CHEMISTRY LETTERS, pp. 1251-1254, 1980. 

# GENERAL BASE CATALYSES BY α-CYCLODEXTRIN IN THE HYDROLYSES OF ALKYL BENZOATES

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The hydrolyses of seven alkyl benzoates are catalyzed by α-cyclodextrin. These results indicate that the general base catalysis by α-cyclodextrin, previously found for the first time in the hydrolysis of 2,2,2-trifluoroethyl 4-nitrobenzoate, is applicable to other alkyl esters.

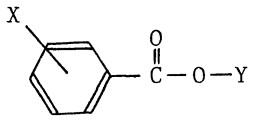
Recently the attention to the mechanisms of the catalyses by cyclodextrins has been increasing.[1)]

In the previous papers,[2,3)] the hydrolysis of 2,2,2-trifluoroethyl 4-nitrobenzoate was catalyzed by α-cyclodextrin. In the catalysis, the nucleophilicity of the oxygen atom of a water molecule to the substrate was enhanced by the partial abstraction of a proton from the water molecule by the secondary alkoxide ion of α-cyclodextrin. Since this was the first finding of the general base catalysis by cyclodextrins in the hydrolysis of an ester and was much different from the previous results on the cleavages of many esters showing either nucleophilic catalyses or retardations by cyclodextrins,[1)] it is important to determine whether the general base catalysis is restricted only to this substrate or not.

In the present paper, the applicability of the general base catalysis by α-cyclodextrin to other alkyl esters will be shown. The rate effects of α-cyclodextrin on the hydrolyses of seven alkyl benzoates, methyl 3-nitrobenzoate (1), methyl 4-nitrobenzoate (2), ethyl 3-nitrobenzoate (3), ethyl 4-nitrobenzoate (4), methyl 3,5-dinitrobenzoate (5), ethyl 3,5-dinitrobenzoate (6) and 2,2,2-trifluoroethyl 3-nitrobenzoate (7), are described.

The substrates 3-7 were synthesized from the corresponding acid chlorides and the alcohols; 3, mp 42.0-42.2°C (lit.[4)] 42°C) ; 4, mp 56.5-56.8°C (lit.[5)] 56.5-56.8°C) ; 5, mp 110.2-110.8°C (lit.[6)] 106.5-106.8°C) ; 6, mp 94.5-95.2°C (lit.[6)] 93.0-93.2°C) ; 7, mp 47.5-48°C. Anal. Found : C, 43.38% ; H, 2.44% ; N, 5.76%. Calcd for $C_9H_6F_3NO_4$ ; C, 43.38% ; H, 2.43% ; N, 5.62%. 1 and 2 were purchased from Tokyo Kasei Chem. Co. and

were purified by recrystallization.



1: X=3-$NO_2$ , Y=$CH_3$ ; 2: X=4-$NO_2$ , Y=$CH_3$
3: X=3-$NO_2$ , Y=$CH_2CH_3$ ; 4: X=4-$NO_2$ , Y=$CH_2CH_3$
5: X=3,5-$(NO_2)_2$ , Y=$CH_3$ ; 6: X=3,5-$(NO_2)_2$ , Y=$CH_2CH_3$
7: X=3-$NO_2$ , Y=$CH_2CF_3$ ; 8: X=4-$NO_2$ , Y=$CH_2CF_3$

The hydrolyses of 1-7 at 25°C, pH 11 were followed by the release of the benzoate ions by absorption spectroscopy. The rate constants of the hydrolyses of the substrates incorporated in the α-cyclodextrin complexes ($k_c$) and the equilibrium constants of the dissociation of the complexes ($K_d$) were determined by plotting $1/(k_{obs} - k_{un})$ vs $1/[C]_0$ according to eq 1 ;

$$1/(k_{obs} - k_{un}) = K_d/(k_c - k_{un}) \cdot 1/[C]_0 + 1/(k_c - k_{un}) \qquad (1)$$

where $k_{obs}$ and $k_{un}$ are the rate constants in the presence and the absence of α-cyclodextrin and $[C]_0$ is the initial concentration of α-cyclodextrin.

Table 1 shows the values of $k_c$ , $k_{un}$ and $K_d$ for the hydrolyses of 1-7 as well as those for the hydrolysis of 2,2,2-trifluoroethyl 4-nitrobenzoate (8). It was found that the hydrolyses of all 1-8 were accelerated by α-cyclodextrin. The magnitudes of the accelerations ($k_c/k_{un}$) by α-cyclodextrin of the hydrolyses of the meta-substituted benzoates (1 and 3) are larger than those of the hydrolyses of the corresponding para-benzoates (2 and 4), whereas the values for the hydrolyses of the 3,5-dinitrobenzoates 5 and 6 are between those for the corresponding meta-compounds (1 and 3) and those for the para-compounds (2 and 4). The hydrolyses of the trifluoroethyl esters 7 and 8 are accelerated in larger magnitudes than the hydrolyses of ethyl esters 3 and 4.

The logarithm of $k_c$ for 1-7 increased linearly with pH in the pH region 9.3-11.3 and the slope was unity. The slope, however, gradually decreased with pH above pH 11.3, showing a saturation around pH 12.5. These results indicate the participation of the secondary alkoxide ion of α-cyclodextrin, the pK of which is about 12[1)], in the catalyses.

Table 1 Values of $k_c$, $k_{un}$ and $K_d$ for the α-cyclodextrin-catalyzed hydrolyses of methyl 3-nitrobenzoate (1), methyl 4-nitrobenzoate (2), ethyl 3-nitrobenzoate (3), ethyl 4-nitrobenzoate (4), methyl 3,5-dinitrobenzoate (5), ethyl 3,5-dinitrobenzoate (6), 2,2,2-trifluoroethyl 3-nitrobenzoate (7) and 2,2,2-trifluoroethyl 4-nitrobenzoate (8) [a]

| Substrate | $k_c$ ($10^{-3}s^{-1}$) | $k_{un}$ ($10^{-3}s^{-1}$) | $k_c/k_{un}$ | $K_d$ ($10^{-2}$mol dm$^{-3}$) |
|---|---|---|---|---|
| 1 | 0.76 | 0.16 | 4.8 | 1.3 |
| 2 | 19 | 11 | 1.7 | 0.81 |
| 3 | 0.16 | 0.08 | 2.0 | 1.0 |
| 4 | 0.86 | 0.84 | 1.0 | |
| 5 | 16 | 7.9 | 2.0 | 6.6 |
| 6 | 5.7 | 3.5 | 1.6 | 1.1 |
| 7 | 28 | 13 | 2.2 | 1.6 |
| 8 [b] | 0.88 | 0.20 | 4.4 | 0.34 |

a. pH 11, 25°C otherwise noted.
b. pH 8.6, 16°C. Taken from ref. 3.

The $k_c$'s for all of 1-7 in $D_2O$ were 1.5±0.1 fold smaller than those in $H_2O$, after the correction for the difference of the dissociation constant of the secondary hydroxyl group of α-cyclodextrin in $D_2O$ from that in $H_2O$ (3.2 fold[1]) was made. The $D_2O$ solvent isotope effects for the α-cyclodextrin-catalyzed hydrolyses of 1-7 are almost identical with the value for the general base-catalyzed hydrolysis of 8 by α-cyclodextrin (1.7 fold[2]). Although these magnitudes of the $D_2O$ solvent isotope effects alone can not be the proofs for the general base catalyses, alternative mechanisms, alkaline hydrolyses assisted by α-cyclodextrin, which are kinetically indistinguishable from the general base catalyses, are unlikely, since they should show inverse $D_2O$ solvent isotope effects because of the larger nucleophilicity of $OD^-$ than $OH^-$.[7]

The nucleophilic catalyses by α-cyclodextrin were ruled out by the lack of the common ion effects. The additions of 0.2 mol dm$^{-3}$ methanol and 2,2,2-trifluoroethanol, respectively, showed little effects on the $k_c$'s for 1 and 8. If the reaction were proceeding via the nucleophilic catalysis, involving the reversible formation of the α-cyclodextrin ester of the benzoate as the intermediate, a significant decrease in the $k_c$ should be observed. In the hydroxide ion-assisted nucleophilic catalysis of the hydrolysis of 2,2,2-trifluoroethyl acetate by imidazole, the addition of 0.05 mol dm$^{-3}$ 2,2,2-trifluoroethanol showed virtually total inhibition of the reaction.[8]

The large magnitudes of the acceleration ($k_c/k_{un}$) for 1 and 8 are due to the shallow inclusions of these substrates in the cavity of α-cyclodextrin, resulting in the proper

orientations of the carbonyl carbon atoms for the general base catalyses by the secondary alkoxide ion of α-cyclodextrin. These conformations of the inclusion complexes are associated with the steric hindrance between the ester moiety of 1 and the wall of α-cyclodextrin for the α-cyclodextrin-1 complex and the polar property of the trifluoromethyl group of 8 for the α-cyclodextrin-8 complex.

The acceleration of the hydrolyses of 1-8 by α-cyclodextrin are in contrast with the deceleration of the hydrolyses of alkyl cinnamates by α-cyclodextrin[9] and of alkyl benzoates[9,10] and alkyl cinnamates[9] by β-cyclodextrin. The decelerations in the latter cases are attributable to the deep inclusions of the substrates in the cavity and/or the formation of the non-productive complex. In the non-productive complex in which the ester portions of the substrates are included in the cavity with the acyl portions protruding from the secondary hydroxyl side, the nucleophilic attack of the secondary alkoxide ion at the substrate should result in drastic strains in the chemical bonds.[11]

This work was partially supported by the Grant-in-Aid for Scientific Research from the Ministry of Education.

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(Received August 11, 1980)