The Stereoselective Retardation of the Alkaline Hydrolysis of Organic Esters by Binuclear Cu(II) Complexes with Cyclodextrins

Yoshihisa MATSUI* and Daisuke SUEMITSU
Department of Agricultural Chemistry, Shimane University, Nishikawatsu, Matsue 690
(Received November 21, 1984)

The alkaline hydrolysis of *p*-nitrophenyl acetate (*p*-NPA) in 1.0 mol dm^{-3} NaOH at 25 °C was almost completely retarded by the addition of a binuclear Cu(II) complex with α-cyclodextrin (Cu_2α-CD). The dissociation constant for an inclusion complex of Cu_2α-CD with *p*-NPA was determined to be 0.059 mmol dm^{-3}, which is about one 200th that for an inclusion complex of α-CD with *p*-NPA. The alkaline hydrolysis of *o*- and *m*-nitrophenyl acetates was also retarded by Cu_2α-CD, though the extent of retardation was much less than that for *p*-NPA. A binuclear Cu(II) complex with β-cyclodextrin (Cu_2β-CD) also caused a stereoselective deceleration of the alkaline hydrolysis of the esters. However, the stereoselectivity of Cu_2 β-CD was not so remarkable as that of Cu_2α-CD. Dissociation constants for inclusion complexes of Cu_2α-CD with several alcohols and other organic substrates were determined by the kinetic examination of the competitive inhibition effect of the substrates on the association of Cu_2α-CD with *p*-NPA. Cu_2α-CD formed stable inclusion complexes with such disk-like molecules as cyclohexanol, cycloheptanol, and *p*-nitrobenzyl alcohol. The geometry of a Cu_2α-CD-*p*-NPA inclusion complex was presumed on the basis of these results.

Copper(II) forms a binuclear complex (Cu_2CD) with cyclodextrin (CD) in an alkaline solution.[1] Although the structure of the complex has not been fully elucidated, it has been suggested that the two pairs of C2 and C3′ secondary hydroxyl groups of contiguous glucose units of CD are cross-linked by the $Cu(OH^-)_2$-Cu or $Cu(OH^-)(O^{2-})$Cu ion bridge (Fig. 1).[2]

The present work was undertaken to examine the binding and catalytic actions of this complex on organic substrates. The complex holds the CD cavity within which an organic molecule is included. The Cu(II) ions or the alkoxide ions of the complex may catalyze some reaction of an included molecule. Thus, it could be anticipated that the complex becomes a good model of metalloenzymes. The alkaline hydrolysis of nitrophenyl acetates (NPA) and the related esters was chosen as a test reaction in the present work, since the reaction has widely been used to examine the catalytic effects of CD itself[3-7] and modified CD's.[8-15] The catalytic property of the Cu_2CD complex has been reported only on the alkaline hydrolysis of a few organic phosphates[16] and monothiophosphates.[17]

Experimental

Materials. The α- and β-CD's commercially available were purified according to the directions of Cramer and Henglein.[18] Methyl α-D-glucopyranoside(MGP) of a reagent grade was used without further purification. $CuSO_4 \cdot 5H_2O$ of a reagent grade was recrystallized from water. The acetates (*o*-, *m*-, and *p*-NPA and 4-NNA) of *o*-, *m*-, and *p*-nitrophenols and 4-nitro-1-naphthol (*o*-, *m*-, and *p*-NP and 4-NN) were prepared by the reactions of the phenols and naphthol with acetic anhydride in pyridine at room temperature. The 4-NN (mp 164—166°, lit,[19] mp 164°) was prepared by the method of Hodgson and Kilner.[20] *p*-Nitrophenyl propionate (*p*-NPP) was prepared by the reaction of *p*-NP with propionyl chloride in pyridine. Mp 61—62 °C. Alcohols such as 1-butanol, 1-pentanol, 2-methyl-2-propanol, 2,2-dimethyl-1-propanol, cyclohexanol, cycloheptanol, benzyl alcohol, and *p*-nitrobenzyl alcohol were commercially available and were used without further purification. *p*-Nitrobenzoic acid and methyl acetate commercially available were also used without further purification.

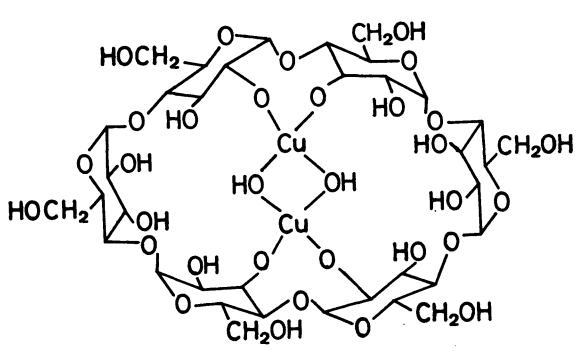


Fig. 1. A suggested structure of a Cu_2α-CD complex.

Kinetics. The rates of the alkaline hydrolyses of the esters were measured by following the appearance of the absorptions of the corresponding phenolate and naphtholate anions with an Union Giken stopped-flow reaction analyzer, Model RA-1100. A typical run is as follows. An alkaline CD solution was mixed with an aqueous $CuSO_4$ solution in such a way that the molar quantity of Cu in a resulting mixture was twice that of CD. The mixture was turbid and was shaken till it became clear, giving a Cu_2CD solution. The solution was rapidly mixed with an equal volume of an aqueous solution containing an organic ester at 25 °C. The initial concentration of the ester in a reaction mixture and the wavelength at which the hydrolysis was followed are listed in Table 1. The change of absorbance with

Table 1. Initial concentration of ester and wavelength at which the hydrolysis was followed

Ester	[Ester] / mmol dm^{-3}	Wavelength / nm
o-NPA	0.12	410
m-NPA	0.20	400
p-NPA	0.030	410
p-NPP	0.031	410
4-NNA	0.020	457

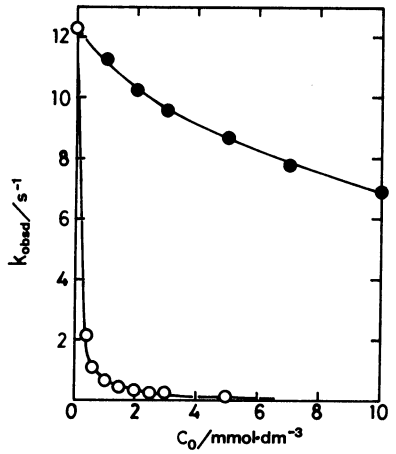


Fig. 2. Plots of k_{obsd} *vs.* c_0 for a Cu_2CD–*p*-NPA system in 1.0 mol dm^{-3} NaOH at 25 °C.
○: $Cu_2\alpha$-CD, ●: $Cu_2\beta$-CD.

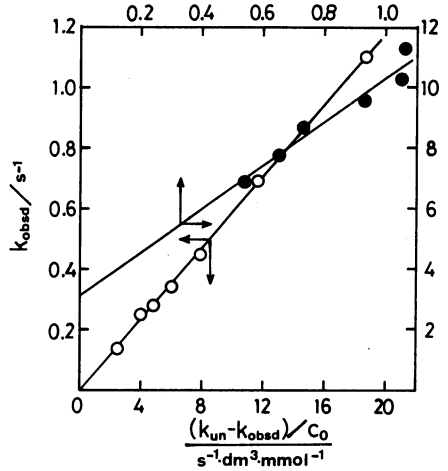


Fig. 3. Plots of k_{obsd} *vs.* $(k_{un}-k_{obsd})/c_0$ for a Cu_2CD–*p*-NPA system.
○: $Cu_2\alpha$-CD, ●: $Cu_2\beta$-CD.

time was treated according to the ordinary pseudo-first-order rate equation. The rate constants were calculated by the least-squares curve-fitting method with a microcomputer. All the reactions examined obeyed good first-order kinetics with regard to substrates irrespective of the absence or the presence of Cu_2CD in solution.

Determination of the Dissociation Constants and Rate Constants of Cu_2CD–Ester Complexes. As is illustrated in Fig. 2 for an example, the observed first-order rate constant (k_{obsd}) for each substrate approached a minimum value as the Cu_2CD concentration (c_0) increased. This saturation behavior suggests that the rate process involves the prior formation of an inclusion complex of Cu_2CD with a substrate. Upon the assumption of the formation of a 1:1 Cu_2CD–substrate complex, k_{obsd} is represented by the following equation if c_0 is much higher than the concentration of a substrate:[3]

$$k_{obsd} = \frac{K_d(k_{un}-k_{obsd})}{c_0} + k_c. \quad (1)$$

In this equation, K_d is the dissociation constant of an inclusion complex, and k_{un} and k_c, the rate constants for free and complexed substrates, respectively. The plot of k_{obsd} *vs.* $(k_{un}-k_{obsd})/c_0$ was virtually linear for each Cu_2CD–substrate system as is shown in Fig. 3. The values of K_d and k_c were calculated from the slope and intercept, respectively, of the straight line obtained by the use of the least-squares method.

Kinetic Determination of Dissociation Constants for Inclusion Complexes of $Cu_2\alpha$-CD with Alcohols and Other Organic Substrates. Dissociation constants (K_i) for inclusion complexes of $Cu_2\alpha$-CD with several alcohols and other organic substrates were determined by the kinetic examination of the competitive inhibition effect of the substrates on the association of $Cu_2\alpha$-CD with *p*-NPA in 1.0 mol dm^{-3} NaOH at 25 °C. An aqueous solution containing 0.06 mmol dm^{-3} *p*-NPA and varying amounts of an organic substrate was rapidly mixed with an equal volume of 2.0 mol dm^{-3} NaOH solution containing 3.0—5.0 mmol dm^{-3} $Cu_2\alpha$-CD at 25 °C. The k_{obsd} value for the alkaline hydrolysis of *p*-NPA in the presence of $Cu_2\alpha$-CD increased with increasing concentration (c_i) of the organic substrate. Relationships between k_{obsd} and c_i were analyzed by an equation derived by VanEtten, *et al.*:[3]

$$c_i = \frac{c_0 \cdot K_i}{K_d} \times \frac{k_{obsd}-k_c}{k_{un}-k_{obsd}} - K_i \quad (2)$$

Polarimetric Determination of Dissociation Constants for the Inclusion Complexes of CD or Cu_2CD with the p-*Nitrophenolate Ion.* The dissociation constant for the inclusion complex of CD or Cu_2CD with the *p*-NP anion was determined by a polarimetric examination of the effect of *p*-NP on the optical rotation of a CD or Cu_2CD solution at 25 °C. A Union Giken Model PM-101 polarimeter was used for the measurement. The optical rotation of the solution at λ=589 nm increased with the addition of *p*-NP. The K_d value was estimated using an ordinary Hildebrand-Benesi plot.

Results and Discussion

The effect of CD itself on the hydrolysis rates of *m*- and *p*-NPA had been examined in aqueous solutions (pH 10.0—10.6).[3] The present investigation was carried out in 1.0 mol dm^{-3} NaOH, since Cu(II) forms a stable 2:1 complex with CD in such a concentrated alkaline solution.[2] Table 2 shows the effects of CD and its Cu(II) complex on the hydrolysis rate of *p*-NPA at 25 °C. Although the hydrolysis was only slightly decelerated by the addition of α- or β-CD, the addition of $Cu_2\alpha$-CD or $Cu_2\beta$-CD markedly retarded the reaction. Among them, $Cu_2\alpha$-CD depressed the hydrolysis rate below one tenth the original rate. On the other hand, the

Table 2. Effects of CD and its Cu(II) complex on the hydrolysis rate of *p*-NPA in 1.0 mol dm^{-3} NaOH at 25 °C

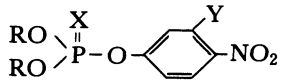
CD	[CD] / mmol dm^{-3}	[Cu] / mmol dm^{-3}	k_{obsd}/s^{-1}
None	0.00	0.00	12.3±0.1
α-CD	5.00	0.00	11.2±0.1
α-CD	5.00	10.00	0.12±0.01
β-CD	5.00	0.00	12.2±0.4
β-CD	5.00	10.00	8.7±0.2
MGP[a]	5.00	2.50	12.8±0.1

a) MGP: Methyl α-D-glucopyranoside.

TABLE 3. K_d AND k_c VALUES FOR Cu_2CD-ORGANIC ESTER SYSTEMS IN 1.0 mol dm^{-3} NaOH AT 25 °C (1mM=1 mmol dm^{-3})

Ester		$Cu_2\alpha$-CD			$Cu_2\beta$-CD		
	k_{un}/s^{-1}	k_c/s^{-1}	k_c/k_{un}	K_d/mM	k_c/s^{-1}	k_c/k_{un}	K_d/mM
o-NPA	10.5	2.8	0.27	12	2.0	0.19	4
m-NPA	8.5	5.5	0.65	6	2.9	0.34	2
p-NPA	12.3	0.00	0.000	0.059	3.1	0.25	7
p-NPP	11.9	0.00	0.000	0.028	—	—	—
4-NNA	12.7	11.2	0.88	3	8.4	0.66	3
1a[a]	42.0[b]	5.8[b]	0.14	7	0.0[b]	0.00	9
1b[a]	11.0[b]	1.5[b]	0.14	17	0.0[b]	0.00	4
1c[a]	26.7[b]	17.2[b]	0.64	9	0.0[b]	0.00	18
2a[a]	3.68[b]	0.68[b]	0.19	2.7	0.07[b]	0.02	1.3
2b[a]	0.65[b]	0.27[b]	0.41	5.1	0.10[b]	0.15	2.4
2c[a]	2.23[b]	2.7[b]	1.2	0.9	0.25[b]	0.11	0.54

a)



1a: R=Me, X=O, Y=H (Ref. 16)
1b: R=Et, X=O, Y=H (Ref. 16)
1c: R=Me, X=O, Y=Me (Ref. 16)
2a: R=Me, X=S, Y=H (Ref. 17)
2b: R=Et, X=S, Y=H (Ref. 17)
2c: R=Me, X=S, Y=Me (Ref. 17).

b) These values are $10^3 \cdot k_{un}$/s^{-1} or $10^3 \cdot k_c$/s^{-1}.

addition of a Cu(II) complex with MGP resulted in a slight acceleration of the hydrolysis. MGP forms a 1:1 complex with Cu(II) in an alkaline solution.[1] Thus, it is obvious that the marked retardation of the *p*-NPA cleavage by $Cu_2\alpha$-CD is not simply related to the direct action of the Cu(II) ion. The hydrolyses of *m*- and *o*-NPA and 4-NNA were also retarded by $Cu_2\alpha$-CD or $Cu_2\beta$-CD, though the extents of the retardation were not so large as that for a $Cu_2\alpha$-CD-*p*-NPA system. Interestingly, the hydrolysis of *p*-NPP was greatly retarded by $Cu_2\alpha$-CD to an extent similar to that of *p*-NPA.

The K_d and k_c values for these Cu_2CD-organic carboxylate systems were determined by the analysis of the relationships between k_{obsd} and the concentration (c_0) of Cu_2CD (Fig. 3). Table 3 gives the values obtained, together with those for Cu_2CD-organic phosphate and monothiophosphate systems reported previously.[16,17] These results indicate that $Cu_2\alpha$-CD causes a markedly stereoselective deceleration of the alkaline hydrolysis of organic carboxylates such as *o*-, *m*-, and *p*-NPA, *p*-NPP, and 4-NNA: The k_c/k_{un} value is virtually equal to zero for *p*-NPA and *p*-NPP, whereas it is 0.27 for *o*-NPA, 0.65 for *m*-NPA, and 0.88 for 4-NNA. Another remarkable stereoselectivity was observed for the binding of the esters to $Cu_2\alpha$-CD: The K_d value was determined to be 0.028 mmol dm^{-3} for *p*-NPP and 0.059 mmol dm^{-3} for *p*-NPA, these values being much smaller than those for *o*- and *m*-NPA and 4-NNA. According to VanEtten, *et al.*,[3] the K_d value for an α-CD-*p*-NPA system is equal to 12 mmol dm^{-3}, which is about 200 times that for a $Cu_2\alpha$-CD-*p*-NPA system. The K_d value for an α-CD-*m*-NPA system is 19 mmol dm^{-3} which is only 3 times that (6.3 mmol dm^{-3}) for a $Cu_2\alpha$-CD-*m*-NPA system. The binding site of $Cu_2\alpha$-CD may be significantly different in structure from that of uncomplexed α-CD.

$Cu_2\beta$-CD also caused a stereoselective deceleration of the alkaline hydrolysis of the carboxylates. However, the stereoselectivity of $Cu_2\beta$-CD is not so remarkable as that of $Cu_2\alpha$-CD with regard to both k_c/k_{un} and K_d. Furthermore, the retardation effect of $Cu_2\beta$-CD was less prominent in the carboxylates than in the phosphates and monothiophosphates. On the other hand, the binding and catalytic actions of $Cu_2\alpha$-CD on the phosphates and monothiophosphates are less stereoselective than those on the carboxylates. These results suggest that the binding and catalytic properties of Cu_2CD depend not only on the structures of the phenyl and acid moieties of the phenyl esters but also on the size of the CD ring.

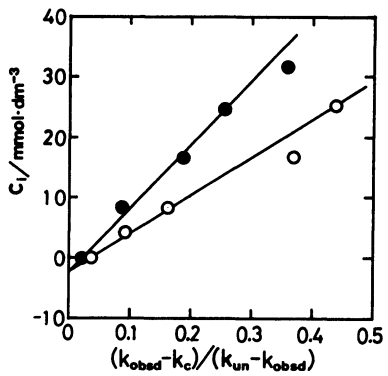


Fig. 4. Plots of c_i *vs.* $(k_{obsd}-k_c)/(k_{un}-k_{obsd})$ for a $Cu_2\alpha$-CD-*p*-NPA-cyclohexanol system in 1.0 mol dm^{-3} NaOH at 25 °C.
○: [$Cu_2\alpha$-CD]=1.5 mmol dm^{-3}, ●: [$Cu_2\alpha$-CD]=2.5 mmol dm^{-3}.

In order to characterize the structure of the binding site of $Cu_2\alpha$-CD, dissociation constants (K_i) for inclusion complexes of $Cu_2\alpha$-CD with several alcohols and other organic molecules were determined by a kinetic examination of the competitive inhibition effect of the molecules on the association of $Cu_2\alpha$-CD with *p*-NPA in 1.0 mol dm^{-3} NaOH at 25 °C. Figure 4 shows the plots of c_i *vs.* $(k_{obsd}-k_c)/(k_{un}-k_{obsd})$, based on Eq. 2,

TABLE 4. K_i VALUES FOR $Cu_2\alpha$-CD COMPLEXES

Substrate	K_i/mM[a] ($Cu_2\alpha$-CD)	K_d/mM[b] (α-CD)	K_i/K_d
	(Normal Alkanol)		
1-Butanol	10.3	11.1	0.93
1-Pentanol	3.3	3.1	1.1
	(Branched Alkanol)		
2-Me-2-Propanol	220	230	1.0
2,2-DiMe-1-Propanol	10	34	0.30
	(Cyclic Alkanol)		
Cyclopentanol	25	22	1.1
Cyclohexanol	2.2	15	0.15
Cycloheptanol	1.5	13	0.12
	(Aromatic Alcohol)		
Benzyl Alcohol	26	46	0.6
p-Nitrobenzyl Alcohol	0.47	—	—
	(Others)		
Methyl Acetate	40	—	—
p-Nitrophenolate ion	6.5	5.8[a]	1.1
p-Nitrobenzoate ion	250	—	—

a) In 1.0 mol dm^{-3} NaOH at 25 °C. b) In 0.10 mol dm^{-3} H_2SO_4 at 25 °C (Ref.21).

for a $Cu_2\alpha$-CD–cyclohexanol system at c_0=1.5 and 2.5 mmol dm^{-3}. The plots were virtually linear in both cases. The extrapolation of the straight lines to $(k_{obsd}-k_c)/(k_{un}-k_{obsd})=0$ gave virtually the same K_i value of 2.2 mmol dm^{-3}. As Eq. 2 suggests, the slopes of the straight lines are equal to $c_0 \cdot K_i/K_d$. The K_d values, thus estimated, were 0.052 mmol dm^{-3} in both cases. The value is very close to that directly determined (K_d=0.059 mmol dm^{-3}). Table 4 shows the K_i values obtained, together with the K_d value for a $Cu_2\alpha$-CD complex with the *p*-NP anion estimated by the polarimetric method. The K_d values for inclusion complexes of α-CD itself with these substances are also shown in the table for the sake of comparison.[21]

Although the K_d values for inclusion complexes of $Cu_2\alpha$-CD with *p*-NPA and *p*-NPP were very small, the K_i value for a $Cu_2\alpha$-CD complex with methyl acetate, as well as the K_d values for $Cu_2\alpha$-CD complexes with *o*- and *m*-NPA, was significantly large. It is obvious that the *p*-nitrophenyl moiety of *p*-NPA or *p*-NPP is essential for the strong binding of *p*-NPA or *p*-NPP to $Cu_2\alpha$-CD. This presumption is supported by the fact that the K_i value for a $Cu_2\alpha$-CD–*p*-nitrobenzyl alcohol system is considerably small (0.47 mmol dm^{-3}). However, the K_d or K_i values for a $Cu_2\alpha$-CD complex with the *p*-nitrophenolate or *p*-nitrobenzoate anion was not so small as the K_d value for a $Cu_2\alpha$-CD complex with *p*-NPA or *p*-NPP. $Cu_2\alpha$-CD holds two negative charges, and the inclusion of the *p*-nitrophenolate or *p*-nitrobenzoate anion within the $Cu_2\alpha$-CD cavity may be retarded by the electrostatic repulsive force. The K_i values for $Cu_2\alpha$-CD complexes with normal and branched alkanols such as 1-butanol, 1-pentanol, and 2-methyl-2-propanol were comparable to the corresponding K_d values for α-CD complexes with the alkanols. On the other hand, the K_i values for $Cu_2\alpha$-CD complexes with cycloalkanols such as cyclohexanol and cycloheptanol were considerably smaller than the corresponding K_d values for α-CD complexes with the cycloalkanols. It has been suggested that the macrocyclic ring of α-CD is distorted to the ellipsoidal form by the formation of a $Cu_2\alpha$-CD complex (Fig. 1),[2] whereas the ring is virtually regular hexagonal in α-CD inclusion complexes.[22,23] The ellipsoidal cavity of $Cu_2\alpha$-CD may be favorable for the inclusion of such disk-like molecules as cycloalkanols, *p*-nitrobenzyl alcohol, *p*-NPA, and *p*-NPP.

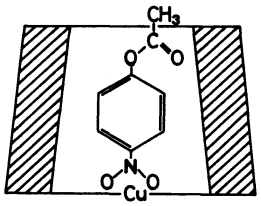


Fig. 5. The proposed geometry of *p*-NPA within the cavity of $Cu_2\alpha$-CD.

The geometry of the $Cu_2\alpha$-CD–*p*-NPA inclusion complex was presumed to be as is shown in Fig. 5 on the basis of the results described above. The substrate, *p*-NPA, may penetrate into the ellipsoidal cavity of $Cu_2\alpha$-CD so deeply that the maximum van der Waals contact with the cavity is attained. The coordination of the Cu(II) ion of $Cu_2\alpha$-CD to the nitro group of *p*-NPA may be possible to occur, resulting in the additional force for the strong binding of the substrate to $Cu_2\alpha$-CD. The carbonyl moiety of *p*-NPA may aloso be included within the cavity, so that the nucleophilic attack of the hydroxide ion on the carbonyl carbon is almost completely retarded by the steric hindrance of the α-CD macrocycle. In the cases of the organic phosphates and monothiophosphates, two methoxyl or two ethoxyl groups attached to the phosphorus atom may be too large to be included deeply within the cavity of $Cu_2\alpha$-CD. Then, the phosphorus atom is subject to the nucleophilic attack of the hydroxide ion from bulk solution. The *o*- and *m*-isomers of NPA may also be impossible to be deeply included within the $Cu_2\alpha$-CD cavity, owing to the steric hindrance of the substituents. $Cu_2\beta$-CD has a larger cavity in size than $Cu_2\alpha$-CD. Thus, *p*-NPA cannot fit the $Cu_2\beta$-CD cavity so closely as it fits the $Cu_2\alpha$-CD cavity, and the K_d and k_c/k_{un} values for a $Cu_2\beta$-CD–*p*-NPA system is much larger than those for a $Cu_2\alpha$-CD–*p*-NPA system. On the contrary, *o*- and *m*-NPA and 4-NNA as well as the organic phosphates and monothiophosphates may be more deeply included within the $Cu_2\beta$-CD cavity than within the $Cu_2\alpha$-CD cavity. Then, the k_c/k_{un} values for $Cu_2\beta$-CD complexes with these substrates are smaller than those for the corresponding $Cu_2\alpha$-CD complexes.

In conclusion, complex formation between Cu(II) and α-CD causes a large conformational change in the macrocycle of α-CD, which is responsible both for the markedly stereoselective binding of *p*-NPA and for the stereoselective retardation of the alkaline hydrolysis of

p-NPA by $Cu_2\alpha$-CD. Similar effects of metal ions on the conformation and binding and catalytic properties of enzymes have often been reported on metalloenzymes.[24,25] Thus, we can refer to the Cu_2CD complex as a good model of metalloenzymes.

References

1) Y. Matsui, T. Kurita, and Y. Date, *Bull. Chem. Soc. Jpn.*, **45**, 3229 (1972).
2) Y. Matsui, T. Kurita, M. Yagi, T. Okayama, K. Mochida, and Y. Date, *Bull. Chem Soc. Jpn.*, **48**, 2187 (1975).
3) R. L. VanEtten, J. F. Sebastian, G. A. Clowes, and M. L. Bender, *J. Am. Chem. Soc.*, **89**, 3242 (1967).
4) H. Kitano and T. Okubo, *J. Chem. Soc., Perkin Trans., 2*, **1977**, 432.
5) M. Komiyama and M. L. Bender, *J. Am. Chem. Soc.*, **100**, 4576 (1978).
6) M. Komiyama and M. L. Bender, *Bull. Chem. Soc. Jpn.*, **53**, 1073 (1980).
7) M. Komiyama and H. Hirai, *Chem. Lett.*, **1980**, 1471.
8) F. Cramer and G. Mackensen, *Chem. Ber.*, **103**, 2138 (1970).
9) R. Breslow and L. E. Overman, *J. Am. Chem. Soc.*, **92**, 1075 (1970).
10) W. B. Gruhn and M. L. Bender, *Bioorg. Chem.*, **3**, 324 (1974).
11) Y. Kitaura and M. L. Bender, *Bioorg. Chem.*, **4**, 237 (1975).
12) Y. Iwakura, K. Uno, F. Toda, S. Onozuka, K. Hattori, and M. L. Bender, *J. Am. Chem. Soc.*, **97**, 4432 (1975).
13) R. Breslow, M. F. Czarniecki, J. Emert, and H. Hamaguchi, *J. Am. Chem. Soc.*, **102**, 762 (1980).
14) K. Fujita, A. Shinoda, and T. Imoto, *J. Am. Chem. Soc.*, **102**, 1161 (1980).
15) K. Fujita, A. Shinoda, and T. Imoto, *Tetrahedron Lett.*, **21**, 1541 (1980).
16) K. Mochida, Y. Ozoe, H. Miyazaki, and Y. Matsui, *Bull. Fac. Agric., Shimane Univ.*, **14**, 158 (1980).
17) K. Mochida, Y. Ozoe, H. Iwasaki, and Y. Matsui, *Bull. Fac. Agric., Shimane Univ.*, **13**, 190 (1979).
18) F. Cramer and F. M. Henglein, *Chem. Ber.*, **91**, 308 (1958).
19) I. Heilbron and H. M. Bunbury, "Dictionary of Organic Compounds," Oxford Univ., New York (1953), Vol. 3, p. 746.
20) H. H. Hodgson and E. Kilner, *J. Chem. Soc.*, **127**, 807 (1924).
21) Y. Matsui and K. Mochida, *Bull. Chem. Soc. Jpn.*, **52**, 2808 (1979).
22) W. Saenger, "Environmental Effects on Molecular Structure and Properties," ed by B. Pullman, D. Reidel, Dordorecht-Holland (1976), p. 265.
23) K. Harata, *Bull. Chem. Soc. Jpn.*, **50**, 1416 (1977).
24) F. R. N. Gurd and G. F. Bryce, "The Biochemistry of Copper," ed by J. Peisach, P. Aisen, and W. E. Blumberg, Academic Press, New York (1966), p. 115.
25) J. E. Coleman and J. F. Chlebowski, *Adv. Inorg. Biochem.*, **1**, 1 (1979).