mixture was recrystallized from ethanol, m.p. 150°, mixed melting point with compound IV, 150°. Infrared spectrum, of this product was identical with IV.

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Keyphrases

Synthesis of 3-substituted benzoexazolinones
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Influence of Cyclodextrins on Ester Hydrolysis

By TING-FONG CHIN, PING-HONG CHUNG, and JOHN L. LACH

The hydrolysis of various ethyl esters of aminobenzoic acids, acetylsalicylic acid, and atropine in alkaline solution was shown to be either accelerated or decelerated in the presence of α and β-cyclodextrin. It is also shown that the stereochemistry of binding and the degree of ionization of cyclodextrin are primarily responsible for these catalytic and inhibitory effects observed.

THE FACT that the cycloamyloses (cyclodextrins) are capable of forming inclusion complexes with various compounds in solution especially with molecules containing aliphatic and aromatic groups has been known for some time and was recently reviewed by Thoma and Stewart (1). Although this aspect of inclusion formation has received considerable study, the present interest in cycloamylose chemistry has been in the kinetic aspect, since these cycloamyloses or cyclodextrins also have been shown to impose both rate accelerations and decelerations on various organic reactions.

Cramer and co-workers (2–4) have studied the cyclodextrin catalyzed decarboxylation of various organic acids and the fission of pyrophosphate. With respect to carboxylic acids, Cramer assumes that the carboxylic acids, after inclusion in the cavity of cyclodextrin, are activated by nucleophilic attack of the ether and hydroxyl O atoms at the carboxyl C atom and that their decarboxylation is consequently accelerated.

Bender and co-workers (5–8) reported that the cyclodextrins accelerated the hydrolysis of the various esters studied and that the accelerations are often large and are markedly substituent dependent. They also stated that this acceleration effect was due primarily to nucleophilic attack on the included ester by alkoxide ion of the cyclodextrin.

Lach and Chin (9) in their study dealing with hydrolysis of ethyl *p*-aminobenzoate in the presence of cyclodextrin, on the other hand, reported a deceleration effect. They attributed this deceleration in rate to a complete occlusion of the total ester in the void space of the cyclodextrin molecule and therefore shielding the ester linkage from hydroxyl ion attack and from alkoxide ion attack in the cyclodextrin molecules. They also stated that in this system the hydrolysis is due only to the free ester in solution resulting from the dissociation of the inclusion

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complex. Such a mechanism, however, cannot be applied to a reaction which exhibits a catalytic effect in that both the complexed ester and free ester in solution undergo hydrolysis. Since no detailed kinetic data or mathematic expressions have been reported dealing with this acceleration and deceleration reaction, the present study was undertaken in order that these two different mechanisms be better understood. Acetylsalicylic acid and the various ethyl esters of aminobenzoic acids were studied with respect to this cyclodextrin effect in alkaline solution.

EXPERIMENTAL

Reagents—Ethyl - *p* - aminobenzoate, recrystallized, m.p. 87–88°; ethyl-*o*-aminobenzoate, b.p. 266–268°; ethyl-*m*-aminobenzoate, b.p. 292–294°; acetylsalicylic acid, recrystallized, m.p. 135°; atropine, recrystallized, m.p. 114–115°; α-cyclodextrin, $[\alpha]_D^{25}$ in water = 150.5 ± .5°; β-cyclodextrin, $[\alpha]_D^{25}$ in water = 162.5 ± .5°.

Buffer Systems—pH range: 1.0–2.2, 5.8–7.8, 8.0–10.0 in HCl–KCl, KH_2PO_4–NaOH, and H_3BO_3–NaOH, respectively.

Analytical Procedure—The ethyl-*p*-aminobenzoate, ethyl-*o*-aminobenzoate, ethyl-*m*-aminobenzoate, and atropine are separated from their degradation product by extracting with chloroform in basic solution. The unhydrolyzed benzoates and atropine were then determined spectrophotometrically at the wavelengths of 285 mμ, 330 mμ, 316 mμ, and 257 mμ, respectively. Acetylsalicylic acid was determined by using two-component analysis determining the absorbance at wavelengths of 278 mμ and 308 mμ spectrophotometrically. The absorptivity of acetylsalicylic acid and salicylic acid at 278 mμ and 308 mμ were previously determined in different pH buffered solutions which were used in these studies. The presence of cyclodextrin in these solutions did not interfere with the spectrophotometric procedure in the concentrations employed for the analysis.

Kinetic Studies—Kinetic studies were carried out at specified temperatures and constant pH buffered solutions in a system with or without cyclodextrin. The reaction course was followed by measuring the absorbance at the given wavelength utilizing a Beckman DU spectrophotometer after proper dilution. An accurate weight of the ester was dissolved in 5 ml. of ethanol and an accurate amount of cyclodextrin was added in a system containing cyclodextrin and brought to exactly 100 ml. with buffer, separated into 10-ml. amber vials, sealed, and placed in the water bath. All these procedures were conducted under nitrogen. The hydrolysis was carried out in a Haake-Thermostate Unitherm constant-temperature water bath at a given temperature. Aliquots were withdrawn periodically from each vial and analyzed for the unhydrolyzed ester. In all cases first-order rate constants were observed at constant pH and constant temperature.

RESULTS AND DISCUSSION

For purpose of discussion some of the data dealing with the deceleration of the hydrolytic rate of ethyl-*p*-aminobenzoate in the presence of cyclodextrin and previously reported (9) are presented here. In this study it is shown that β-cyclodextrin and ethyl-*p*-aminobenzoate formed a 1:1 complex in aqueous solution and that the hydrolysis was due to the free or uncomplexed ester in solution resulting from the dissociation of the inclusion complex. This was verified mathematically and is presented, in part, in Scheme I,

$$(\text{BCD} \ldots \text{BZA}) \underset{K_F}{\overset{K_D}{\rightleftharpoons}} (\text{BZA})_f + (\text{BCD})_f, \quad (\text{BZA})_f \xrightarrow{k_h} \text{PABA} + \text{EtOH}$$

Scheme I

where K_D is the dissociation constant, K_F is the formation constant, k_h is the hydrolysis constant, $(\text{BZA})_f$ is the free ethyl-*p*-aminobenzoate, $(\text{BZA})_t$ is the total ethyl-*p*-aminobenzoate, $(\text{BCD})_f$ is the free β-cyclodextrin, (BCD . . . BZA) is the complex, PABA is the *p*-aminobenzoic acid.

$$K_D = \frac{(\text{BZA})_f \cdot (\text{BCD})_f}{(\text{BCD} \ldots \text{BZA})} \qquad \text{(Eq. 1)}$$

$$(\text{BZA})_f = \frac{K_D \cdot (\text{BCD} \ldots \text{BZA})}{(\text{BCD})_f} \qquad \text{(Eq. 2)}$$

Since in solution $(\text{BCD} \ldots \text{BZA}) = (\text{BZA})_t - (\text{BZA})_f$ therefore:

$$(\text{BZA})_f = \frac{K_D \cdot [(\text{BZA})_t - (\text{BZA})_f]}{(\text{BCD})_f} \qquad \text{(Eq. 3)}$$

Simplified Eq. 3 gives:

$$(\text{BZA})_f = \frac{K_D}{K_D + (\text{BCD})_f} (\text{BZA})_t \qquad \text{(Eq. 4)}$$

The rate equation for ethyl-*p*-aminobenzoate hydrolysis at constant pH is:

$$-d(\text{BZA})_f/dt = k_h(\text{BZA})_f \qquad \text{(Eq. 5)}$$

The rate equation for ethyl-*p*-aminobenzoate hydrolysis in solution containing β-cyclodextrin should be:

$$-d(\text{BZA})_t/dt = k_h(\text{BZA})_f = k_h \frac{K_D}{K_D + (\text{BCD})_f} (\text{BZA})_t \qquad \text{(Eq. 6)}$$

$$k_{\text{app.}} = k_h \frac{K_D}{K_D + (\text{BCD})_f} \qquad \text{(Eq. 7)}$$

$$k_h/k_{\text{app.}} = 1 + \frac{(\text{BCD})_f}{K_D} \qquad \text{(Eq. 8)}$$

From experimental data, K_D has been determined to be 2.34×10^{-3}. The apparent rate constants, evaluated for the reaction in a system containing β-cyclodextrin are thus related to the true rate constant by Eqs. 7 and 8. From Eq. 7 the apparent rate constants can be calculated and can be compared with the experimental rate constant data obtained in a system containing β-cyclodextrin. These comparisons are given in Table I.

The close agreement of the calculated and experimental apparent rate constants gives additional support to the assumptions that were made. Equation 8 shows a linear relationship between the ratio of $k_h/k_{\text{app.}}$ and the concentration of free β-

Table I—Comparison of Calculated and Experimental Apparent Rate Constants of Ethyl-*p*-aminobenzoate Hydrolysis in a System Containing β-Cyclodextrin in 0.04 *N* $Ba(OH)_2$ Solution at 30°

% of BCD	Apparent Rate Constants, hr.$^{-1}$/*M* Exptl.	Calcd.
0.00	0.666	
0.25	0.358	0.342
0.50	0.229	0.228
1.00	0.129	0.139

cyclodextrin. This linear relationship is shown in Fig. 1 which further substantiates our hypothesis.

The rate of hydrolysis of acetylsalicylic acid (ASA) in alkaline solution in the presence of cyclodextrin was accelerated indicating that the cyclodextrin exerted a catalytic effect. Previous study (10) has shown ASA and β-cyclodextrin interact in aqueous solution to form a 1:1 complex. It is believed that ASA and cyclodextrin undergo only partial inclusion with the phenyl portion of the organic acid occupying the void space of the cyclodextrin molecule, and being sterically fixed in this position, thus allowing a favorable approach of the carbonyl group to the hydroxyl group of the cyclodextrin. This catalytic effect then is due to the interaction of the ester with hydroxyl group of the cyclodextrin. The data also indicated that this catalytic effect only occurred at a pH where the hydroxyl group of the cyclodextrin existed as an alkoxide ion. The hydrolysis of ASA in alkaline medium and in the presence of cyclodextrin is due to the hydrolysis of the free ASA in solution resulting from the dissociation of this complex and to the hydrolysis of the ASA in the complex resulting from the catalytic effect due to the cyclodextrin, both of these reactions occurring simultaneously. A mechanistic scheme and the mathematical relationship for this hypothesis describing these reactions are shown in Scheme II,

$$\begin{array}{ccc} (BCD)_f + (ASA)_f & \overset{K_F}{\rightleftharpoons} & (BCD \ldots ASA) \\ \downarrow k_h & K_D & k_c \downarrow \\ SA + ACA & & (BCD)_f + SA + ACA \end{array}$$

Scheme II

where $(ASA)_f$ is the free acetylsalicylic acid, SA is the salicylic acid, ACA is the acetic acid, k_c is the constant of cyclodextrin catalysis, (BCD . . . ASA) is the complex.

$$K_F = \frac{(BCD \ldots ASA)}{(BCD)_f \cdot (ASA)_f} \quad \text{(Eq. 9)}$$

$$(BCD \ldots ASA) = K_F \cdot (BCD)_f \cdot (ASA)_f \quad \text{(Eq. 10)}$$

Rate of hydrolysis of ASA in alkaline solution containing cyclodextrin at constant pH should be:

$$\begin{aligned} -d(ASA)_t/dt &= k_h \cdot (ASA)_f + k_c \cdot (BCD \ldots ASA) \\ &= k_h \cdot (ASA)_f + k_c \cdot K_F (BCD)_f (ASA)_f \\ &= k_h[1 + k_c/k_h \cdot K_F (BCD)_f](ASA)_f \end{aligned} \quad \text{(Eq. 11)}$$

$$k_{app.} = k_h[1 + k_c/k_h \cdot K_F (BCD)_f] \quad \text{(Eq. 12)}$$

$$k_{app.}/k_h = 1 + k_c/k_h \cdot K_F (BCD)_f \quad \text{(Eq. 13)}$$

From experimental data, K_F has been determined to be 1.7×10^2; k_c to be 0.74 at pH 10 and at 35°.

From Eq. 12, one can then calculate the rate constants in systems containing cyclodextrin. Experimental rate constants and those calculated are given in Table II.

It is interesting to note here the close agreement obtained for these constants, indicating that the assumptions made are reasonable. Further verification of the assumptions is shown in Fig. 2, a plot of $k_{app.}/k_h$ against the concentration of free cyclodextrin should result in a straight line as indicated in Eq. 13.

Since the hydrolysis of ASA was carried out at pH = 10, it was felt that additional information with respect to this catalytic effect would be obtained if this reaction was carried out at various pH's.

An examination of Table III which lists these data indicated that this catalytic effect exhibited by the cyclodextrin is not operative at acid pH, and that this catalytic effect increased substantially with an increase in pH in the alkaline range. This suggested that the hydroxyl groups of the cyclodextrin must be in the ionized form in order that they act as a

Table II—Comparison of Calculated and Experimental Apparent Rate Constants of ASA Hydrolysis in Systems Containing β-Cyclodextrin in a Buffered Solution of pH = 10, at 35°

% of BCD	Apparent Rate Constants, hr.$^{-1}$/*M* Exptl.	Calcd.
0.00	0.258	
0.25	0.530	0.535
0.50	0.807	0.811
0.75	1.085	1.089

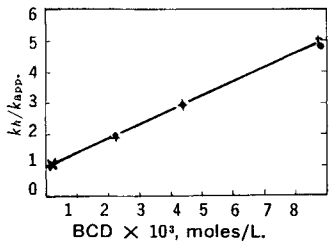

Fig. 1—Effect of β-cyclodextrin on the rate of ethyl-p-aminobenzoate hydrolysis in 0.04 N $Ba(OH)_2$ at 30°. Key: +, experimental; ●, calculated.

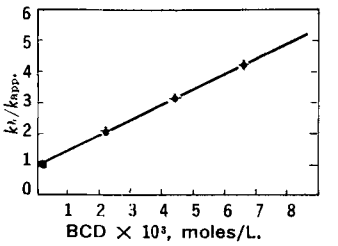

Fig. 2—Effect of β-cyclodextrin on the rate of acetylsalicylic acid hydrolysis at pH = 10 at 35°. Key: +, calculated; ●, experimental.

TABLE III—APPARENT RATE CONSTANTS OF HYDROLYSIS OF ASA AT DIFFERENT pH'S IN SYSTEMS WITH AND WITHOUT β-CYCLODEXTRIN

Temp.	pH	Apparent Rate Constants, hr.$^{-1}$/M			% Rate Increase
70°	1.0	0.5%	BCD	0.455	0.00
		No	BCD	0.454	
35°	7.0	0.5%	BCD	0.026	0.00
		No	BCD	0.026	
35°	8.0	0.5%	BCD	0.066	3.95
		No	BCD	0.063	
35°	9.0	0.5%	BCD	0.149	34.00
		No	BCD	0.110	
35°	10.0	0.5%	BCD	0.807	212.79
		No	BCD	0.258	

TABLE IV—HALF-LIFE OF ESTERS' BASIC HYDROLYSIS IN SYSTEMS WITH AND WITHOUT CYCLODEXTRINS

Compd.	Half-Life, hr. No CD[c]	0.5% ACD[d]	0.5% BCD[e]
Ethyl-*p*-aminobenzoate[a]	5.52	7.56	13.04
Ethyl-*o*-aminobenzoate[a]	37.06	23.40	41.25
Ethyl-*m*-aminobenzoate[a]	7.00	4.06	8.40
Atropine[b]	9.65	6.05	15.37
Acetylsalicylic acid[b]	2.67	0.956	0.855

[a] pH = 10.0, T = 70°. [b] pH = 10.0, T = 35°. [c] No CD = no cyclodextrin. [d] ACD = α-cyclodextrin. [e] BCD = β-cyclodextrin.

nucleophile. Cramer (3) also speculated as to this effect. For this reason a study was undertaken to investigate the ionization of cyclodextrin at different pH's. The pK value of β-cyclodextrin was found to be 12.2 which was in agreement with the previous reported value (6) and the percent of ionization was calculated using the following equation:

$$\% \text{ ionization} = \frac{100}{1 + \text{antilog}\,(pK_a - pH)} \quad \text{(Eq. 14)}$$

According to Eq. 14, the percent of ionization of β-cyclodextrin at different pH's is listed below:

pH	% of Ionization of BCD
12.2	50.000
11.0	5.940
10.0	0.627
9.0	0.063

Figure 3, which shows a plot of log percent of hydrolytic rate increase against pH and also a plot of log percent of ionization of β-cyclodextrin against pH, indicated that a direct relationship exists between the ionization of β-cyclodextrin and the rate increase of ASA hydrolysis in a system containing cyclodextrin. It seems reasonable therefore that the ASA undergoes only partial inclusion with cyclodextrin, is rigidly fixed with the void, and is catalyzed by the ionized hydroxyl groups of the cyclodextrin molecule and that this catalytic effect depends on the degree of ionization of these hydroxyl groups. In the case of deceleration effect noticed in the ethyl-*p*-aminobenzoate—β-cyclodextrin system, the ester linkage is totally shielded and therefore not subject to this nucleophilic attack. This was readily seen when Stuart models were prepared of these two systems. It should also

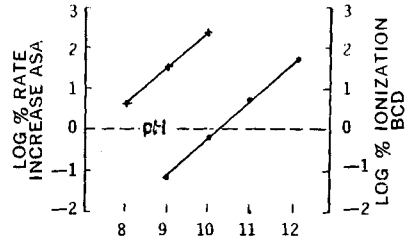

Fig. 3—A plot of log percent of hydrolytic rate increase of acetylsalicylic acid (+) hydrolysis in the system containing β-cyclodextrin against pH and log percent of ionization of β-cyclodextrin (●) against pH at 35°.

be pointed out here, that the cyclodextrin molecule exists in the C_1 conformation (11) with the hydroxyl groups existing on the outside of the cyclic structure. Since the pK value of some organic acids is decreased in the presence of cyclodextrin, and Henglein (12) also suggested that the catalytic effect may be due to this phenomenon, however, our own data with respect to this pK decrease or increase of various acids (acetic acid, hexanoic acid, benzoic acid, salicylic acid, acetylsalicylic acid, *p*-hydroxybenzoic acid, *p*-aminobenzoic acid, *m*-aminobenzoic acid, and *p*-nitrobenzoic acid) and the small pK change observed in the presence of cyclodextrin would not account for the large change in this hydrolytic rate and will be discussed later.

Additional information concerning the nature of the acceleration and deceleration effect was obtained in a study of the hydrolysis of various ethyl esters of aminobenzoic acids and atropine in the presence of α and β-cyclodextrin. Results of this study are given in Table IV.

These compounds were chosen in order to show that the rate of alkaline hydrolysis is determined primarily by the stereochemistry of the fit between guest and host in the relatively rigid cyclodextrin system. An examination of Table IV shows that the rates of hydrolysis of ethyl aminobenzoates (*para-*, *meta-*, and *ortho-*) were inhibited in the presence of β-cyclodextrin. This suggests that these molecules undergo total inclusion with the β-cyclodextrin and are shielded from nucleophilic attack by the alkoxide ion of the cyclodextrin and also by hydroxyl ion from solution. In the case of atropine due to its large size, total inclusion is not possible; however, it is highly likely that the phenyl and ester portion of the molecule is enclosed in the void space of the cyclodextrin and thus is shielded from attack. In these two cases the hydrolysis is due primarily to the free ester in solution resulting from the dissociation of the complexes. On the other hand, compounds, which do not totally fit into the void space of the cyclodextrin molecules and undergo only partial inclusion, exhibit an increase in hydrolytic rates due to the catalytic effect of the cyclodextrin in alkaline solution. For example, ASA which undergoes only partial inclusion with both α and β-cyclodextrin as seen in Table IV shows an increase in the rate of hydrolysis. Atropine, ethyl-*o*-aminobenzoate, and ethyl-*m*-aminobenzoate with α-cyclodextrin also show this catalytic reaction. Since the void space of β-cyclodextrin (8 Å.) is larger than the alpha void (6 Å.), it is readily seen by constructed molecular models that all of the ethyl esters of aminobenzoic acid can readily fit into the

void of β-cyclodextrin. On the other hand, only the *para* derivative readily fits into the void the of α-cyclodextrin molecule. The *meta* and *ortho* derivatives do not totally fit into the void of the α-cyclodextrin due to steric hindrance resulting from the amino group and thus are accelerated with respect to the rate of hydrolysis. With respect to ASA the large carbonyl group in the *ortho* position next to the leaving group prevents a total fit in both of the α and β-cyclodextrins and consequently it undergoes a catalytic reaction. In such cases the over-all hydrolytic rate is due not only to the free ester in solution but due also to the degradation of the ester in the complexed form.

CONCLUSION

The effect of cyclodextrins on the alkaline hydrolysis of various esters has been shown to be one of acceleration or deceleration depending on the nature of the complexes formed. Compounds which form a true inclusion compound or a compound in which the active center is included in the void of cyclodextrin exhibit a deceleration effect, and the hydrolytic rate is dependent primarily on the amount of free ester in solution resulting from dissociation of the complex. Compounds which do not totally fit into the void or are only partially included leaving the active center sterically fixed in close proximity to the hydroxyl group of cyclodextrin undergo an acceleration effect. In this case the hydrolytic rate is due not only to the free ester in solution resulting from the dissociation of the complex but also to nucleophilic attack of the ester linkage by the alkoxide ion of the cyclodextrin molecules. This catalytic effect is related to degree of ionization of these hydroxyl groups in the cyclodextrin molecule. Although it has been suggested that this catalytic effect may be due to a decrease in pK_a in the presence of cyclodextrin, the present data do substantiate this. For example, both α and β-cyclodextrin increase the pK_a value of *m*-aminobenzoic acid by approximately 0.1 unit, yet in the hydrolytic rate study, α-cyclodextrin exhibits an acceleration effect with respect to the hydrolysis of ethyl-*m*-aminobenzoate, whereas β-cyclodextrin has an opposite effect. This suggested that the stereochemistry of binding and the degree of the ionization of cyclodextrin are primarily responsible for the catalytic effect. This catalytic effect is absent when the hydroxyl groups are in the unionized form as in acid solution even though the ester is present in the complexed form.

The interest (13) in the kinetic aspect of these cyclodextrins has been due to the fact that these cyclodextrins have been used as models in the study of enzyme catalysis. Although such a model cannot explain completely the mechanism of enzyme action, kinetic data present in this investigation do illustrate some of the physical-chemical aspects involved in enzyme catalysis.

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Keyphrases

Ester hydrolysis
Cylodextrins influence on alkaline hydrolysis of esters
Acetylsalicylic acid hydrolysis catalyzed by cyclodextrins
Ethyl-(*para*, *ortho*, and *meta*) aminobenzoates hydrolysis decelerated by cyclodextrins
Atropine hydrolysis catalyzed by cyclodextrins
UV spectrophotometry—analysis