Reactivity and Enantioselectivity in the Cleavage of Chiral Esters in the Presence of Native and Chiral Group-Appended β-Cyclodextrins

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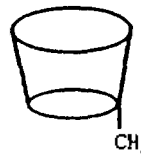
Cyclodextrins (CDs) and their derivatives have attracted great attention as enzyme mimics because of their ability to form inclusion complexes with substrates in their cavities.[1-3] It is well known that cyclodextrins can accelerate many kinds of reactions: deacylation of phenyl esters is one of the most precisely and extensively studied systems of the cyclodextrin-accelerated reactions, and the mode of action has been clearly established by Bender and his coworkers.[4] Also, enantiomeric selectivity has been found in the deacylation of optically active esters in accord with the chiral environment provided by the CD cavity.[5-7]

We have been interested in functionalization of β-cyclodextrin (β-CD), and have shown that there are large differences in the binding affinity among functionalized β-CDs.[8] We now report the preparation of mono-6-deoxy-6-(1-carboxy-1-phenylmethylamino)-β-cyclodextrins (CDPG: CD-*R*-PG or CD-*S*-PG) and kinetic analysis of the hydrolytic cleavage of enantiomeric pair of *p*-nitrophenyl α-methoxyphenylacetate. CDPG has an additional chiral center, and is expected to affect the binding of the chiral esters and the enantioselectivity for the reaction of the chiral esters.

CD-*R*-PG (**2**) and CD-*S*-PG (**3**) were prepared by treating mono-6-deoxy-6-iodo-β-cyclodextrin[9] with (*R*)- and (*S*)-phenylglycine (Aldrich), respectively, in dry N,N-dimethylformamide at 110℃ for 24 h.[10] *p*-Nitrophenyl (*R*)- or (*S*)-α-methoxyphenylacetate (**4**) was obtained from optically active mandelic acid (Aldrich) as described in the literature.[11]



1 : β-CD, X=OH
2 : CD-*R*-PG, X=−NH−CHPhCOOH (*R*)
3 : CD-*S*-PG, X=−NH−CHPhCOOH (*S*)

Rate measurements were carried out by monitoring the formation of *p*-nitrophenol at 420 nm. Reactions were carried out in 1 : 4 mixture of 0.015 M pH 7.4 aqueous phosphate buffer and DMSO:[12] the concentration of the ester was 1.0×10^{-4} M. The reaction obeyed pseudo-first-order kinetics with respect to the ester regardless of the presence of the hosts, and the first-order rate constants were determined in the absence (k_ψ°) and in the presence of the hosts (k_ψ), using 5 different host concentrations from 1.0×10^{-3} M to 7.0×10^{-3} M.

Figure 1 shows variation of k_ψ for the cleavage of *p*-nitrophenyl (*R*)-α-methoxyphenylacetate depending on the concentration of the hosts, *i.e.*, β-CD, CD-*R*-PG, or CD-*S*-PG: the rate constants get larger with the increased concentration of the hosts. The effects of host on k_ψ are explained in terms of different reaction rates for free and host-complexed ester

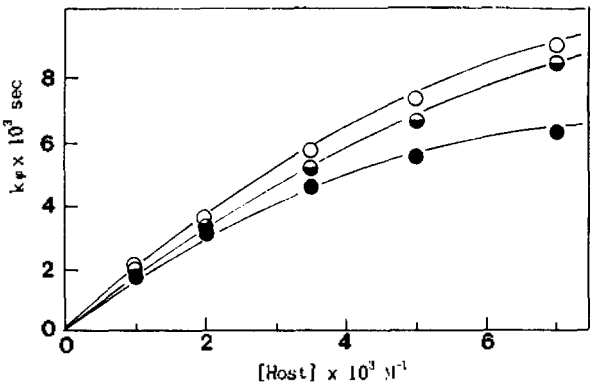


Figure 1. Dependence of apparent first-order rate constant (k_ψ) for the cleavage of *p*-nitrophenyl (*R*)-α-methoxyphenylacetate on [host]. Hosts are CD-*S*-PG (●), β-CD (◒), and CD-*R*-PG (○).

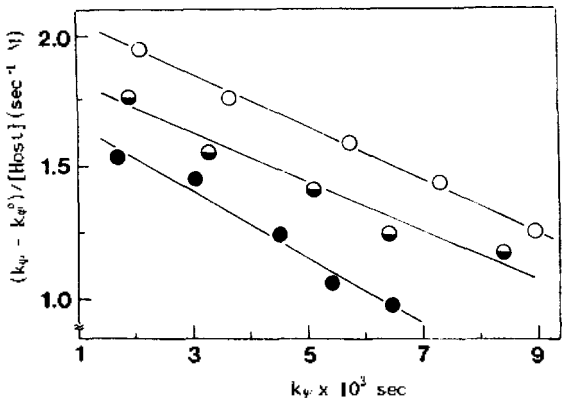
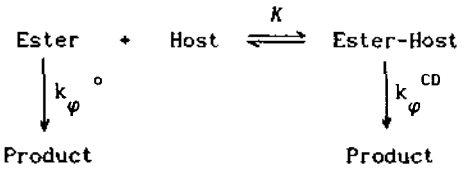


Figure 2. Plot of data of Figure 1 according to Eqn. (1). Hosts are CD-*S*-PG (●), β-CD (◒), and CD-*R*-PG (○).



Scheme 1.

as shown in Scheme 1: we assume 1 : 1 complexation.[5-7]

The apparent k_ψ determined at host concentration [host] is related with K, k_ψ° and k_ψ^{CD} by Eqn. (1):[4a]

$$(k_\psi - k_\psi^\circ)/[\text{host}] = -K k_\psi + K k_\psi^{CD} \quad (1)$$

Data in Figure 1 were analyzed according to Eqn. (1) and the results were presented in Figure 2. Good linearities in Figure 2 clearly indicate that the ester forms 1 : 1 complexes with CDPG as well as β-CD and the kinetic model shown in Scheme 1 is relevant. The binding constants K of the host-ester complex and the pseudo-first-order rate constants k_ψ^{CD} for the cleavage of the fully complexed ester were obtained from the slopes and intercepts of the lines in Figure 2, and summarized in Table 1. Parallel experiments were performed for the cleavage of *p*-nitrophenyl (*S*)-α-methoxyphenylacetate and the values are included in Table 1.

In Table 1, we also included the reported[7] K and k_ψ^{CD}/k_ψ°

Table 1. Kinetic Parameters for the Cleavage of *p*-Nitrophenyl (*R* or *S*)-α-Methoxyphenylacetate in the Presence of β-CD, CD-*R*-PG or CD-*S*-PG at 25℃

Host	Medium[a]	Ester config.	$(k_\psi^{CD}/k_\psi^{\circ})^b$	K/M^{-1}	$(k_\psi^{CD})_R/(k_\psi^{CD})_S$	$(k_\psi^{CD}K)_R/(k_\psi^{CD}K)_S$
β-CD[c]	A	*R*	14.1	330	7.9	12
		S	1.8	220		
β-CD	B	*R*	159	90	1.4	3.8
		S	111	34		
CD-*R*-PG	B	*R*	168	97	4.7	4.4
		S	36	102		
CD-*S*-PG	B	*R*	108	126	2.0	4.5
		S	53	57		

[a] A: 99% 0.020 M pH 10.5 carbonate buffer −1% CH_3CN; B: 1 : 4 mixture of 0.015 M pH 7.4 phosphate buffer and DMSO. [b] k_ψ°'s are 2.8×10^{-2} s^{-1} and 1.3×10^{-4} s^{-1} in medium A and medium B, respectively. [c] from ref. 7.

values obtained in 99% H_2O-1% CH_3CN media in the presence of β-CD. The *K* values obtained in this work (in 80% DMSO-20% H_2O) are much less than those determined in the mostly aqueous media, presumably due to the diminution of hydrophobic effect in the binding in the DMSO-rich solvent. However, $k_\psi^{CD}/k_\psi^{\circ}$, enhancement in the rate constant upon binding to host, is much greater in the present system.

The table shows that $k_\psi^{CD}/k_\psi^{\circ}$ is different for each enantiomeric ester and the enantioselectivity factor expressed as the ratio of the k_ψ^{CD} values for the two enantiomeric pairs is biggest in the presence of CD-*R*-PG (more than 3 times bigger than β-CD itself). With CD-*S*-PG, the enantioselectivity is slightly larger than with β-CD. This implies that the host with an additional chiral center exhibits enhanced enantioselectivity. On the other hand, the order of binding enantioselectivity is β-CD>CD-*S*-PG≫CD-*R*-PG. In the case of CD-*R*-PG, the binding enantioselectivity is close to zero. This reverse order in the values of k_ψ^{CD} and *K* makes the ratio $(k_\psi^{CD}K)_R/(k_\psi^{CD}K)_S$, which is formally the second-order rate constant for the reaction between the substrate and the host, to be not much different among the hosts. The binding constants themselves are slightly bigger with CD-PG than with β-CD, probably due to the contribution of β-CD-appended phenyl group to hydrophobic interaction between the hosts and the substrate.

The faster reaction for the complexed *R*-enantiomer has been reported by Fornasier *et al.*[7] with other enantiomeric nitrophenyl carboxylic esters and with other β-cyclodextrin derivatives substituted on the bottom side such as **2** and **3**: they suggested that insertion of the nitrophenyl group rather than the phenyl group of the substrate **4** in the β-CD cavity prevails, and the *R*-enantiomer is better suited than the *S*-enantiomer for the interaction between the C-2 hydroxyl group and the carbonyl carbon of the substrate. The results of our work are in line with this.

In conclusion, binding of the chiral substrates **4** to β-CD itself in 80% DMSO-20% H_2O shows a large enantioselectivity, whereas the enantioselectivity of the reaction of the complexes in the same medium is small, in spite of largely enhanced reactivity upon the binding. Functionalization of β-CD with PG benefits enantioselectivity of the reaction, but sacrifices selectivity of binding. It is clear from this study that enantioselectivity of the reaction in the host-guest complex and binding of the guest with the host are highly dependent on the chirality of the appended group and solvent media employed. Synthesis of CD derivatives having other chiral groups on the bottom and/or upper side of CD, and kinetics and solvent effects for the deacylation reaction of various chiral esters are under investigation.

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