), $Cu(OH)_2$ is practically insoluble and cyclodextrin is a neutral molecule, so that the contribution of these compounds to the specific conductance

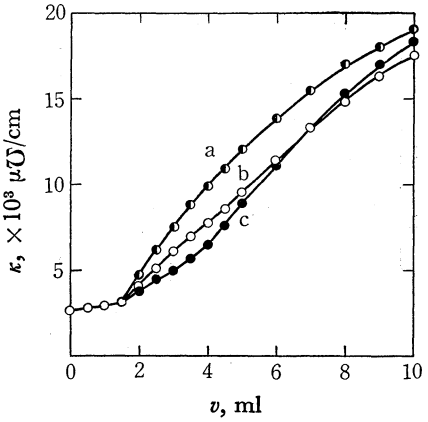

Fig. 4. Conductometric titration of 0.02 M $CuSO_4$ with 0.5 M NaOH in the absence (a) and in the presence of 0.01 M α- and β-cyclodextrins (b and c, respectively).

of a solution is negligible. Since there is no doubt that the ionic equivalent conductance of the hydroxide ion is much greater than that of the complex ion, the specific conductance of an alkaline solution would be appreciably decreased by the formation of a complex between $Cu(OH)_2$ and cyclodextrin.

When an aqueous solution of 0.5 M NaOH was added, drop by drop, to 25 ml of 0.02 M $CuSO_4$, the specific conductance (κ) of the solution changed, as is shown by Curve a of Fig. 4. No significant increase in κ was observed until *ca.* 2.0 ml of NaOH had been added. It was also observed that this process is accompanied by the precipitation of $Cu(OH)_2$ in the conductivity cell. Since the ionic equivalent conductance of Cu(II) and Na^+ (53.6 and 50.1 $cm^2℧$/equiv. respectively at 25 °C[9]) are approximately equal, a decrease in κ due to the consumption for the formation of insoluble $Cu(OH)_2$ may almost be compensated for by an increase in κ due to the addition of Na^+. The value of κ then increased with the continued addition of NaOH over 2.0 ml. A similar titration was carried out in the presence of 0.01 M α-cyclodextrin (Curve b of Fig. 4). After the addition of NaOH over 2.0 ml, the value of κ was somewhat less than that for the solution containing no cyclodextrin. This fact indicates that a part of the hydroxide ion is consumed for the formation of the Cu(II)–cyclodextrin complex. No clear inflection point was observed, although it could be said that an inflection point exists at v=*ca.* 4.0 ml. This may be due to the fact that the cyclodextrin is a weak acid and does not fully ionize even in the presence of Cu(II) until the pH of the solution becomes sufficiently high.

In order to estimate more accurately the amount of the hydroxide ion consumed, the difference ($\Delta\kappa$) in κ between the two solutions was plotted against the volume (v) of NaOH added. As is shown in Fig. 5, the value of $\Delta\kappa$ increased rapidly after the value of v exceeded 1.5 ml. Then, it reached its maximum. After that, $\Delta\kappa$ decreased almost linearly with an increase in v. The decrease in $\Delta\kappa$ may be due to an increase in the volume of the cell solution, to an increase in the ionic strength, and/or to the consumption of the hydroxide ion to form $Cu(OH)_4^{2-}$ in a strong alkaline solution

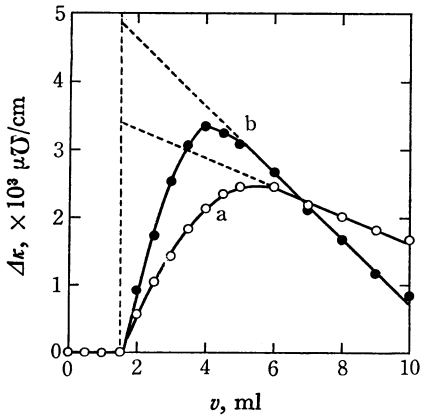

Fig. 5. Plots of $\Delta\kappa$ *vs.* the volume of 0.5 M NaOH added.
a, 0.01 M α-cyclodextrin; b, 0.01 M β-cyclodextrin.

containing no cyclodextrin. To exclude these effects on $\Delta\kappa$, the linear portion of the $\Delta\kappa$ *vs.* v plot was extrapolated to v=1.5 ml, where the solubilization of $Cu(OH)_2$ began to occur in the presence of cyclodextrin. The value of $\Delta\kappa$ thus obtained ($\Delta\kappa_0$) was 3.40×10^3 μ℧/cm. Similar results were obtained with regard to the formation of the complex between Cu(II) and β-cyclodextrin (Curve c's of Figs. 4 and 5). The $\Delta\kappa_0$ value was 4.85×10^3 μ℧/cm in this case.

If the ionic equivalent conductance of the complex ion (λ_a) is known, the amount (x) of the hydroxide ion consumed for the complex formation can be estimated by means of the following equation:

$$x = \Delta\kappa_0/(\lambda_b-\lambda_a) \qquad (2)$$

where λ_b is the ionic equivalent conductance of the hydroxide ion (198.3 cm²℧/equiv. at 25 °C[9]). This was done by means of polarography. Figure 6 shows the

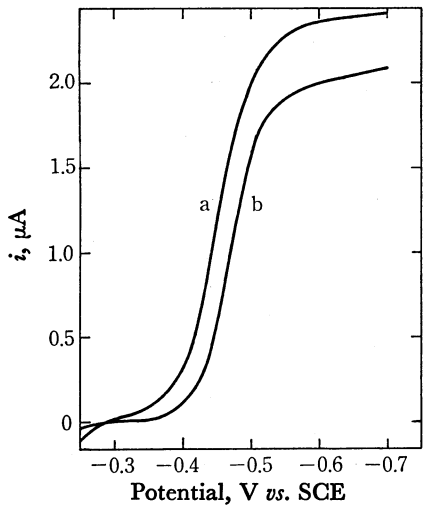

Fig. 6. Polarograms of the Cu(II) complexes with α- and β-cyclodextrins (a and b, respectively) in 1 M NaOH.
[Cu(II)], 0.466 mM; [Cyclodextrin], 20.0 mM

polarograms of the Cu(II)-cyclodextrin complexes in 1 M NaOH. The limiting current for each wave was proportional to the square root of the effective pressure on the mercury drop; this fact indicates that each wave is diffusion-controlled. The diffusion constants of the Cu(II)-α- and β-cyclodextrin complexes were evaluated to be 3.13×10^{-6} and 2.32×10^{-6} cm²/s respectively on the basis of the Ilkovic equation.[10] The diffusion constant (D) is related to the ionic equivalent conductivity (λ) by the Nernst equation:[11]

$$D = \lambda RT/ZF^2 \qquad (3)$$

where R is the gas constant; T, the temperature; Z, the ionic valence, and F, the Coulomb constant. To calculate the value of λ_a, the value of Z was assumed to be 2 for the α-cyclodextrin complex and 3 for the β-cyclodextrin complex on the basis of Eq. (1). The λ_a values thus obtained were 23.4 and 26.0 cm²℧/equiv. for the α- and β-cyclodextrin complexes respectively. Accordingly, the x values were determined to be 0.019 and 0.028 M for the α- and β-cyclodextrin complexes respectively; that is, about 2 mol of the hydroxide ion was consumed for the reaction of one mole of α-cyclodextrin with 2 mol of $Cu(OH)_2$, whereas 3 mol of the hydroxide ion were consumed for the same reaction of β-cyclodextrin. These results agree with those of the potentiometric titration.

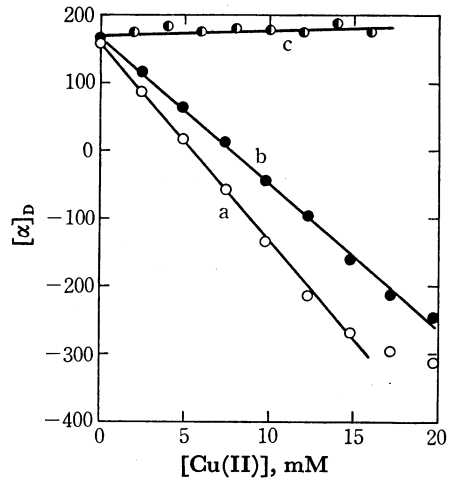

Fig. 7. Plots of the specific rotations of α- and β-cyclodextrins (a and b, respectively) and methyl α-D-glucopyranoside (c) *vs.* the concentration of Cu(II) in 1 M NaOH.

Optical Rotation of Cu(II)–Cyclodextrin Complexes. The specific rotation of cyclodextrin was drastically changed by the formation of the Cu(II) complex. Cyclodextrins themselves are dextrorotatory. The specific rotations of α- and β-cyclodextrins in 1 M NaOH are virtually the same as those in distilled water. However, upon the addition of Cu(II) in an alkaline solution of each cyclodextrin, the specific rotation ($[\alpha]_D$) of the cyclodextrin became levorotatory. Figure 7 shows the plots of $[\alpha]_D$ *vs.* the concentration of Cu(II) added to a solution of 10.3 mM cyclodextrin in 1 M NaOH. The $[\alpha]_D$ value for each cyclodextrin decreased linearly with an increase in the concentration of Cu(II). The slope of the plot for α-cyclodextrin is larger than that for β-cyclodextrin. On the other hand, the specific rotation of methyl α-D-glucopyranoside in an alkaline solution showed virtually no change upon the addition of Cu(II) to form the complex between Cu(II) and

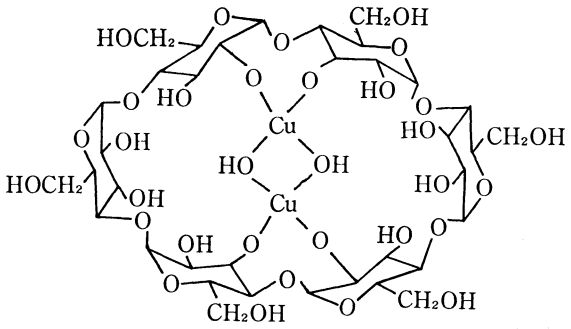

Fig. 8. The suggested structure of the Cu(II)–α-cyclodextrin complex.

methyl α-D-glucopyranoside. These results indicate that the conformation of cyclodextrin remarkably changes upon the formation of the Cu(II) complex and that the conformation change occurs in the whole cyclodextrin ring rather than in the glucopyranose-unit ring alone.

The structure of the complexes was studied with framework molecular models. It was presumed that two Cu(II) ions are bond by two hydroxide ions in the complex of $Cu_2(A^{4-})(OH^-)_2^{2-}$ for α-cyclodextrin.[3] The models showed that the secondary hydroxyl groups in α-cyclodextrin coordinate to the $Cu(OH^-)_2Cu$ residue, as is shown in Fig. 8; that is the C_2 and C_3' hydroxyl groups of contiguous glucopyranose units coordinate to the Cu(II) ions. It was impossible for the $Cu(OH^-)_2Cu$ residue to be bound to another combination of the hydroxyl groups, such as two pairs of the hydroxyl groups at C_2 and C_3, in the same glucopyranose unit. Furthermore, it was revealed that the distance between the two pairs of the C_2 and C_3' hydroxyl groups (*ca.* 10 Å) was considerably longer than that of the $Cu(OH^-)_2Cu$ ion bridge (*ca.* 6 Å). Accordingly, if the $Cu(OH^-)_2Cu$ residue was connected to the secondary hydroxyl groups of the cyclodextrin, the overall ring was significantly distorted from circular to ellipsoidal, as is depicted in Fig. 8. This fact may be related to the great change in the optical rotation of the cyclodextrin with the formation of the Cu(II) complex.

In the Cu(II)-β-cyclodextrin complex, the degree of the distortion of the overall ring may be somewhat smaller than that in the Cu(II)–α-cyclodextrin complex, for β-cyclodextrin is larger and more flexible than the α-cyclodextrin ring. This may be the reason why the

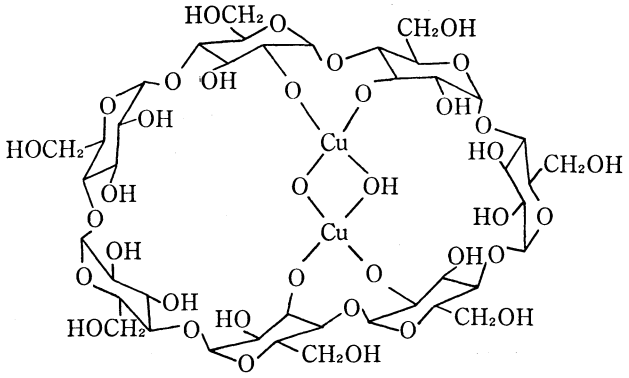

Fig. 9. The suggested structure of the Cu(II)–β-cyclodextrin complex.

slope of $[\alpha]_D$ *vs.* the concentration of Cu(II) for β-cyclodextrin is smaller than that for α-cyclodextrin (Fig. 7). The structure of the Cu(II)–β-cyclodextrin complex was presumed to be as is depicted in Fig. 9.

The spectrophotometrical and the detailed polarographical behavior of the Cu(II)–cyclodextrin complexes will be reported in subsequent articles.

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References

1) For recent reviews, see D. W. Griffiths and M. L. Bender, *Advan. Catal.*, **23**, 209 (1973); T. Kuge and K. Takeo, *Denpun Kagaku*, **21**, 151 (1974).
2) R. E. Reeves and P. Bragg, *J. Amer. Chem. Soc.*, **84**, 2491 (1962).
3) Y. Matsui, T. Kurita, and Y. Date, This Bulletin, **45**, 3299 (1972).
4) A. G. Lane and S. J. Pirt, *J. Appl. Chem. Biotechnol.*, **21**, 330 (1971).
5) F. Cramer and F. M. Henglein, *Chem. Ber.*, **91**, 308 (1958).
6) N. Nelson, *J. Biol. Chem.*, **153**, 375 (1944).
7) D. French, *Advan. Carbohyd. Chem.*, **12**, 189 (1957).
8) The activity coefficient of HCl was reported to be 1.147 at the molality of 2.5 (Ref. 9, p. 491); this value indicates that the assumption is approximately valid.
9) R. A. Robinson and R. H. Stokes, "Electrolyte Solutions," Butterworth, London (1965), p. 463.
10) D. Ilkovic, *Collect. Czech. Chem. Commun.*, **6**, 498 (1934).
11) W. Nernst, *Z. Physik. Chem. (Leipzig)*, **2**, 613 (1888).