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HYDROLYSIS OF NITROPHENYL ESTERS CATALYZED BY MODIFIED CYCLODEXTRIN IN WATER POOLS IN REVERSED MICELLES

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Bis-trimethylammonio-β-cyclodextrin diiodide (2) solubilized in organic media, such as water-contained reversed micelles, catalyzed the hydrolysis of nitrophenyl esters with remarkable rate acceleration and/or substrate selectivity, due to the catalytic effect of the cyclodextrin and the micellar effects.

KEYWORDS —— nitrophenyl ester hydrolysis; sodium di-2-ethylhexyl sulfosuccinate; reversed micelle; bis-trimethylammonio-β-cyclodextrin; α-cyclodextrin

Biomimetic reactions using cyclodextrins1) or micellar systems2) have been studied extensively. The reactions in (normal) micellar systems have received much more attention than those in reversed micellar systems. Some reversed micelles, such as sodium di-2-ethylhexyl sulfosuccinate (AOT) in heptane, can solubilize large amounts of water in the micellar center, forming "water pools."3) The water pools provide a unique reaction field in the organic media.4) Cyclodextrins can include various organic guest molecules in the hydrophobic cavity in aqueous media as a result of hydrophobic interactions.1) Reactions using cyclodextrins have ben investigated exclusively in aqueous media, while little attention has been given to the reaction in organic media. We report here hydrolysis of nitrophenyl esters catalyzed by a modified β-cyclodextrin solubilized in water pools in reversed micellar systems, i.e. in organic media.

To increase the solubility of β-cyclodextrin in the water pools, bis-trimethylammonio-β-cyclodextrin diiodide (2)5) was prepared from the capped cyclodextrin (1)6) (Fig. 1). The modified cyclodextrin (2) was solubilized at 0.50 and 1.25 mM concentrations in 3% AOT-heptane solutions containing 1% and 3% water (RM1 and RM3), respectively, while β-cyclodextrin was not solubilized in the reversed micellar systems. The modified cyclodextrin (2) in the reversed micelles exists exclusively in the water pools because of the insolubility in the AOT-heptane solution. It sholud be noted that the (2) and α-cyclodextrin (α-CD) solubilized in the reversed micelles, i.e. in organic media, form the inclusion-complexes with hydrophobic guest molecules, such as nitrophenols.7)

Hydrolysis of p-nitrophenyl acetate (3a) in the reversed micellar system (RM3) was carried out in the absence or the presence of (2), α-CD,8) or tetramethylammonium iodide (TMAI) used as an electrostatically compound equivalent to (2). The reaction conditions and experimental results are shown in Table 1.

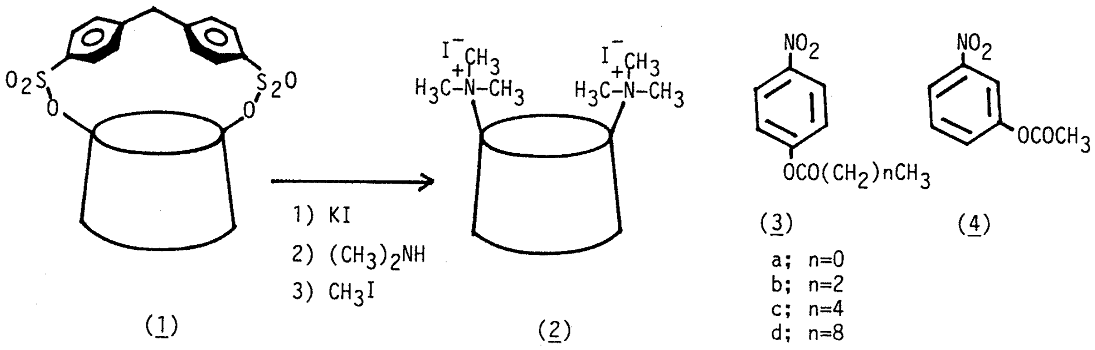

Fig. 1

In the presence of α-CD or TMAI, the relative rate acceleration (k_{obsd}/k_{un}) and the catalytic effect (k_{cat}) on the reactions were very low. In contrast, marked acceleration and high catalytic activity occurred in the presence of (2). In this case, the trimethylammonium groups of (2) may not behave as a catalytic group since no practical catalytic effect of TMAI was observed. The results mentioned above indicate that reactions catalyzed by a modified cyclodextrin, such as (2), are possible in organic media using water-contained reversed micellar systems as well as in aqueous media, with high catalytic activity.

In order to investigate the influences of the acyl chain length and the concentration of water in the reversed micelles, i.e. the size of water pools, the hydrolyses of phenyl esters (3a) - (3d) and (4) were examined in the reversed micellar systems and in aqueous buffer solutions. The experimental results shown in Table 2 and 3 indicate that i) in the absence or presence of (2), the relative reaction rates in the RM3 increased with decreasing carbon chain length of the acyl groups, due to partitioning of the substrates into water pools[4a)] (Table 2), but in aqueous solution, the rates were almost independent of the chain lengths (Table 3); ii) when the concentration of water in the reversed micelles decreased from 3% to 1%, marked acceleration was observed in the hydrolysis of (3a) and (4), i.e., the k_{obsd}/k_{un} was 650 and 2000 for (3a) and (4), respectively, although the rate constants (k_{obsd} or k_{un}) decreased (Table 2).

Hydrolysis of an equivalent mixture of (3a) and (3c) in the absence or presence of (2) in the RM3 system was examined. The results shown in Fig. 2 indicate that in the presence of the catalyst (2), substrate selectivity occurred; only (3a) was hydrolyzed over 98% in spite of the continued presence of (3c) after 60 min. This selectivity did not occur to any practical degree in the absence of (2).

Our experimental results indicate that in the reactions using modified cyclodextrins in reversed micellar system, distributions of substrates between the water pools and organic bulk phases, condensation effects of micelles on the substrate or catalyst (2), and/or the variation of physical property of water molecules in the pools[3)] play important roles in the rate acceleration or substrate selectivity.

Table 1. Observed Rate Constants and Catalytic Activities in the Hydrolysis of *p*-Nitrophenyl Acetate (3a) in the RM3 Systema)

Catalyst	Concentration of catalyst (mM)	k_{obsd}(min^{-1})x10^4	k_{obsd}/k_{un}	k_{cat}(min$^{-1}\cdot$M^{-1})b)
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(2)	0.50	290	58	58
α-CD	0.40	8.4	1.7	0.83
TMAI	1.35	6.6	1.3	0.11

a) All determinations were made at 40°C and 0.02 mM of (3a) in the RM3 system. The pseudo-first-order rate constants were determined by following the release of phenol spectrophotometrically. Each rate constant is the average of at least two determinations.

b) $k_{cat} = (k_{obsd} - k_{un})/[\mathrm{cat.}]$.

c) In the absence of catalyst (k_{un}).

Table 2. Observed Rate Constants in the Hydrolyses of *p*-Nitrophenyl Esters (3a)-(3d) and *m*-Nitrophenyl Acetate (4) in the RM1 and RM3 Systemsa)

Micellar system	Substrate	k_{un}(min^{-1})x10^4	k_{obsd}(min^{-1})x10^4	k_{obsd}/k_{un}
RM3	(3a)	5.1	580	110
	(3b)	0.19	14	72
	(3c)	0.057	0.83	15
	(3d)	0.038	0.15	3.9
	(4)	1.2	280	230
RM1	(3a)	0.02	13	650
	(4)	0.019	38	2000

a) All determinations were made at 40°C, 0.02 mM of (3) - (4), and 0.50 and 1.25 mM of catalyst (2) in the RM1 and RM3 systems, respectively.

Table 3. Observed Rate Constants in the Hydrolyses of *p*-Nitrophenyl Esters (3a)-(3c) in Carbonate Buffera)

Substrate	k_{un}	k_{obsd}(min^{-1})		k_{obsd}/k_{un}	
		(2)	α-CD	(2)	α-CD
(3a)	0.33	2.9	0.44	8.7	1.3
(3b)	0.19	2.1	0.22	11	1.2
(3c)	0.13	2.0	0.22	15	1.7

a) All determinations were made at 30°C, 0.02 mM of the substrates (3a) - (3c), and 1.0 mM of the catalysts (2) and α-CD in carbonate buffer (pH 10.4).

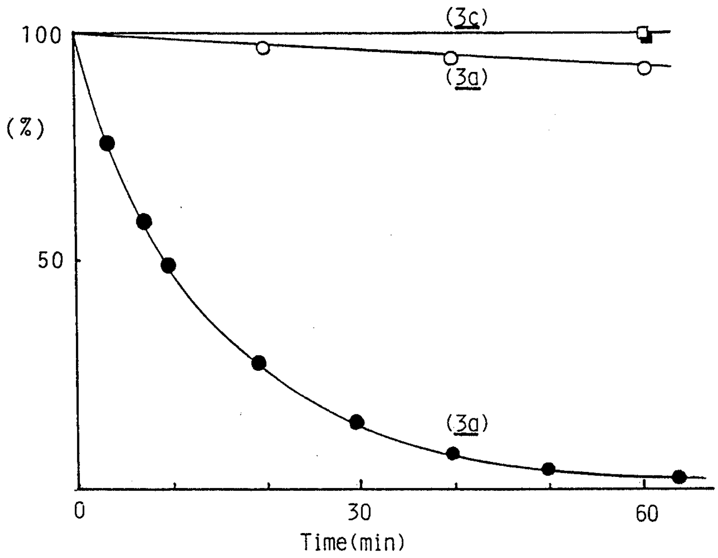

Fig. 2. Plots of Concentrations (%) of Substrates vs. Time for Hydrolysis of an Equivalent Mixtures of (3a) and (3c) (0.02 mM) -●-■- in the presence of (2) (1.25 mM), -○-□- in the absence of (2). The reactions were conducted at 40°C in the RM3 system and were followed by gas chromatography.

REFERENCES AND NOTES

1) a) M. L. Bender and M. Komiyama, "Cyclodextrin Chemistry," Spring-Verlag, (1978); b) I. Tabushi, Acc. Chem. Res., 15, 66 (1982).

2) a) L. H. Fendler and E. J. Fendler, "Catalysis in Micellar and Macromolecular Systems," Academic Press, New York, (1975); b) Y. Nakamura, Y. Imakura, T. Kato, and Y. Morita, J. Chem. Soc., Chem. Commun., 1977, 887; c) Y. Nakamura, T. Kato, and Y. Morita, Tetrahedron Letters, 1981, 1025.

3) M. Wong, J. K. Thomas, and T. Nowak, J. Am. Chem. Soc., 99, 4730 (1977).

4) a) F. Menger, J. A. Don-hue, and R. F. Williams, J. Am. Chem. Soc., 95, 286 (1973); b) J. Sumitomo, H. Kondo, and K. Akimaru, Chem. Lett., 1978, 821.

5) The modified cyclodextrin (2) showed correct elemental analysis.

6) I. Tabushi, Y. Kuroda, and A Mochizuki, J. Am. Chem. Soc., 102, 1152 (1980).

7) α-Cyclodextrin was solubilized at 0.40 mM concentration in the RM3 system. The UV absorption maximum of p-nitrophenol in the presence of (2) or α-CD in the reversed micellar systems shifted from 400 to 405 nm.1a)

8) As a reference compound of the modified CD (2), we used α-CD7) instead of β-CD because the latter was practically insoluble in the reversed micellar systems.

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