procedure[10]. To a heated solution of **5a** (1.00 g, 2.21 mmol) in acetic anhydride (30 mL), was added a drop of conc sulfuric acid and the mixture was refluxed for 1 h. The reaction mixture was poured into 200 mL of ice water, and stirred for 3 h. The resulting precipitate was collected by filtration and recrystallized from chloroform and methanol to afford 1.00 g (84%) of the desired product.

25,27-Diactoxy-26,28-dipropyloxycalix[4]arene 6b. yield 77%; mp. 226-227°C; IR (KBr) 1756 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 6.95 (d, 4, ArH, J=7.5 Hz), 6.77 (t, 2, ArH, J=7.5 Hz), 6.70 (s, 6, ArH), 4.10 (d, 4, CH_2, J=13 Hz), 3.89 (t, 4, OCH_2, J=8.1 Hz), 3.27 (d, 4, CH_2, J=13 Hz), 2.59 (s, 6, $COCH_3$), 1.96 (sextet, 4, CH_2, J=7.2 & 8.1 Hz), 0.99 (t, 6, CH_3, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 170.66 (C=O), 155.91, 146.32, 134.90, 133.92, 129.13, 128.01, 125.19, 123.08 (Ar), 77.24 (OCH_2), 30.57 ($ArCH_2Ar$), 21.56 (CH_2), 9.83 (CH_3).

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Large Acceleration Effects of Mono-6-(alkylamino)-β-cyclodextrins on the Cleavage of *p*-Nitrophenyl α-Methoxyphenylacetate

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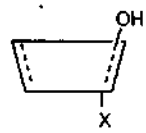
Kinetic studies of the deacylation reactions of *p*- and *m*-nitrophenyl esters of (*R* or *S*)-α-methoxyphenylacetic acid were performed in β-CD, mono-6-deoxy-6-[*N*-(2-aminoethyl)]amino-β-CD (β-CDen) and mono-6-deoxy-6-[*N*-(2-aminoethyl)-2-aminoethyl]amino-β-CD (β-CDdien) media. The binding constants (K) of the substrates to the hosts and the rate constants (k_ψ^{CD}) for the complexed substrates were determined. k_ψ^{CD} values are highly dependent on the hosts and the substrates, whereas differences in K values among them are modest. The *p*-nitrophenyl esters show larger acceleration by β-CDen and β-CDdien than the corresponding *m*-isomers, while the *m*-isomers are more reactive than the *p*-isomers in β-CD media. This is taken as an indication that the amino groups attached to the primary side of β-CD participate in the deacylation reaction.

Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides composed of six or more α-1,4-linked D-glucopyranose units and possess hydrophobic cavities. They have attracted great interest as enzyme mimics because CDs form inclusion complexes with a variety of substrates and exhibit large catalytic activity for many kinds of reactions.[1] The cleavage of aryl esters in basic solution is the most widely investigated of such CD-catalyzed reactions. Bender and his coworkers established that the cleavage of the ester within an inclusion complex takes places by acyl transfer from the ester to a hydroxyl group of the cyclodextrin.[2] It has also been shown that the catalytic effects of CDs on the ester cleavage is greater for *meta*-substituted aryl esters than for *para*-substituted ones.[2-5] CD cavity has a chiral environment and induces stereoselective reactions for complexed substrates.[1] Enantiomeric selectivities have been found in the deacylation of complexed optically active esters.[3,5,6] To improve catalytic activity and enantioselectivity, modified CDs have been extensively used.[3,7-10]

We have been interested in functionalized β-CDs and have shown that there are differences in reactivity and enantioselectivity among functionalized β-CDs.[11] We now report the kinetic studies of the deacylation reactions of *p*- and *m*-nitrophenyl esters of (*R* or *S*)-α-methoxyphenylacetic acid in mono-6-deoxy-6-[*N*-(2-aminoethyl)]-amino-β-CD (β-CDen) and mono-6-deoxy-6-[*N*-(2-aminoethyl)-2-aminoethyl]amino-β-CD (β-CDdien) media, which showed larger acceleration for the *p*-isomers than for the *m*-isomers. The binding constants (*K*) of the substrates to the hosts and the rate constants (k_ψ^{CD}) for the complexed substrates are determined, and their differences between enantiomeric pairs and between *m*- and *p*-isomers are discussed.



1: β-CD, X = OH

2: β-CDen, X = $NHCH_2CH_2NH_2$

3: β-CDdien, X= $NHCH_2CH_2NHCH_2CH_2NH_2$

1-3

$C_6H_5CH(OMe)COOAr$

4: Ar = p-nirophenyl

5: Ar = m-nitrophenyl

4,5

Experimental

Materials. β-CDen **2** and β-CDdien **3** were prepared by reacting primary monotosylate of β-CD with ethylenediamine or diethylenetriamine under N_2 atmosphere.[11c] *p*-Nitrophenyl ester **4** and *m*-nitrophenyl ester **5** of (*R* or *S*)-α-methoxyphenylacetic acid were obtained from optically active mandelic acid (Aldrich) as described in the literature.[5,12]

Kinetic studies. Deacylation reactions of the nitrophenyl esters were initiated by adding 20 μl of 0.01 M solution of *p*-nitrophenyl ester or 20 μl of 0.02 M solution of *m*-nitrophenyl ester in acetonitrile to 2.00 ml of the host (β-CD, β-CDen, or β-CDdien) solutions (0-10 mM) in 0.2 M pH 8.0 borate buffer in a cuvette preequilibrated at 25℃. The appearance of *p*-nitrophenol and *m*-nitrophenol was monitored at 400 nm and 380 nm, respectively, using a Varian Cary 3 spectrophotometer equipped with a thermostatically controlled cell holder.

Results and Discussion

The kinetic measurements were carried out by monitoring the appearance of the nitrophenol. The reactions obeyed pseudo-first-order kinetics with respect to the ester, regardless of the presence of β-CDs, and the observed first-order rate constants, k_ψ, were determined in the absence (k_ψ^o) and in the presence of various concentrations (1-10 mM) of the hosts.

Figure 1 and 2 show variation of k_ψ for the deacylation reaction of *p*-nitrophenyl ester **4** and *m*-nitrophenyl ester **5** of (*R*)- or (*S*)-α-methoxyphenylacetic acid depending on the concentration of β-CDs, respectively. Except for the case of *p*-nitrophenyl (*S*)-α-methoxyphenylacetate **4***S* in the presence of β-CD, the rate constants get larger with the increased concentration of the hosts. The rate increase is the largest by β-CDen and the smallest by β-CD for the deacylation

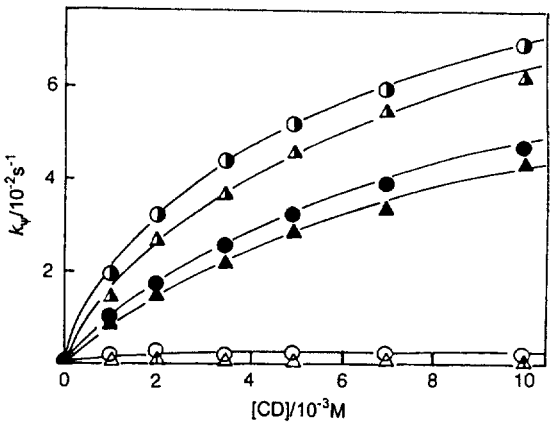


Figure 1. Effects of the concentration of β-CD (○, △), β-CDen (◑, ▲), and β-CDdien (●, ▲) on the observed pseudo-first order rate constants of the decaylation reaction of 4*R* (circles) and 4*S* (triangles).

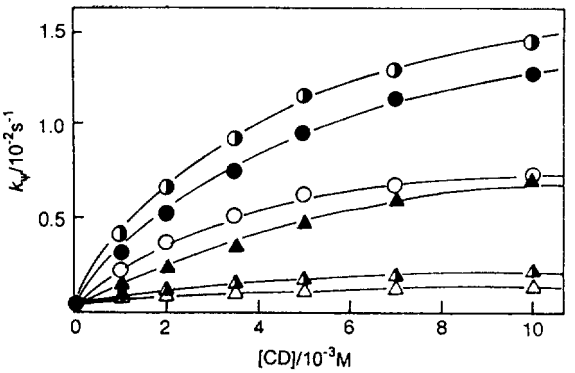


Figure 2. Effects of the concentration of the host on the observed pseudo-first order rate constants of the deacylation reaction of 5*R* and 5*S*. See Figure 1 for legends.

reaction of 4*R*, 4*S*, and 5*R*. In case of 5*S*, β-CDdien gives the most significant effect and β-CD does the least. The effect of β-CDen and β-CDdien is larger for the *p*-nitrophenyl esters **4** than for the *m*-nitrophenyl esters **5**, whereas β-CD has larger effects on **4** than on **5**. The latter observation agrees well with the reported works.[2-5]

To examine whether the rate increases observed in the presence of β-CDen and β-CDdien for the cleavage of the aryl esters are caused directly by the amines themselves rather than by the β-CD derivatives, we measured the rate constants in the presence of various combinations of the amines and β-CD. The results are given in Table 1. Table 1 indicate clearly that the great acceleration effects on the deacylation reactions by the polyamine-functionalized β-CDs are not merely the effects of the amines themselves. The amines alone do not have significant effects on the reaction rate. It is also noteworthy that the acceleration effect of β-CD alone is larger than those of the equimolar mixtures of β-CD and the amines. This seems to be arised from less or improper binding of the ester to β-CD since the amines and the ester might compete for the binding site of β-CD.

The effects of CDs on k_ψ are explained in terms of diffe-

Table 1. The pseudo-first-order rate constants (k_ψ) for the deacylation reaction of **5***R* in pH 8.0, 0.20 M borate buffer at 25℃ under various conditions

Reaction Media	$k_\psi \times 10^4/s^{-1}$
no additional reagents	3.3
0.01 M ethylenediamine (en)	6.1
0.01 M en+0.01 M β-CD	12
0.01 M diethylenetriamine (dien)	5.7
0.01 M dien+0.01 M β-CD	7.8
0.01 M β-CD	72
0.01 M β-CDen	150
0.01 M β-CDdien	130

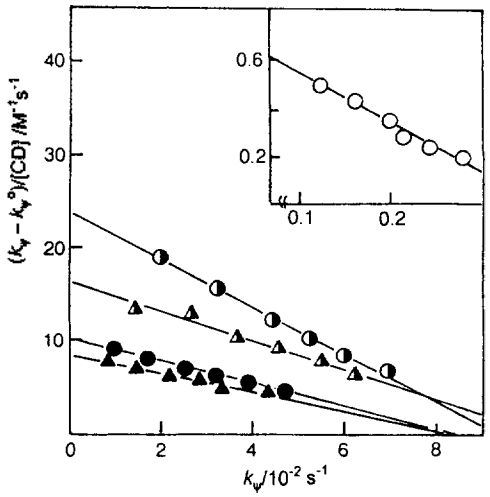


Figure 3. Plot of data of Figure 1 according to Eqn. (1). See Figure 1 for legends.

rent reaction rates for free and CD-complexed esters as shown in Scheme 1: we assume 1 : 1 complexation.[4-6,11]

The observed k_ψ is related with K, k_ψ^o, k_ψ^{CD}, and the concentration of CD by Eqn. (1).[2a]

$$(k_\psi - k_\psi^o)/[CD] = -Kk_\psi + Kk_\psi^{CD} \quad (1)$$

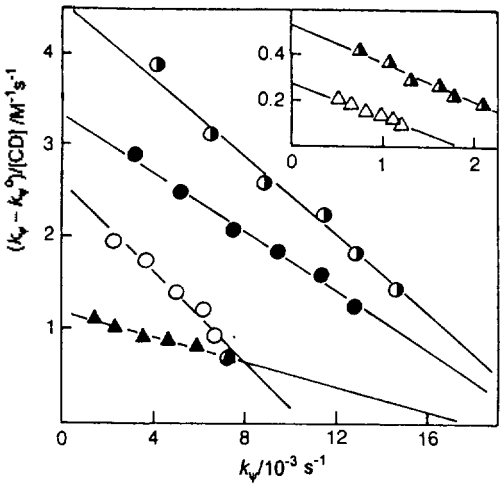
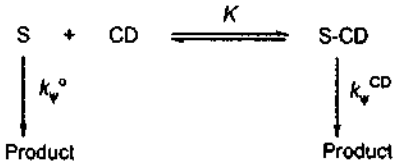


Figure 4. Plot of data of Figure 2 according to Eqn. (1). See Figure 1 for legends.



Scheme 1.

Data in Figures 1 and 2 were plotted according to Eqn. (1) and the results are presented in Figures 3 and 4, respectively. Good linearities in Figures 3 and 4 clearly indicate that the esters indeed form 1 : 1 complexes with the host molecules and the kinetic model shown in Scheme 1 is relevant. The binding constant K of the substrate to the host and the rate constant k_ψ^{CD} for the complexed substrate were evaluated from the slopes and intercepts of the lines in the

Table 2. Kinetic Parameters and Binding Constants for the Deacylation Reactions of Nitrophenyl Esters of (*R* or *S*)-α-Methoxyphenylacetate in pH 8.0, 0.20 M borate buffer at 25℃ in the Presence of β-CDs

Host	Substrate	$k_\psi^{CD} \times 10^3/s^{-1}$	$(k_\psi^{CD}/k_\psi^o)^a$	K/M^{-1}	$(k_\psi^{CD})^R/(k_\psi^{CD})^S$
β-CD	4*R*	3.7	5.0	210	*--b*
β-CD	4*S*	*--b*	*--b*	*--b*	
β-CDen	4*R*	95	130	250	0.9
β-CDen	4*S*	100	140	160	
β-CDdien	4*R*	85	110	120	1.0
β-CDdien	4*S*	84	110	100	
β-CD	5*R*	11	32	240	5.9
β-CD	5*S*	1.8	5.5	160	
β-CDen	5*R*	21	64	220	7.1
β-CDen	5*S*	3.0	9.0	190	
β-CDdien	5*R*	21	65	160	1.2
β-CDdien	5*S*	18	55	62	

[a] k_ψ^o was 7.4×10^{-4} s^{-1} for **4** and 3.3×10^{-4} s^{-1} for **5**; [b] No appreciable effect of β-CD on the rate was observed upon the addition of β-CD up to 10 mM.

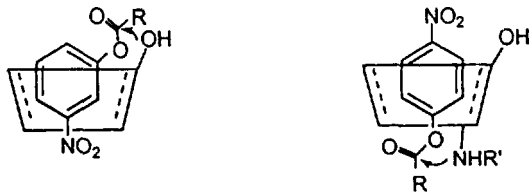
figures, and are summarized in Table 2.

Table 2 shows that the rate constants (k_ψ^{CD}) of the CD-complexes are highly dependent on the host and the substrate. The k_ψ^{CD} values of β-CDen and β-CDdien complexes of the *p*-isomers **4** are more than 20 times greater than that of β-CD complexes, while the corresponding values for the *m*-isomers **5** are about twice greater for β-CDen and β-CDdien complex than for β-CD complex: an exception to the latter is 5*S* of which β-CDdien complex reacts ten times faster than β-CD complex. On the other hand, differences in the binding constants among the substrates and the hosts are modest. These results indicate that the greater acceleration effects shown in Figures 1 and 2 on the deacylation reations of **4** and **5** by the polyamine-functionalized β-CDs than the native β-CD arise primarily from the greater reactivity of the complexes between the esters and the modified β-CDs, rather than the larger binding constants.

It has been known that *meta*-substituted phenyl esters show larger acceleration by cyclodextrin than the corresponding *para*-compounds.[2-5] Our results with β-CD agree well with the general trend. However, the '*meta*' selectivity is reversed in β-CDen and β-CDdien: the *p*-isomers **4** were more reactive than the *m*-isomers **5** in β-CDen and β-CDdien. A possible explanation for this is that the amino group attached to the primary side of β-CD can also participate in the deacylation reaction of the *para*-isomers **4**. It has been reported that the amino groups present on a β-CD derivative, β-CD covalently attached to poly (ethylenimine), act as the nucleophile instead of the hydroxyl group on the CD rim.[8]

The '*meta*' selectivity observed with nitrophenyl α-methoxyphenylacetate in native β-CD indicates that the esters **4** and **5** react via the complex with the nitrophenyl group rather than the phenyl group inserted into the β-CD cavity.[5] VanEtten *et al.*[2] showed that if the *m*-substituent of *m*-aryl acetate is inserted into the β-CD cavity from the secondary hydroxyl side (mode A), the ester function is positioned in close proximity to the secondary hydroxyl groups, whereas if the *p*-substituent of *p*-isomer is inserted first into the secondary side, then the ester function is located at a considerable distance from the hydroxyl groups. For *p*-isomer, *p*-substituent can be included into the cavity from the primary hydroxyl side (mode B), while this cannot be done for the *m*-isomer. In this mode B, the ester function is located in close proximity to the unreactive primary hydroxyl groups of β-CD. This accounts for the '*meta*' selectivity.[2] In case of the polyamine-functionalized β-CDs, the insertion mode B would result in positioning the ester function very close to the amine groups. More nucleophilic amino groups than the hydroxyl groups attack readily the carbonyl carbon of the ester, causing large acceleration in the cleavage of *p*-isomer by β-CDen and β-CDdien. This explains the higher reactivity for *p*-isomer than *m*-isomer in β-CDen or β-CDdien-containing media, in contrast to the '*meta*' selectivity by native β-CD. Schematic representation of the inclusion complexes with the probable modes of the reaction is shown in Scheme 2.

Very high enantioselectivity in favor of the *R*-enantiomer has been observed for the two enantiomeric pairs of **4** and **5** in β-CD: the enantioselectivity factor expressed as $(k_\psi^{CD})^R/(k_\psi^{CD})^S$ value was reported to be 7.9 for **4** at pH 10.5 and 5.4 for **5** at pH 9.5.[5] In our experimental conditions at pH 8.0, the value for **4** could not be determined due to the insignificant effect of β-CD on **4***S*, but is obviously large. Our value (5.9) for **5** at pH 8.0 is slightly larger than the reported one. In the presence of β-CDen, the enantioselectivity gets higher for **5**, but becomes insignificant for **4**. Since the upper (secondary hydroxyl) side of the β-CD cavity is more open than its bottom (primary hydroxyl) side, -CH-PhOMe group could be partially included into the cavity or in close proximity to the β-CD rim in the case of mode A insertion, while the chiral group would stay outside of the cavity in mode B insertion. Prevailing participation of mode B shown in Scheme 2 in the deacylation reaction of **4** seems to be responsible for diminution of the enantioselectivity in the polyamine-functionalized β-CD.



A B

Scheme 2. Schematic representation of inclusion complexes of nitrophenyl α-methoxyphenylacetates with β-CDs. The arrows indicate the nucleophilic interaction between the carbonyl carbon atom of the substrate and the C-2 oxido group (A) or amino group (B) present on the β-CDs.

In conclusion, this paper describes that the catalytic and enantioselective effects of β-CDs on the deacylation reactions of chiral esters are highly dependent on the structure and/or configuration of the hosts and substrates. The amino group attached to the primary side of β-CD participates in the deacylation reaction. This accelerates the rate, but decreases the enantioselectivity for the cleavage of the *p*-isomers **4** in the presence of β-CDen or β-CDdien.

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