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GENERAL BASE-CATALYZED HYDROLYSIS OF 2,2,2-TRIFLUOROETHYL 4-NITROBENZOATE BY α-CYCLODEXTRIN

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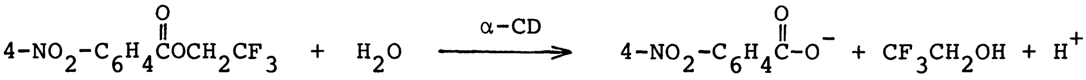
α-Cyclodextrin accelerated the hydrolysis of 2,2,2-trifluoroethyl 4-nitrobenzoate at pH 9.6, 20°C. Kinetic analyses and considerable D_2O solvent isotope effect (1.7 fold) showed that the reaction proceeds mostly through general base catalysis by α-cyclodextrin with minor contribution of nucleophilic catalysis. This is the first finding of general base catalysis of ester hydrolysis by cyclodextrin.

Recently much attention has been given to cyclodextrins (CDs), cyclic oligosaccharides composed of α-(1,4)-linkage of a number of glucopyranose units, as both a model of enzymes and useful chemical reagents.1) The most characteristic feature of the CD-accelerated reactions is the formation of inclusion complexes of substrates with CDs, which is followed by catalytic function of CDs.

Most of the CD-accelerated reactions so far examined proceed through a nucleophilic attack by the secondary hydroxyl anion of CD at the electrophilic center of the substrate included in the cavity of CD, resulting in the formation of a covalent intermediate.2) In the CD-accelerated hydrolyses of phenyl esters, for example, the formation of acyl-CD as intermediates was shown by spectroscopic analyses of reaction solutions.3) Furthermore, absence of measurable D_2O solvent isotope effect confirmed nucleophilic catalyses by CDs.4)

In spite of many examples of nucleophilic catalyses and an example of general acid catalysis5) by CDs, however, the report of general base catalyses by CDs has been scanty. The CD-accelerated cleavage of diaryl methylphosphonates, which involves some contribution of general base catalysis by CD in addition to nucleophilic catalysis by CD, is the only report on the general base catalysis by CD6) to the best knowledge of the authors. This communication will show that the α-CD-catalyzed hydrolysis of 2,2,2-trifluoroethyl 4-nitrobenzoate (1) proceeds overwhelmingly via general base catalysis by α-CD (eq. 1).



$$4\text{-}NO_2\text{-}C_6H_4\overset{\overset{O}{\|}}{C}OCH_2CF_3 + H_2O \xrightarrow{\alpha\text{-CD}} 4\text{-}NO_2\text{-}C_6H_4\overset{\overset{O}{\|}}{C}\text{-}O^- + CF_3CH_2OH + H^+ \quad \text{(eq. 1)}$$

(1)

Compound 1 was synthesized from 4-nitrobenzoyl chloride and 2,2,2-trifluoroethanol and was recrystallized from ethanol.[7)] Hydrolysis of 1 was carried out in bicarbonate buffer, I = 0.1 M (KCl), at 20°C, and was followed by the liberation of 4-nitrobenzoate ion at 296 nm. Reaction was initiated by the addition of 20 μl stock solution of 1 in acetonitrile to 3 ml buffer solution and the initial concentration of 1 was approximately 10^{-4} M. For D_2O experiments, pD was determined by using the equation : pD = pH meter reading + 0.4.[8)]

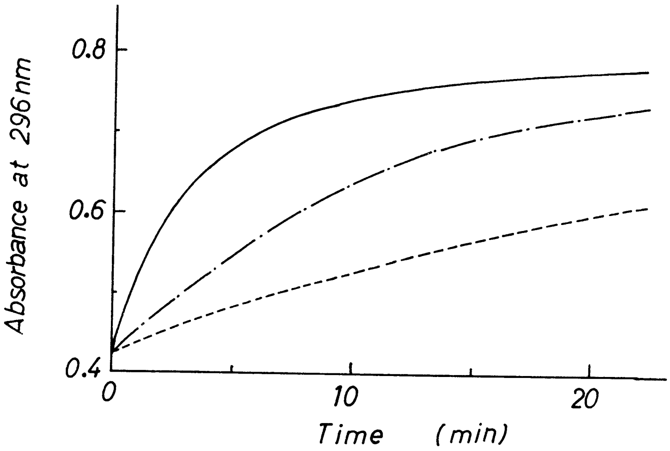


Fig. 1. Change of the absorbance at 296 nm in the hydrolysis of 1 at pH 9.6, I = 0.1 M, at 20°C ; the initial concentration of 1 is about 10^{-4} M. ; ——— in the presence of 0.05 M α-CD ; —·— in the absence of α-CD ; ------ the theoretical line showing the maximal contribution of the nucleophilic catalysis by α-CD (see the text.).

Fig. 1 shows the change of the absorbance at 296 nm in the presence and the absence of 0.05 M α-CD. Clearly 0.05 M α-CD exhibited a considerable (about 3 fold) acceleration of the hydrolysis of 1. Precise determination of the rate constant, however, was not successful, since the hydrolysis of 1 in the presence of α-CD did not follow the first-order kinetics, although the hydrolysis of 1 in its absence did.

The logarithm of the half-life of 1 in the presence of 0.05 M α-CD decreased linearly with pH and the slope was unity, which is equivalent to the linear increase of the rate of the hydrolysis of 1 in the presence of 0.05 M α-CD with pH (the slope unity). Thus, this result indicates the participation of a hydroxyl group (anionic) of α-CD in the catalysis.

β-Cyclodextrin, which has a larger cavity than α-CD, exhibited little acceleration of the hydrolysis of 1 in contrast to acceleration by α-CD.

Acceleration by α-CD (in large excess) did not increase linearly with the concentration of α-CD ([α-CD]), but the effect was gradual, indicating the complex formation of 1 with α-CD prior to the reaction. Rough estimation of the dissociation constant of this complex by using the dependence of the initial rate on [α-CD] gave the value of 0.005 M at pH 9.6. Thus, about 90% of 1 forms the complex with α-CD, when [α-CD] = 0.05 M.

Quite importantly, the rate of the hydrolysis of 1 in the presence of α-CD is much larger than that estimated for the reaction scheme involving the nucleophilic attack by α-CD. In this reaction scheme 4-nitrobenzoyl-α-CD is formed first (the rate constant k_1), followed by the hydrolysis of 4-nitrobenzoyl-α-CD (the rate constant k_2). k_2 under the reaction conditions was independently determined to be

3.1×10^{-2} $\min^{-1}$ by the measurement of the change of the absorbance at 260 nm (due to the liberation of 4-nitrobenzoate ion from 4-nitrobenzoyl-α-CD) in the α-CD-accelerated hydrolysis of 3-chlorophenyl 4-nitrobenzoate.9) The dotted line in Fig. 1 is the theoretical line calculated by using this value and taking k_1 as infinite, and thus shows the maximal contribution of nucleophilic catalysis by α-CD in this reaction. Furthermore, the accumulation of 4-nitrobenzoyl-α-CD, which should take place if the nucleophilic catalysis by α-CD were predominant and k_1 were much larger than k_2 , was not observed by the measurement of the absorbance at the isosbestic point of 1 and 4-nitrobenzoate ion, 276 nm. Consequently, the acceleration by α-CD should be mostly attributed to general base catalysis which does not show the formation of 4-nitrobenzoyl-α-CD.

The general base catalysis by α-CD was further confirmed by the observation of the considerable D_2O solvent isotope effect. The hydrolysis of 1 in the presence of 0.05 M α-CD in D_2O was found to be 1.7 fold10) slower than that in H_2O in the pH range 8.8-10.0, after the correction of the difference of the dissociation of the secondary hydroxyl groups of α-CD in D_2O from H_2O (3.2 fold11)). This is definitely a kinetic isotope effect and is not due to the difference of the dissociation constant of the inclusion complex in D_2O from that in H_2O, since most of 1 (about 90%) forms inclusion complex with α-CD in H_2O as well as in D_2O when [α-CD] = 0.05 M.

In the absence of CD, however, the hydrolysis of 1 in D_2O is 1.2 fold faster than that in H_2O, which is mostly attributable to larger nucleophilicity of OD^- than OH^-.12)

The deviation from the first-order kinetics in the presence of α-CD is due to the small contribution of the nucleophilic catalysis by α-CD to the overall reaction in addition to the general base catalysis by α-CD. This contribution, however, can not be larger than 20%, which was estimated from the change of the absorbance (at 296 nm) calculated for the maximal rate by the nucleophilic catalysis (the dotted line in Fig. 1) and the observed one (the solid line in Fig. 1).

The effect of CDs on the hydrolyses of esters drastically depends on the leaving groups of the substrates. Hydrolyses of phenyl esters1) and thiolesters,13) which have good leaving groups, are accelerated by nucleophilic catalyses by CDs, whereas the hydrolyses of alkyl esters,14) which have poor leaving groups, are retarded or sometimes totally inhibited by CDs. As shown in this communication, trifluoroethyl ester 1, which has a moderately good leaving group (the pK_a of 2,2,2-trifluoroethanol is 12.3715)), is accelerated by the general base catalysis by α-CD. However, the lack of the general base catalyses by CDs in the hydrolyses of alkyl esters, which effectively functions in the hydrolysis of 1, can not be explained only in terms of the difference of pK_a's of the leaving groups.16) Probably the structure of inclusion complexes, which governs the orientation and distance of the catalytically active secondary hydroxyl group(s) of CD with respect to the reactive center of the substrates, has also a large effect in determining what kind of catalysis by CD is predominant. Negligible catalysis of the hydrolysis of 1 by β-CD in contrast to an appreciable catalysis by α-CD supports the importance of the stereochemistry of inclusion complexes for catalysis, since α-CD and β-CD are different from each other only in the size of the cavity and should be similar in other chemical and physical properties.

In conclusion, the general base catalysis of ester hydrolysis by α-CD was found for the first time in the hydrolysis of 1. This finding can be a clue for the better understanding of the catalyses by CDs.

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References and Notes

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2) CDs catalyze decarboxylation and oxidation without the formation of the covalent intermediates. Catalyses by CDs in these reactions, however, should be assigned to a category different from that described in this paper, since CDs do not provide catalytic functional group(s) there but simply provide their cavities as apolar and sterically restricted reaction field (see ref. 1, chapter Vl.).
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10) This value was determined by use of the half-life of 1.
11) Ref. 1, p35.
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14) Ref. 1. All alkyl esters studied before have unactivated alcohols as the leaving groups.
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16) Plots of the rate constants of alkaline hydrolyses of alkyl esters vs. those of the general base-catalyzed hydrolyses by imidazole showed linearity and the slope was around unity (J. P. Kirsch and W. P. Jencks, J. Am. Chem. Soc., 86, 837 (1964)). This result infers that the rates of the general base-catalyzed hydrolyses by CDs depend on the leaving groups in a similar magnitude as those of alkaline hydrolyses do. Thus, consideration of pK_a's of the leaving groups alone indicates that general base catalysis by CD should be observed in the hydrolyses of alkyl esters as in the hydrolysis of 1. Obviously, it is not the case.

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