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Effects of Modified β-Cyclodextrins on the Hydrolysis Reaction of *p*-Nitrophenyl α-Methoxyphenylacetate

JOON WOO PARK[1,⋆], JI HYUN HONG[1] and KWANGHEE KOH PARK[2]
[1]*Department of Chemistry, Ewha Womans University, Seoul 120-750, Korea;* [2]*Department of Chemistry, Chungnam National University, Taejon 305-764, Korea*

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Abstract. Effects of β-cyclodextrin (β-CD) **1** and its derivatives **2**–**7** on the deacylation reaction of *p*-nitrophenyl (*R* or *S*)-α-methoxyphenylacetate were studied. The β-CD derivatives used were 6-α-D-glucosyl-β-CD **2**, sulfated β-CD (7–11 sulfate groups/CD ring) **3**, dimethylated β-CD **4**, carboxymethylated β-CD (3.5 carboxymethyl groups/CD ring) **5**, 2-tri(2-hydroxypropyl)-β-CD **6**, and β-CD appended on poly(allylamine) **7**. The rate constant (k_{ψ}^{CD}) of the substrate/β-CD complexes and the formation constants (K) of the complexes were determined from the dependence of the pseudo-first order rate constants of the deacylation reaction on the concentration of β-CDs. The order of k_{ψ}^{CD} for the *R*-enantiomer at pH 8.0 is $\mathbf{4} \ll \mathbf{5} < \mathrm{H_2O} < \mathbf{3} \cong \mathbf{6} < \mathbf{1} \cong \mathbf{2} \ll \mathbf{7}$, while that for the *S*-enantiomer is $\mathbf{4} \ll \mathbf{5} \cong \mathbf{6} < \mathrm{H_2O} \cong \mathbf{1} \cong \mathbf{2} < \mathbf{3} \ll \mathbf{7}$: $\mathrm{H_2O}$ denotes the rate in the absence of β-CDs. The order of K values is $\mathbf{3} < \mathbf{7} < \mathbf{6} \cong \mathbf{2} \cong \mathbf{1} < \mathbf{4} < \mathbf{5}$. This work indicates that, though the secondary hydroxyl groups of β-CD play critical roles in the deacylation reactions of the esters complexed with β-CDs, the reactivity of the ester/β-CD complexes depends highly on the nature of the substituents at the secondary face of β-CD. It also suggests that the substrates inserted from the secondary side as well as the primary side of β-CD of poly(allylamine)-bound β-CD undergo the reaction by attack of amino groups on the polymer chain.

Key words: modified β-cyclodextrin, hydrolysis, catalysis, enantioselectivity, poly(allylamine).

1. Introduction

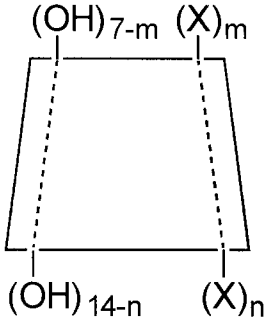
β-Cyclodextrin (β-CD) has been widely used as an artificial enzyme for a variety of reactions [1] and as a stabilizing agent and drug carrier [2]. These two typical applications require contrasting effects of β-CD on the substrates: the former application requires a catalytic effect, while the latter demands an inhibitory effect of β-CD on the reactions of inclusates. Among the reactions affected by β-CD, the hydrolysis of aryl esters has been most widely investigated [1, 3–13]. It is generally believed that the catalytic activity of β-CD arises from formation of inclusion complexes between the aryl ester substrates and β-CD and then acyl transfer to a secondary hydroxyl group of β-CD in the complexes [3–5]. Since β-CD is a

⋆ Author for correspondence.

chiral host for the substrates, a significant enantiomeric selectivity in the reactions of optically active esters has also been observed [8–13].

Various types of modified β-CD have been extensively used for improvement of catalytic properties and elucidation of the reaction mechanism. One is introduction of a catalytic residue such as imidazole, bipyridine, and amines to β-CD [2, 14, 15]. The deacylation reactions of esters also have been carried out with β-CD-appended polymers bearing amine or imine groups which act as catalytic residues [16, 17]. Simple modifications of β-CD also affect the catalytic and enantioselective properties of β-CD due to changes in binding properties and geometries of the β-CD-substrate complexes [11–13]. Fornasier et al. reported that 6-deoxy-6-(*N*-methylacetamido)-β-CD (6-NMeAc-β-CD) exhibits an enantioselective catalytic effect on the hydrolysis of chiral esters, whereas 2,6-dimethyl-β-CD (2,6-Me_2-β-CD), and permethylated β-CD (2,3,6-Me_3-β-CD) retard the reaction [11]. The enantioselective effects of β-CD derivatives on the reactions of chiral esters have also been studied with hydroxyalkylated–β-CD and methylated-β-CD [12, 13].

In this paper, we report the hydrolysis reaction of *p*-nitrophenyl esters of (*R* or *S*)-α-methoxyphenylacetic acid in the presence of various simply modified β-CDs **2**–**6** and poly(allylamine) (PAA) appended β-CD **7**. The binding constants (K) of the substrates to β-CDs and the rate constants (k_{ψ}^{CD}) for the β-CD-substrates complexes are determined, and their differences among the various β-CDs are discussed.



1. β-CD : X = OH

2. 6-Glu-β-CD : X = -O-α-D-Glucosyl; m = 1, n = 0

3. SO_4-β-CD : X = $-OSO_3^-Na^+$; m + n = 7-11

4. Me_2-β-CD : X = OCH_3; m + n = 14

5. CM-β-CD : X = $OCH_2COO^-Na^+$; m + n ≅ 3.5

6. 2-HP_3-β-CD : X = $OCH_2CH(OH)CH_3$; m = 0, n ≅ 3

2. Experimental

2.1. MATERIALS

The simply modified β-CDs used in this work are schematically represented above. They are 6-α-D-glucosyl-β-CD (6-Glu-β-CD) **2**, sulfated β-CD (SO_4-β-CD) **3**, dimethylated β-CD (Me_2-β-CD) **4**, carboxymethyl β-CD (CM-β-CD) **5**, 2-tri[2-(hydroxy)propyl]-β-CD (2-HP_3-β-CD) **6**. β-CD and SO_4-β-CD were purchased from Aldrich and 6-Glu-β-CD was obtained from Tokyo Kasei. Me_2-β-CD, CM-β-CD, and 2-HP_3-β-CD were available from Cyclolab, Hungary. The poly(allylamine)-bound β-CD (PAA-β-CD: **7**) was prepared by reacting mono-6-

deoxy-6-iodo-β-CD with PAA (av. MW 50,000–65,000; Aldrich) in water at 80 °C for 20 h [18]. The unreacted β-CD derivative was removed by dialyzing the reaction mixture for 7 days using a dialysis tubing of molecular weight cutoff of 6000–8000 and the product was precipitated by the addition of ethanol to the dialyzed solution after adjusting its pH to 3. The degree of substitution of β-CD to the amine groups of PAA was estimated as 11% from the NMR spectrum taken in D_2O using the integration ratio of the peaks corresponding to seven anomeric protons (at 5.05–5.15 ppm) of the β-CD moiety and two methylene protons (at 2.9–3.3 ppm) attached to the nitrogen of the PAA moiety. The substrate, *p*-nitrophenyl (*R* or *S*)-α-methoxyphenylacetate was prepared from optically active mandelic acid (Aldrich) [15].

2.2. KINETIC STUDIES

Deacylation reactions of the nitrophenyl esters were initiated by adding 20 μl of a 6.0×10^{-3} M solution of the ester in acetonitrile to 2.00 ml of the host solutions (0–10 mM) in 0.025 M pH 8.0 (Ionic strength I ≈ 0.1) or 0.013 M pH 9.0 (I ≈ 0.05) borate buffer in a cuvette pre-equilibrated at 25 °C. The release of *p*-nitrophenol was monitored at 400 nm using a GBC Cintra 20 UV-VIS spectrophotometer equipped with a thermostatically controlled cell holder.

3. Results and Discussion

The kinetics of the deacylation reaction of *p*-nitrophenyl (*R* or *S*)-α-methoxyphenylacetate (PNMPA) were studied in the presence of native β-CD **1** and the modified β-CDs **2**–**7**. The reaction obeyed pseudo-first-order kinetics with respect to the ester. The pseudo-first-order rate constants, k_ψ, were determined in the absence (k_ψ°) and in the presence of various concentrations of **1**–**7** (Figures 1–4). The effects on the deacylation reactions of the enantiomeric pair are very much variable depending on the position and nature of the substituent on β-CD.

As reported by this group [15] and others [8, 11, 13], the native β-CD (**1**) accelerates the deacylation reaction of the *R*-enantiomer, but shows little effects on the reaction of the *S*-enantiomer in pH 8.0 buffer. At higher pH (pH 9.0), the *S*-isomer also shows some rate enhancement by **1** (Table I). The effect of 6-Glu-β-CD (**2**) on the rate of deacylation reaction of the ester was very similar to that of the native β-CD (Figure 1). The deacylation rates of both enantiomers increased substantially in the presence of SO_4-β-CD (**3**), but decreased drastically in the presence of Me_2-β-CD (**4**). No appreciable enantioselectivity of the reactions was observed with **3** and **4**. CM-β-CD (**5**) slows down the reaction of both isomers, but the effects are considerably smaller than **4** (Figure 2). A moderate enantioselectivity showing less retardation for the *R*-isomer is observed with **5**. 2-HP_3-β-CD (**6**) enhances the reaction of the *R*-enantiomer, but inhibits the reaction of the

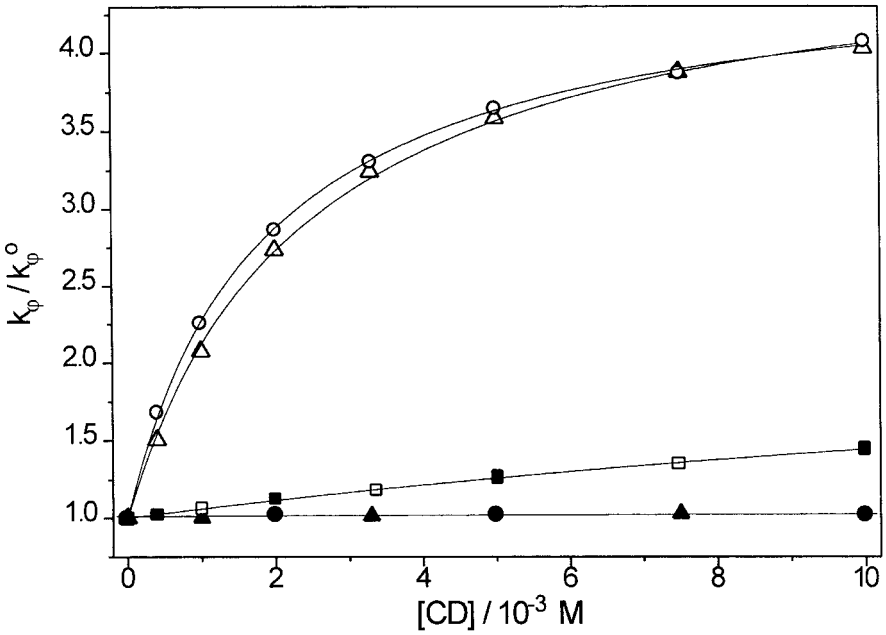
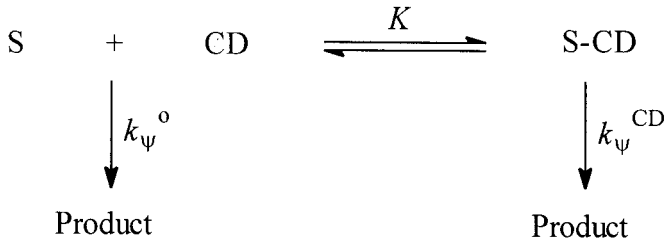


Figure 1. Dependence of the pseudo first-order rate constants for the deacylation reaction of *p*-nitrophenyl (*R* or *S*)-α-methoxyphenylacetate on the concentrations of β-CD **1** (○, ●), 6-α-D-glucosyl β-CD **2** (△, ▲), and sulfated β-CD **3** (□, ■) in pH 8.0, 0.025 M borate buffer. Open symbols are for the *R*-enantiomer and filled symbols are for the *S*-enantiomer.

S-enantiomer (Figure 3). PAA-β-CD (**7**) greatly accelerates the deacylation reaction of both enantiomers (Figure 4).

The effects of the native β-CD **1** and the modified β-CDs **2**-**6** on k_ψ are explained in terms of different reaction rates for free and β-CD-complexed substrates as shown in Scheme 1: we assume 1 : 1 complexation.



Scheme I.

The observed k_ψ is related to K, k_ψ°, k_ψ^{CD}, and the concentration of β-CD by Equation (1) [15].

$$(k_\psi - k_\psi^\circ)^{-1} = (k_\psi^{CD} - k_\psi^\circ)^{-1} + \{(k_\psi^{CD} - k_\psi^\circ)K\}^{-1}[\beta - CD]^{-1}. \quad (1)$$

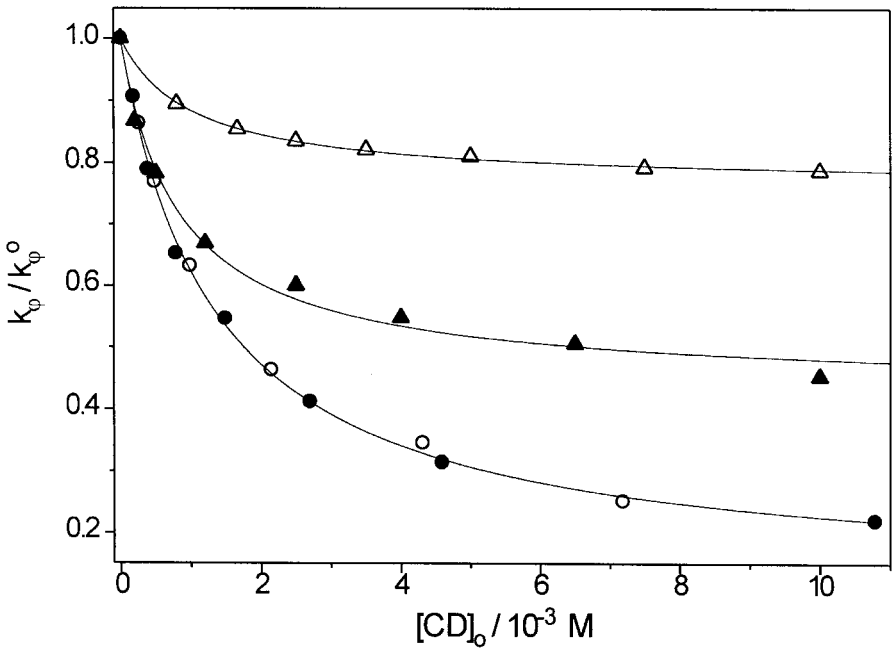


Figure 2. Dependence of the pseudo first-order rate constants for the deacylation reaction of *p*-nitrophenyl (*R* or *S*)-α-methoxyphenylacetate on the concentrations of dimethylated β-CD **4** (○, ●) and carboxymethyl β-CD **5** (△, ▲) in pH 8.0, 0.025 M borate buffer. Open symbols are for the *R*-enantiomer and filled symbols are for the *S*-enantiomer.

As the initially added concentration of the host, $[\beta\text{-CD}]_0$ is in large excess compared to the concentration of the substrate, $[\beta\text{-CD}]$ can be replaced by $[\beta\text{-CD}]_0$. The rate constant data in the presence of various concentrations of β-CD derivatives shown in Figures 1–3 were analyzed by Equation (1): Figure 5 shows examples of the plots. Good linearity in the plots indicates that the esters indeed form 1 : 1 complexes with the host molecules **1**–**6** and the kinetic model shown in Scheme 1 is relevant. The binding constants (K) of the substrates with the modified β-CD and the rate constants (k_ψ^{CD}) of the complexed substrates were evaluated from the slopes and intercepts of the lines and are included in Table I.

It may not be proper to attribute the absence of appreciable effects of **1** and **2** on the deacylation of the *S*-isomer at pH 8.0 as a result of negligible binding of the ester with the hosts. Rather, the observation can be attributed to a consequence of fortuity that the rate constant of the complexes is the same as that of the free substrate. The balance of the rate constants seems to be disrupted at pH 9.0 resulting in measurable enhancement of the rate by the hosts. It has been well established that the cleavage of the ester within an inclusion complex takes place by acyl transfer from the ester to a secondary hydroxyl group of β-CD [3–5]. Thus the substituent at the primary face of β-CD is not expected to effect the rate unless there is a change in the structures of the complex which gives alternation of the geometry

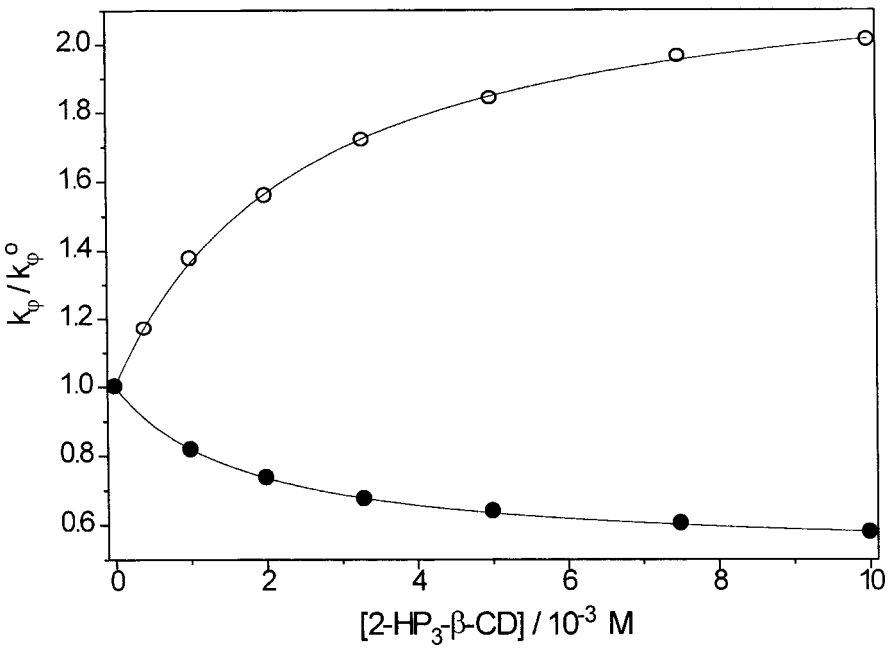


Figure 3. Dependence of the pseudo first-order rate constants for the deacylation reaction of *p*-nitrophenyl (*R* or *S*)-α-methoxyphenylacetate on the concentration of 2-tri[2-(hydroxy)propyl]-β-CD **6** in pH 8.0, 0.025 M borate buffer. (○): *R*-enantiomer; (●): *S*-enantiomer. Similar behavior was reported with other source of (hydroxy)propyl-β-CD in Ref. 13.

of the transition state for the reaction. Similarity between the native β-CD **1** and 6-Glu-β-CD **2** in the rate enhancement and binding property for the substrates is quite a contrast to the large rate-enhancing effect of the *N*-methylacetamido group bonded to the primary face of β-CD, which was attributed to the presence of the intrusive and flexible floor [11]. This suggests that the 6-O-α-D-glucosyl group of **2** is pointing out from the cavity and does not affect the binding of the substrates and reactivity of the complexes.

The smaller catalytic or inhibitory effects of the modified β-CD (**3**)–(**6**) are in line with the general trend: derivatization of secondary hydroxyl groups decreases the catalytic property of β-CD. However, no direct relationship between the degree of substitution and catalytic property is found. Assuming random substitution of the hydroxyl groups of β-CD for (**3**)–(**5**), the order of the degree of substitution at the secondary face is **5** < **6** < **3** < **4**, whereas the decreasing orders of the reactivity of complexes are **6** ≅ **3** > **5** > **4** for the *R*-isomer and **3** > **6** ≅ **5** > **4** for the *S*-isomer. This implies that the reactivity of the substrates/modified β-CD complexes and enantioselectivity of the reaction are highly dependent on not only the extent of the substitution at the secondary hydroxyl groups but also the nature of the substituents.

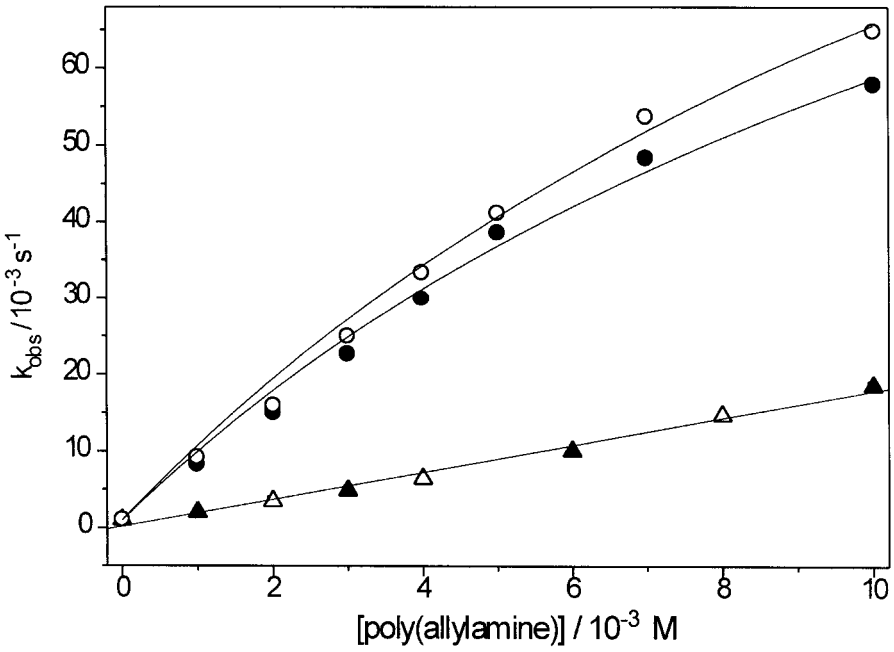


Figure 4. Dependence of the pseudo first-order rate constants for the deacylation reaction of *p*-nitrophenyl (*R* or *S*)-α-methoxyphenylacetate on the concentrations of poly(allylamine) (△, ▲) and β-CD-modified poly(allylamine) (○, ●) in pH 8.0, 0.025 M borate buffer. Open symbols are for the *R*-enantiomer and filled symbols are for the *S*-enantiomer. The concentration of polymer is expressed in terms of the monomeric unit.

The substrate esters complexed with the sulfated β-CD **3** exhibit two-fold enhanced reactivity as compared with the free substrates. This is quite unexpected results as 2,6-dimethylated β-CD (2,6-Me_2-β-CD), where the extent of substitution at the secondary face of β-CD is similar to that of **3**, shows a large retardation of the reaction [11]. Since the negatively charged sulfate groups of **3** shield the β-CD-encased substrates from the hydroxide ions present in the bulk phase electrostatically, the enhancement of reaction rate of the substrate by **3** can be ascribed to the increase in intracomplex reactivity. The enhancement of the reactivity cannot arise from the change of pK_a of the secondary hydroxyl groups of **3** since the presence of sulfate groups disfavors dissociation of the hydroxyl groups to alkoxide, but is due to a suitable geometry for the transition state of the reaction in the complexes.

The effects of dimethylated β-CD **4** is virtually the same as that of 2,6-dimethylated-β-CD (2,6-Me_2-β-CD) reported by Fornasier et al. [11] suggesting that **4** is essentially 2,6-Me_2-β-CD. Though half of the secondary hydroxyl groups of the β-CD moiety of **4** remains unsubstituted, the reaction is essentially quenched. In connection with this, it would be worth to mention that permethylated β-CD (Me_3-β-CD) also inhibits the deacylation reaction of esters, but the reactiv-

Table I. Kinetic Data for the hydrolysis of *p*-nitrophenyl (*R* or *S*)-α-methoxyphenylacetate in the presence of β-CD and its derivatives in pH 8.0, 0.025 M borate buffer at 25 °C.[a]

Host	Substrate	$k_\psi^{CD} \times 10^3/s^{-1}$	$(k_\psi^{CD}/k_\psi^\circ)^a$	K/M^{-1}	$(k_\psi^{CD})^R/(k_\psi^{CD})^S$
1	*R*	3.59 (23.5)[c]	4.60 (7.25)[c]	560 (510)[c]	4.4 (5.3)[c]
	S	0.78[b] (4.38)[c]	1.0[b] (1.37)[c]	(350)[c]	
2	*R*	3.74 (27.9)[c]	4.79 (8.71)[c]	520 (520)[c]	4.8 (5.5)[c]
	S	0.78[b] (5.06)[c]	1.0[b] (1.58)[c]	(200)[c]	
3	*R*	1.81	2.32	50	1.0
	S	1.74	2.23	60	
4	*R*	0.062	0.08	660	1.0
	S	0.062	0.08	660	
5	*R*	0.66	0.85	1000	1.8
	S	0.37	0.48	1200	
6	*R*	1.85	2.37	400	4.5
	S	0.41	0.53	580	
7	*R*	170	220	330	1.0
	S	170	220	300	

[a] k_ψ^{CD} at pH 8.0 is 0.78×10^{-3} s^{-1} for both enantiomers.

[b] Assumed to be the same as k_ψ° from the independence of the reaction rates on the concentration of β-CDs.

[c] The values in parentheses were obtained at pH 9.0 in 0.013 M borate buffer. The k_ψ° value at pH 9.0 is 3.24×10^{-3} s^{-1}.

ity of the complexes is much higher than that of the 2,6-Me_2-β-CD complexes [11]. A reasonable explanation for this apparently contradicting phenomena is the following. The *p*-nitrophenyl moiety of the substrates is included in the cavity of the host molecules both from the primary and secondary faces. The inclusion from the secondary face is facilitated by interaction between the methyl group and the protruded part of the substrate as evidenced by the increase in the binding constant of the substrate. However, the interaction makes the structure of the complexes from the secondary face less favorable for tetrahedral intermediate formation. The complexes from the primary side may have improper geometries to form such reactive intermediates. Thus the major reaction pathway for these complexes is the attack by hydroxide ion in the bulk phase, but the reaction rate would be much slower than that of the uncomplexed free substrate due to steric shielding by the host. On the other hand, 14 methyl groups at the secondary face of Me_3-β-CD make protective shielding from inclusion from the secondary face. Thus the complexation arises mainly from inclusion from the primary face. Smaller binding constants of the substrates to Me_3-β-CD than to Me_2-β-CD support this [11]. For the Me_3-β-CD complexes, the intracomplex reaction through acyl transfer is not

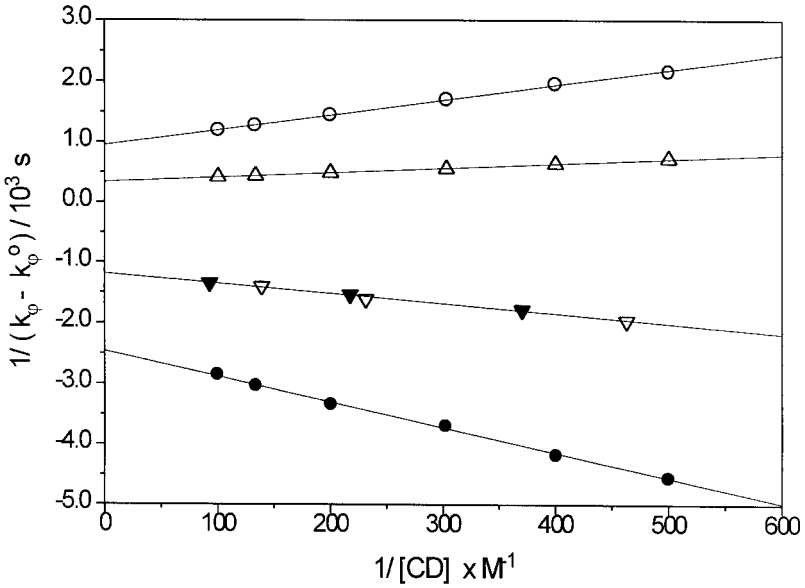


Figure 5. Plots of the variation of the pseudo first-order rate constants for the deacylation reaction of *p*-nitrophenyl (*R* or *S*)-α-methoxyphenylacetate on the concentrations of the modified β-CDs according to Equation (1). (○), *R*-enantiomer with 2-HP_3-β-CD **6**; (●), *S*-enantiomer with 2-HP_3-β-CD **6**; (△), *R*-enantiomer with the native β-CD **1**; (▽), *R*-enantiomer with Me_2-β-CD **4**; (▼), *S*-enantiomer with Me_2-β-CD **4**.

feasible, as all of the nucleophilic sites are derivatized. Thus the reaction is due to hydroxide ions in the bulk phase. Since the floor at the secondary face consisted of methyl groups raises the substrates, the substrates encased in Me_3-β-CD are more or less open to hydroxide ions.

Carboxymethyl β-CD **5** also causes retardation of the reaction, but the extent is not very large and considerable enantioselectivity of the reaction is exhibited. This seems reasonable since more than 80% of the hydroxyl groups on the secondary face remain unsubsitituted. The β-CD derivative **5** shows the highest binding constants with the substrates, but an explanation for this is not clear at this point.

2-Tri[2-(hydroxy)propyl]-β-CD **6** has a unique characteristic showing contrasting behavior between the enantiomers: it enhances the reaction of the *R*-enantiomer, but inhibits the reaction of the *S*-enantiomer[12,13]. The enantioselectivity for the reaction of the complexed substrates is the largest among β-CD derivatives studied here and similar to that of the native β-CD. About 80% of the secondary hydroxyl groups of the β-CD moiety of **6** remain unsubstituted, which is comparable to the host **5**. Considering only the number of the remaining hydroxyl groups, it is expected that **6** would also cause retardation of the reaction of both enantiomers as observed with **5**. Indeed, the effect of the host **6** on the *S* enantiomer is almost same as that of **5**, but its effect on the *R*-isomer is opposite to that of **5**. Though further evidences are needed, this can be taken as a suggestion that the 2-

(hydroxy)propyl group attached at the C-2 position of the secondary face of β-CD participates in the deacylation reaction of the *R*-isomer. Contrasting effects of **6** on the two enantiomers imply that the complexed *R*-isomer is properly situated for the attack of the hydroxyl group in the attached 2-(hydroxy)propyl substituent, but the geometry of the *S*-isomer is not suitable for that. If this is the case, the reaction by the hydroxyl group of the 2-hydroxypropyl substituent could be less efficient than that by the secondary hydroxyl group of β-CD moiety.

The deacylation rate of both enantiomers is greatly enhanced by the presence of PAA-β-CD (**7**) as compared to underivatized PAA (Figure 4). This observation accords with the reports on the hydrolysis of *p*-nitrophenylacetate in the presence of β-CD-functionalized PAA [16a] and poly(vinylamine) [17].

Since the underivatized PAA also increases the reaction rate, presumably due to the nucleophilic reactivity of the amine groups, the reaction Scheme 1 and Equation (1) should be modified to include this. We assumed that the increase in the reaction rate by the presence of PAA-β-CD is the sum of two independent contributions: one is the enhanced reactivity of the substrate included in the cavity of β-CD and the other is reaction of the substrate with amine groups. In this case, the Equation (1) is modified as (2);

$$\begin{aligned}(k_\psi - k_\psi^\circ)^{-1} \;=\; & K\{k_{2,\mathrm{PAA}}(\alpha^{-1}-1) + (k_\psi^{\mathrm{CD}} - k_\psi^\circ)K\}^{-1} + \\ & +\{k_{2,\mathrm{PAA}}(\alpha^{-1}-1) + (k_\psi^{\mathrm{CD}} - k_\psi^\circ)K\}^{-1}[\beta - \mathrm{CD}]^{-1}. \qquad (2)\end{aligned}$$

Here, α is 0.11, the fraction of amine groups substituted by β-CD in PAA. The term $k_{2,\mathrm{PAA}}$ denotes the second-order rate constant of the uncomplexed substrate with the amine group of PAA-β-CD and is assumed to be 1.1 M^{-1} s^{-1} which was obtained with underivatized PAA. The complex formation constant (K) of the substrates with the β-CD moiety of PAA-β-CD and the first-order rate constant of the inclusion complexes (k_ψ^{CD}) are evaluated by analyzing the experimental data of Figure 4 according to Equation (2). The results are included in Table I.

The catalytic activity of β-CD bonded to PAA is much greater than that of native β-CD and other simply modified β-CD. This can be attributed to the greater nucleophilic character of amine groups and the deacylation may proceed mainly via attack of amine groups to the substrate encased in the β-CD cavity. In a previous report [15], we showed that the reaction rate of the ester substrate used in this work is enhanced about 100 fold by the presence of ethylenediamine(en)- or diethylenetriamine(dien)-modified β-CD at the primary hydroxyl group. This was explained in terms of the nucleophilic attack of the amine group attached to β-CD to the substrate included in the β-CD moiety from the primary face. The reactivity of substrate/PAA-β-CD complexes is about twice of that of β-CD-en or β-CD-dien. This is an indication that the inclusion from the secondary face of the β-CD moiety of PAA-β-CD also leads to deacylation reaction by the attack of the amine groups of the polymer chain.

In conclusion, it was shown that the effects of modified β-CDs on the deacylation reaction of *p*-nitrophenyl α-methoxyphenylacetate are highly dependent on the

nature of the substituents of β-CD and the chirality of the substrate. The presence of the 6-O-α-D-glucosyl group gives little effects on the binding and catalytic properties of β-CD: the native β-CD shows large rate enhancement for the *R*-enantiomer but little effect on the rate of the *S*-enantiomer. The sulfated β-CD substantially enhances the reaction rates of both enantiomers, but no significant enantioselectivity is observed. Methylated β-CD **4** and carboxymethylated β-CD **5** stabilize the ester substrates and the binding constants of the substrate to these modified β-CD are greater than that to the native β-CD. The stabilization effect of **4** is much greater than that of **5**, but the binding constants of the substrates to **5** is greater than that to **4**. 2-Tri[2-(hydroxy)propyl]-β-CD **6** accelerates the reaction of the *R*-enantiomer but retards the reaction of the *S*-enantiomer exhibiting the enantioselectivity similar to that of the native β-CD. The deacylation reaction rate of the ester substrates included in the β-CD cavity of PAA-β-CD **7** is enhanced about 200-fold. The substrates inserted from the primary side as well as the secondary face undergo the reaction by attack of the amine groups where β-CD is attached and the distant amine groups on the polymer chain, respectively.

Acknowledgements

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