Retardation of the Cleavages of Nitrophenyl 1-Adamantanecarboxylates by Cyclodextrins

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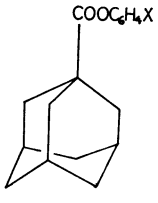
Cleavages of *p*- and *m*-nitrophenyl 1-adamantanecarboxylates (**1** and **2**) were carried out in the presence of α-, β-, and γ-cyclodextrins at 16 °C. The complex formation of **1** with α-, β-, and γ-cyclodextrins decelerated its cleavage by 3.2, 28, and 13 fold, respectively, in the 99 : 1 (v/v) mixture of 0.1 mol dm^{-3} NaOH aqueous solution and acetonitrile. All α-, β-, and γ-cyclodextrins showed decelerations of the cleavages of **1** and **2** also in the 66 : 34 mixture of 0.1 mol dm^{-3} NaOH aqueous solution and acetonitrile, although the magnitudes of the rate effects were smaller. The decelerations of the cleavages of **1** and **2** by cyclodextrins were markedly in contrast with the accelerations of the cleavages of other phenyl esters by cyclodextrins previously reported, and were ascribed to the formation of the complexes, in which **1** and **2** were protected sterically and/or electrostatically by cyclodextrins.

Cyclodextrins (CDs), cyclic oligosaccharides composed of 6—8 glucose units, have been used as an enzyme model, since they form complexes with substrates prior to their catalytic functions, resulting in many specificities exhibited by enzymes. The stereochemistry in the complex formation was shown to have quite important roles in the catalyses by CDs.[1]

Of many kinds of catalyses by CDs, hydrolyses of esters have been most widely and precisely studied, and much information has been obtained, especially on the effects of different leaving groups on the catalyses by CDs. Thus, CDs accelerated cleavages of phenyl esters of acetic acid,[2] benzoic acids,[2] and 3-carboxy-2,2,5,5-tetramethyl-1-pyrrolidinyloxyl.[3] The cleavages of trifluoroethyl benzoate[4] and *S*-ethyl thiobenzoate[5] were also accelerated by CDs, whereas the cleavages of ethyl and methyl esters of benzoic acids and cinnamic acids were retarded or totally inhibited by CDs.[2,6,7]

However, little is known about the role of the acyl portions of esters in the catalyses by CDs.

In this paper, the effects of α-, β-, and γ-cyclodextrins (α-, β-, and γ-CD) on the cleavages of *p*-nitrophenyl 1-adamantanecarboxylate (**1**) and *m*-nitrophenyl 1-adamantanecarboxylate (**2**) are described. The acyl portions of **1** and **2**, adamantanecarbonyl groups, are much more bulky and apolar than the acyl portions of any esters ever studied. Furthermore, a ^{13}C-NMR spectrometry on the CD–1-adamantanecarboxylate (**3**) system was carried out to shed light on the interactions of the adamantane moieties of **1** and **2** with CDs.



1 : X= p-NO_2
2 : X= m-NO_2

Experimental

Materials. **1** and **2** were synthesized from 1-adamantanecarbonyl chloride and the corresponding phenols and were recrystallized from ethanol. **1**: mp 132.5—132.8 °C (lit, 130—131 °C[8]). **2**: mp 137.8—138.3 °C. Found: C, 67.79; H, 6.37; N, 4.59%. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65%. α-CD and β-CD were recrystallized from water. γ-CD was purchased from Nakarai Chem. Co. and was used without further purification.

Kinetics. The cleavage of **1** was carried out at 16 °C in the 99 : 1 (v/v) mixture of 0.1 mol dm^{-3} NaOH aqueous solution and acetonitrile. The small amount of acetonitrile was due to the initiation of the reaction by the addition of the 30 μl stock solution of **1** in acetonitrile to 3 ml 0.1 mol dm^{-3} NaOH aqueous solution.

The attempt to examine the cleavage of **2** in the similar way, however, was not successful because of poor solubility of **2** in aqueous solution.

For the purpose of comparison, the cleavages of both **1** and **2** were carried out in the 66 : 34 (v/v) mixture of 0.1 mol dm^{-3} NaOH aqueous solution and acetonitrile. The reactions were also initiated by the addition of 30 μl stock solutions in acetonitrile to the mixture of 2 ml 0.1 mol dm^{-3} NaOH aqueous solution and 1 ml acetonitrile.

The initial concentrations of **1** and **2** were approximately 2×10^{-5} and 10^{-4} mol dm^{-3}, and their cleavages were followed by the release of the corresponding phenols at 410 and 390 nm, respectively. The rate constant of the cleavage, k_{obsd}, was determined by the usual first-order plot.

^{13}C-NMR Spectrometry. ^{13}C-NMR spectra were taken in D_2O solutions at pDs 9 and 13 at 60 °C on a JEOL PFT-100 spectrometer operating at 25.03 MHz by use of a deuterium lock. The chemical shifts were referenced to external benzene and the accuracy was within ±0.03 ppm.

Results

All α-, β-, and γ-CDs retarded the cleavages of both **1** and **2**. Figure 1 shows the dependence of k_{obsd} on the concentrations of CDs ($[CD]_0$) for the cleavage of **1** in the 99 : 1(v/v) mixture of 0.1 mol dm^{-3} NaOH aqueous solution and acetonitrile. Obviously, k_{obsd} asymptotically decreased with $[CD]_0$. Similar results were observed also in the cleavages of **1** and **2** in the 66 : 34(v/v) mixture of 0.1 mol dm^{-3} NaOH aqueous solution and acetonitrile.

These retardations of the cleavages of **1** and **2** by CDs are markedly in contrast with the accelerations of the cleavages of phenyl esters by CDs previously reported.[1-3]

The dependences of k_{obsd} on $[CD]_0$ were analyzed according to the Scheme 1 involving the complex

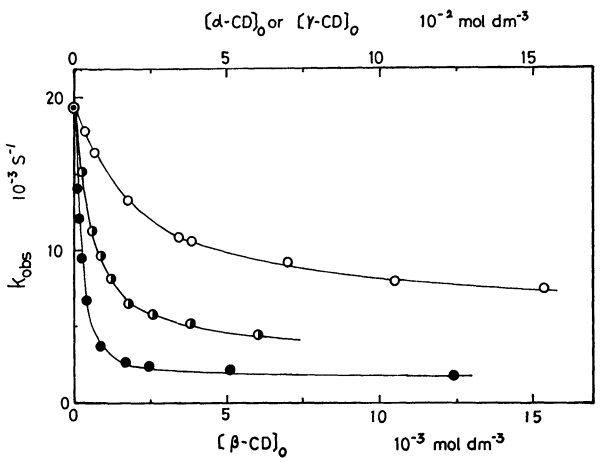


Fig. 1. Dependences of the rate constants of the cleavage of **1** (k_{obsd}) upon the initial concentrations of cyclodextrins ([CD]$_0$); in the 99 : 1 (v/v) mixture of 0.1 mol dm^{-3} NaOH aqueous solution and acetonitrile at 16 °C. ●: β-CD (the lower scale), ○: α-CD, ◑: γ-CD (the upper scale).

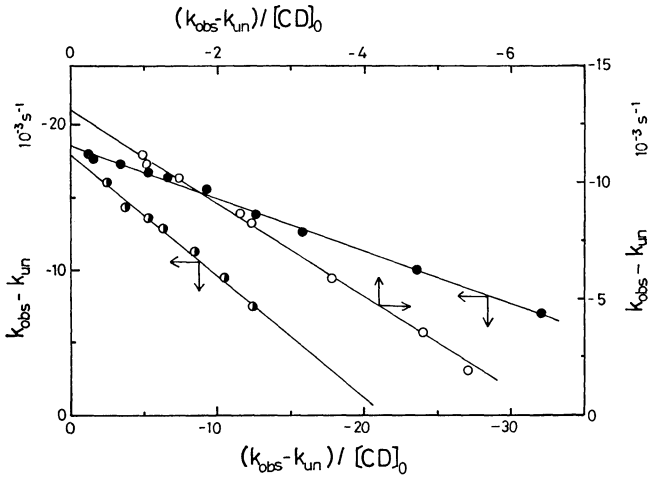


Fig. 2. Plots of $(k_{obsd}-k_{un})$ *vs.* $(k_{obsd}-k_{un})/[CD]_0$ in the cleavage of **1** in the presence of CDs. ○, ●, and ◑ refer to α-, β-, and γ-CDs, respectively; the data in Fig. 1 are used here.

formation of the substrate (S) with CD prior to the reaction:

$$S + C \underset{K_d}{\rightleftharpoons} S\cdot C \xrightarrow{k_c} \text{products}$$
$$\downarrow k_{un}$$
products

Scheme 1.

The rate constants of the cleavage of the substrate in the S·C complex, k_c, and the dissociation constant of the S·C complex, K_d, were determined by use of the Eadie-type plot Eq. 1:

$$(k_{obsd}-k_{un}) = -K_d(k_{obsd}-k_{un})/[CD]_0 + (k_c-k_{un}). \quad (1)$$

Table 1 lists the values of k_c and K_d, determined from the slope and intercept of the straight lines in the Eadie-type plots as shown in Fig. 2.

Table 1. Values of k_c, k_c/k_{un}, and K_d for the cleavages of *p*- and *m*-nitrophenyl 1-adamantanecarboxylates (**1** and **2**) in the presence of cyclodextrins (CDs)

Substrate	CD	k_c / 10^{-4} s^{-1}	k_c/k_{un}	K_d / 10^3 mol dm^{-3}
1[a]	α-CD	60±6	0.31	13±2
	β-CD	6.9±0.7	0.036	0.36±0.04
	γ-CD	15±2	0.078	0.82±0.06
1[b]	α-CD	39.2[c]	—	—
	β-CD	14±3	0.30	4.7±0.9
	γ-CD	35.3[c]	—	—
2[b]	α-CD	43.3[c]	—	—
	β-CD	28±5	0.60	2.2±0.5
	γ-CD	45.2[c]	—	—

a) In the 0.1 mol dm^{-3} NaOH aqueous solution–acetonitrile mixture (99 : 1 in volume), at 16 °C; k_{un} under these conditions was 1.93×10^{-2} s^{-1}. b) In the 0.1 mol dm^{-3} NaOH aqueous solution–acetonitrile mixture (66: 34 in volume) at 16 °C; k_{un}'s of **1** and **2** under these conditions were 4.75×10^{-3} and 4.65×10^{-3} s^{-1}, respectively. c) k_{obsd} in the presence of 3×10^{-2} mol dm^{-3} CD.

It was found that the complex formation of **1** with α-, β-, and γ-CDs decelerated its cleavage by 3.2, 28, and 13 fold, respectively, in the 99 : 1(v/v) mixture of 0.1 mol dm^{-3} NaOH aqueous solution and acetonitrile. Similarly, the cleavages of **1** and **2** were retarded by 3.3 and 1.7 fold, respectively, by the complex formations with β-CD in the 66 : 34 mixture of 0.1 mol dm^{-3} NaOH aqueous solution and acetonitrile.

Determinations of k_c and K_d for the cleavages of **1** and **2** by α- and γ-CDs in the 66 : 34 mixture by use of the Eadie-type plots were not successful because of small magnitudes of effects by CDs, although these CDs showed decelerations in these reactions.

The magnitudes of the deceleration of the cleavage of *p*-nitrophenyl ester **1** by CDs were similar to those of the cleavage of *m*-nitrophenyl ester **2** by CDs. These small effects of the positions of the phenyl substituents on the rate constants of their cleavages in the presence of CDs were also in contrast with the predominant roles of the positions of the phenyl substituents in the acceleration of the cleavages of phenyl acetates by CDs. For example, the cleavages of *p*- and *m*-nitrophenyl acetates were accelerated by α-CD by 3.4 and 300 fold, respectively.[6]

Table 2 shows the changes of the ^{13}C-NMR chemical shifts on the complex formation of CDs with **3** in D_2O. At pDs 9 and 13, the secondary hydroxyl groups of CDs are overwhelmingly in the unionized and ionized states, respectively, since their pK_a is around 11 at 60 °C.[9]

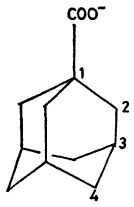
Furthermore, at pD 9, almost all of CD and **3** form complexes under the experimental conditions, in consideration of the previously determined dissociation constants of these complexes (for the α-CD–**3** complex, 1.1×10^{-3} mol dm^{-3} and for the β-CD–**3** complex, 1.4×10^{-3} mol dm^{-3} at 60 °C[10]).

On the complex formation of **3** with α-CD at pD 9, the C-4 atoms showed shifts toward the lower magnetic field, whereas the C-2 and C-3 atoms showed shifts

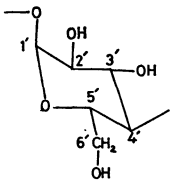
TABLE 2. CHANGES OF THE ^{13}C CHEMICAL SHIFTS ON THE COMPLEX FORMATION BETWEEN CYCLODEXTRINS (CDs) AND 1-ADAMANTANECARBOXYLATE (**3**)[a]

Carbons[b,c]	α-CD		β-CD	
	pD 9[d]	pD 13	pD 9	pD 13
1	0.00(0.00)	0.00	+0.12	+0.02
2	+0.09(+0.08)	+0.02	−0.15	−0.42
3	+0.12(+0.12)	+0.02	+0.34	+0.40
4	−0.20(−0.22)	0.00	−0.49	−0.61
1′	−0.13(−0.15)	0.00	−0.32	−0.36
2′	−0.03(−0.02)	+0.04	+0.06	−0.09
3′	−0.06(−0.06)	0.00	−0.06	−0.25
4′	−0.09(−0.09)	+0.04	−0.20	−0.55
5′	−0.03(0.00)	0.00	−0.25	−0.12
6′	+0.02(+0.01)	+0.02	+0.21	0.00

a) In ppm at 60 °C, and $[CD]=[\mathbf{3}]=5\times10^{-2}$ mol dm^{-3} in D_2O; +signs refer to the shifts toward the higher field with reference to the chemical shifts of **3** (or CD) in the absence of CD (or **3**). b) The numbering systems are as follows;



3



CD

c) Assignment following Ref. 11. d) The values in parentheses show the results of the duplicate experiments.

toward the higher magnetic field. The C-1 atom, however, exhibited little shift.

At pD 13, where virtually all of α-CD is in the anionic form, however, no changes of the chemical shifts for both α-CD and **3** were observed considering experimental error. This indicates that no complex is formed between α-CD and **3** at pD 13.

Larger changes of the chemical shifts of both the guest and host molecules were observed on the complex formation between β-CD and **3** at pDs 9 and 13.

Discussion

The retardation of the cleavages of **1** and **2** by CDs in spite of the acceleration of the cleavages of many other phenyl esters previously studied is attributable to the apolar and bulky properties of the adamantane moieties of **1** and **2**. These groups can be included in the cavity of β-CD (and also the cavity of γ-CD) as indicated by the considerable changes of the ^{13}C-NMR chemical shifts on the complex formation of **3** with β-CD. The adamantane moieties of **1** and **2**, however, can not be included in the small cavity of α-CD and only sit on the top of the cavity, as proposed by the study using the molecular models.[6] This is consistent with the small changes of the ^{13}C chemical shifts on the complex formation of **3** with α-CD. In the hydrolyses of phenyl esters accelerated by CDs, the phenyl portions are included in the cavity, followed by the nucleophilic attack of CDs at the substrates.[1]

Two Structures A and B are possible for the complex of **1** or **2** with β-CD or γ-CD, both of which are nonproductive or less productive. Structure A is formed by the inclusion of **1** and **2** in the cavity from the secondary hydroxyl side with their phenyl portions first, whereas Structure B is formed by the inclusion of **1** and **2** in the cavity from the same side with their adamantane portions first.[12] In Structure A, the carbonyl carbon atoms of the substrates should be located deeply in the cavity, since the apolar property of the adamantane portions require most of them as well as the phenyl portions to be included in the cavity. Consequently, nucleophilic attack of the secondary alcoholate anion of CDs at the carbonyl carbon atoms is sterically unfavorable. Furthermore, steric protection by the walls of CDs and electrostatic repulsion by the negative charges of CDs retard alkaline hydrolyses of **1** and **2**.

In Structure B, nucleophilic attack by the secondary alcoholate anions of CDs can not produce the acyl-CD (the intermediate) with the release of the phenols, since the acyl-CD with the acyl portion inside the cavity involves too drastic distortion(s) in bond(s). Furthermore, alkaline reactions are retarded sterically and electrostatically in the similar way as in Structure A.

The retardation of the cleavages of **1** and **2** by α-CD indicates that the phenyl portions of **1** and **2** are included in the cavity with the adamantane portions sitting on the top of the cavity. In this structure, nucleophilic attack both by the secondary alcoholate anion of CD and by hydroxide ion are prevented sterically and/or electrostatically. If the adamantane portions alone is located in the cavity and the phenyl portion is outside, any retardation by α-CD is unlikely.

Much smaller deceleration effects by CDs on the cleavages of **1** and **2** in the 66 : 34 mixture of 0.1 mol dm^{-3} NaOH aqueous solution and acetonitrile than in the 99: 1 mixture is attributable to shallower inclusions of the substrates in the cavities of CDs because of apolar properties of the adamantane portions. In this structure, any effect by CDs should be small. This interpretation is supported by the 13 fold large K_d of the β-CD–**1** complex (corresponding to less stable complex) in the 66: 34 mixture than that in the 99: 1 mixture.

In conclusion, the cleavages of **1** and **2** were retarded by CDs, which is in contrast with the acceleration of the cleavages of many other phenyl esters by CDs. The present results show that the acyl portions of the substrates can have a predominant effect on the catalyses by CDs.

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12) These descriptions do not mean that the inclusion of **1** and **2** in β- and γ-CDs should take place only from the secondary hydroxyl side of the cavities. Inclusion from the primary hydroxyl side can also form Structures A and B.