Inclusion Complex Formation and Hydrolysis of Lactones by Cyclodextrins

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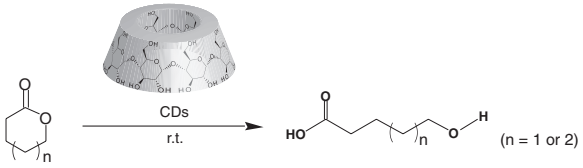
Cyclodextrins (CDs) have been found to form inclusion complexes with lactones in aqueous solutions and/or in the solid states; hydrolysis of lactones has been found to be suppressed or promoted by CDs according to the combination of lactones and CD.

In recent years, much attention has been focused on biodegradable polymers, such as poly(lactic acid) and poly(ε-caprolactone) from point of view of environmental protection.[1] Previously, we found and reported that CDs form inclusion complexes with some aliphatic polyesters, such as poly(ε-caprolactone)[2,3] and poly(1,4-butylene adipate).[4] Later, the others reported that some other polyesters are included in CDs.[5,6]

In the course of the studies on the complex formation between CDs and polyesters, we found that hydrolysis of the polyesters is accelerated by CDs. CDs are known to accelerate hydrolysis of activated esters, such as *p*-nitrophenyl esters. Accordingly, CDs have been studied as one of enzyme models for a long time.[7] However, there are few reports on hydrolysis of alkyl esters by CDs. Therefore, we have decided to study inclusion complex formation of lactones (cyclic esters), which are the starting monomers of above mentioned polyesters, with CDs and hydrolysis of these lactones by CDs. We have prepared inclusion complexes of cyclodextrins with some lactones, and tested their hydrolysis with CDs. We found that the hydrolysis of some lactones has been promoted or retarded by CDs. Now we report here that β-CD promoted hydrolysis of ε-caprolactone (ε-CL) and α-CD suppressed its hydrolysis, although γ-CD has no effects. In addition, β-cyclodextrin suppressed hydrolysis of δ-valerolactone (δ-VL) strongly, although α-CD did not show any effects on hydrolysis of this lactone (Eq 1).



(1)

When ε-caprolactone was added onto saturated aqueous solution of α-CD, the solution became turbid and crystalline complexes were formed. When the lactone was added onto β-CD solution, some crystalline complexes were also obtained, although γ-CD did not give any complexes with this lactone at all. Figure 1 shows the ^{1}H NMR spectra of ε-caprolactone in the absence and presence of CDs in D_2O solutions at room temperature. Although γ-CD showed small effects on the ^{1}H NMR spectrum of lactone, the methylene peaks of the lactone shifted toward lower magnetic fields on addition of β-CD and α-CD. The spectral changes are even larger by β-CD than α-CD. These results indicate that ε-CL is included in both α-CD and β-CD, and β-CD is more favorable for binding the lactone than α-CD.

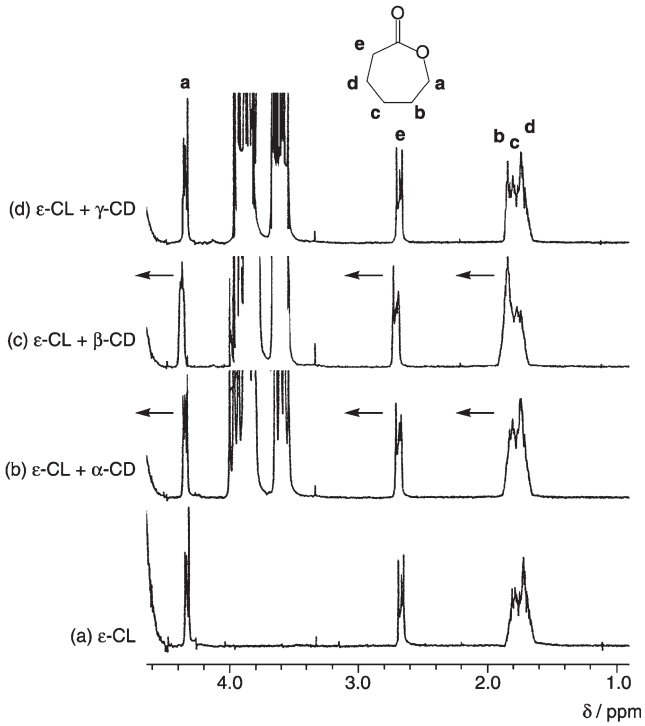


Figure 1. 400 MHz ^{1}H NMR spectra of ε-caprolactone in the absence (a) and presence of α-CD (b), β-CD (c), and γ-CD (d) in D_2O. [ε-CL] = 9.3 mM, [CD] = 11.7 mM.

While we have been measuring the ^{1}H NMR spectra of lactones in the presence of CDs, we found that the spectra changed with time. The time changes are different from each other between α-CD and β-CD. These differences have been found to be due to hydrolysis of lactones to hydroxycarboxylic acids. Figures 2 and 3 show the degree of hydrolysis of ε-CL and δ-valerolactone with various CDs as a function of time. The degree of hydrolysis was determined by the sum of integrated values of methylene proton adjacent to carbonyl carbon. When ε-CL was added onto dilute aqueous solutions of α-CD, the hydrolysis of ε-CL has been suppressed. When β-CD was used, the hydrolysis was facilitated, although γ-CD did not show any effects (Figure 2).

Although γ-CD did not show any effects, α-CD retarded hydrolysis of δ-valerolactone and β-CD suppressed its hydrolysis strongly.

The differences between the results with ε-caprolactone and those by δ-valerolactone are due to the differences between the relative sizes of CDs and the lactones. δ-Valerolactone might fit well in the α-CD and β-CD cavities so as to block the carbonyl group of the ester. ε-caprolactone and δ-valerolactone is included in the γ-CD cavity so as to susceptible to attack by base or acids.

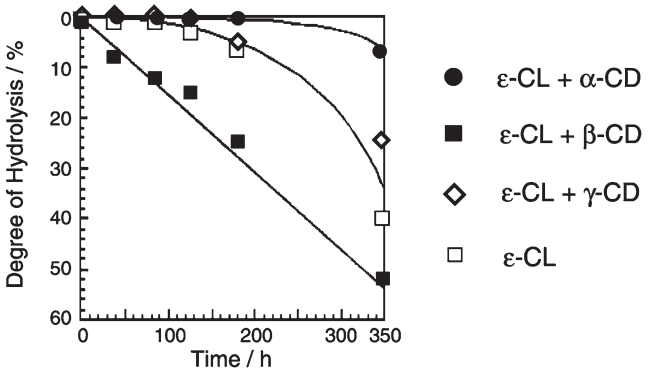


Figure 2. Degree of hydrolysis of ε-caprolactone as a function of time (hour) at room temperature. [ε-CL] = 9.3 mM, [CD] = 11.7 mM.

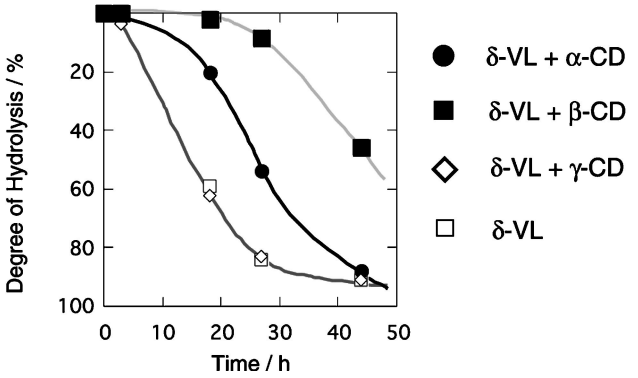


Figure 3. Degree of hydrolysis of δ-valerolactone as a function of time (hour) at room temperature. [δ-VL] = [CD] = 16.0 mM.

CDs did not show any effects on the hydrolysis of γ-butyrolactone. γ-Butyrolactone is even smaller than ε-caprolactone and δ-valerolactone, which can be included in CDs. However, γ-butyrolactone is stable in aqueous solutions.

Hydrolysis of activated esters, such as *p*-nitrophenyl esters, is accelerated by cyclodextrins. In this case, the secondary hydroxy groups of cyclodextrins were found to ionize under basic conditions and to function as nucleophiles. As a result, acyl groups of the activated esters were found to transfer to the hydroxy groups of cyclodextrins. Acylated cyclodextrins have been isolated. In the case of lactone hydrolysis, we could not isolate acylated cyclodextrins. In addition, these reactions were performed under neutral conditions. Hydroxy groups of cyclodextrins do not ionize under these conditions.

There are a few studies on the hydrolysis of oxazolines. However, to our knowledge, there are no reports on the hydrolysis of lactones by cyclodextrins. ε-Caprolactone is supposed to be included in α-CD tightly, so that the carbonyl groups of the ester buried into the CD cavity are not susceptible to general acids or base. In contrast, ε-caprolactone is included in the β-CD cavity, in such a way that ester carbonyl groups are susceptible to be attacked by acid or base. The structures of the complexes and mechanism of the hydrolysis are now under investigations.

References

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