Effects of cyclodextrin on hydrolysis and the Smiles rearrangement of salicylic acid esters

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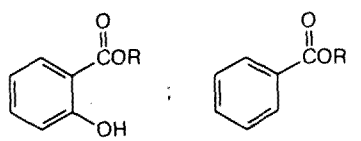
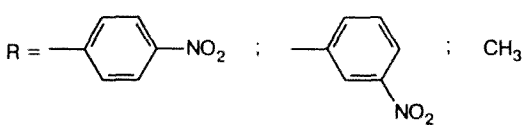
The effect of β-cyclodextrin (β-CD) on "aqueous" hydrolysis of methyl, *p*-, and *m*-nitrophenyl salicylates as well as on the Smiles rearrangement of *p*-nitrophenyl salicylate was studied. No effect of β-CD on the pH-independent rate constant of "aqueous" hydrolysis of methyl ester was observed, while β-CD accelerated "aqueous" hydrolysis of nitrophenyl esters by *ca.* 10 times. The inclusion of these esters into the cavity of β-CD is accompanied by a change in the mechanism of hydrolysis: free ester in the deprotonated form undergoes hydrolysis through the mechanism of intramolecular general base catalysis, while the ester bound to cyclodextrin is hydrolyzed due to the nucleophilic attack of the deprotonated hydroxyl group of β-CD at a neutral substrate molecule. The effects of cyclodextrin on the rate constant of borate-catalyzed hydrolysis were interpreted by assuming that the substrate bound to β-CD undergoes borate-assisted attack at the deprotonated cyclodextrin hydroxyl group. The Smiles rearrangement, which is an intramolecular nucleophilic substitution reaction, is accelerated in the presence of β-CD.

Key words: nitrophenyl salicylate, methyl salicylate, β-cyclodextrin, intramolecular general base catalysis, Smiles rearrangement.

The unique reactivity of enzymes[1–4] has attracted attention to the kinetics of intramolecular reactions. The chemical modeling of enzymatic processes has led to the study of the influence of macrocyclic "host" molecules on the rates and equilibria of intramolecular processes. For example, it has been shown that β-cyclodextrin (β-CD)[5] and erythromycin[6] induces lactonization of some dyes. A sixfold acceleration of the transfer of the acyl group of 2-hydroxymethyl-4-nitrophenyl trimethylacetate in the presence of α-CD has been observed.[7] In this paper, the effect of β-CD on the kinetics of intramolecular hydrolysis and on the Smiles rearrangement of salicylic acid esters **1a—c** is described.

Salicylic acid esters were chosen as substrates for several reasons. First, hydrolysis of these esters proceeds *via* the mechanism of intramolecular general base catalysis involving the deprotonated *ortho*-hydroxyl group, which mimics the deacylation step in the mechanism of action of serine proteases.[8a] Therefore, these esters are widely used for modeling enzymatic processes.[8] Second, the borate-catalyzed hydrolysis of salicylates is also intramolecular, but occurs through a nucleophilic mechanism. Third, simultaneously with hydrolysis, *p*-nitrophenyl salicylate undergoes the Smiles rearrangement, which is an intramolecular aromatic nucleophilic substitution.[8a,b] Thus, it is possible to compare the





effects of cyclodextrins on reactions with different mechanisms (general base and nucleophilic) using one substrate as an example. All reaction routes discussed are presented in Scheme 1.

The effect of cyclodextrins on the hydrolysis of benzoates **2a,b** was studied for comparison.

Reaction routes. Hydrolysis of esters **1a—c** (the first route) resulting in the formation of salicylic acid was monitored by spectrophotometry detecting elimination of 4-nitrophenoxide (4-NP), 3-nitrophenoxide (3-NP), and the salicylate anion, respectively. For esters **1b** and **1c**, the final concentrations of 3-nitrophenoxide and salicylate anions corresponded to those calculated from the weighted samples. However, for *p*-nitrophenyl salicylate, the yield of *p*-nitrophenoxide was ~50 % of the calculated

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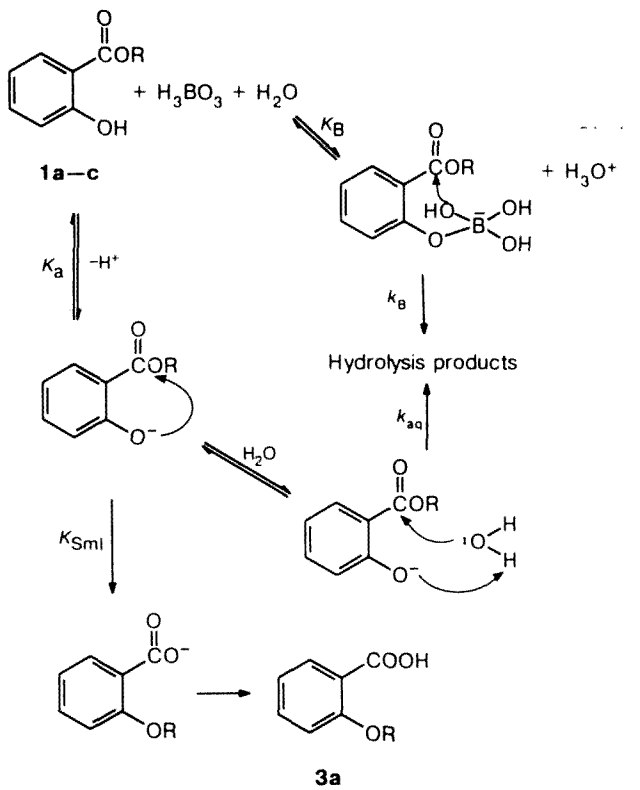
Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 11, pp. 2658—2665, November, 1996.
1066-5285/96/4511-2517 $15.00

Scheme 1



one. It is known[8a,b, 9] that the second route, the Smiles rearrangement, occurs in parallel with hydrolysis, which results in the formation of *o*-carboxyphenyl *p*-nitrophenyl ether (**3a**). Thus, free nitrophenoxide and salicylate ions form only *via* the first route.

Therefore, the following approach was used for calculating the rate constants of reaction **1a** *via* each route. The observed rate constant for the reaction of the pseudo-first order (k_{obs}) was obtained for different concentrations of the borate buffer and β-CD at the constant value of pH. The typical form of these dependences is presented in Fig. 1. In each case, the reaction was performed to the end, and the yield of 4-NP was determined (it usually was 50% of the initial concentration of the ester). The rate constant of the Smiles rearrangement (k_{Sml}) and the sum of the rate constants of "aqueous" hydrolysis (k_{aq}) and borate-catalyzed hydrolysis ($k_B[H_3BO_3]_t$) were calculated from these data:

$$k_{obs} = k_{Sml} + k_{aq} + k_B[H_3BO_3]_t, \quad (1)$$

$$(k_{aq} + k_B[H_3BO_3]_t)/k_{obs} = 1 - k_{Sml}/k_{obs} = [4\text{-NP}]_\infty/[\mathbf{1a}]_0, \quad (2)$$

where $[4\text{-NP}]_\infty$ is the final concentration of *p*-nitrophenol after the reaction was completed, $[\mathbf{1a}]_0$ is the initial concentration of the ester, and $[H_3BO_3]_t$ is the total concentration of boric acid. Then the dependence of the observed reaction rate constant, corrected for the rate constant of the Smiles rearrangement ($k_{obs} - k_{Sml}$), on the total concentration of boric acid was plotted. According to Eq. (1), this dependence is linear, the interception is equal to k_{aq}, and the slope is equivalent to k_B.

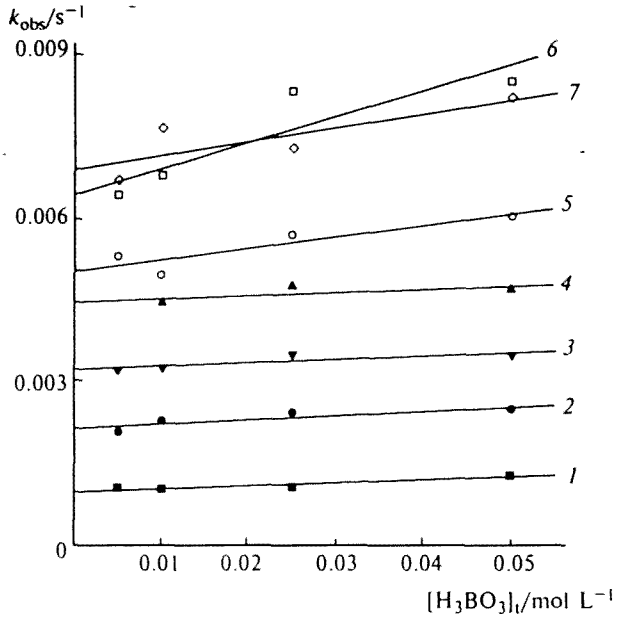


Fig. 1. Dependences of the observed rate constant of cleavage of **1a** on the concentration of the borate buffer at pH 10.0 and at different concentrations of β-CD/mol L^{-1}: 0 (*1*); 0.001 (*2*); 0.002 (*3*); 0.004 (*4*); 0.006 (*5*); 0.009 (*6*), and 0.01 (*7*).

Since no Smiles rearrangement (in parallel with the hydrolysis route) was observed for the two other substrates, the data similar to those presented in Fig. 1 were used without a correction for k_{Sml}. The k_{aq} and k_B were also calculated from Eq. (1), from which the term k_{Sml} was excluded.

Effect of cyclodextrin on the aqueous hydrolysis route. The dependences of k_{aq} on the concentration of β-CD at various pH values for substrates **1a—c** are presented in Figs. 2—4. Hydrolysis of **1b** in the presence of cyclodextrin has been studied previously,[10] however, we reproduced the results to have the rate constants for all substrates studied under the same conditions. For any substrates, these and the other dependences obtained at different pH values obey Eq. (3), which is derived from a simple scheme of the simultaneous transformation of free substrate molecules (S) and molecules of a substrate bound to cyclodextrin (S—CD)[11] (Scheme 2).

Scheme 2

$$S \xrightarrow{k_0} P,$$

$$S + CD \underset{}{\overset{K_S}{\rightleftharpoons}} S\text{—}CD \xrightarrow{k_c} P,$$

$$k_{aq} = (k_0 + k_c K_S[\beta\text{-CD}])/(1 + K_S[\beta\text{-CD}]), \quad (3)$$

where k_0 and k_c are the observed rate constants of hydrolysis of free substrates and substrates bound with

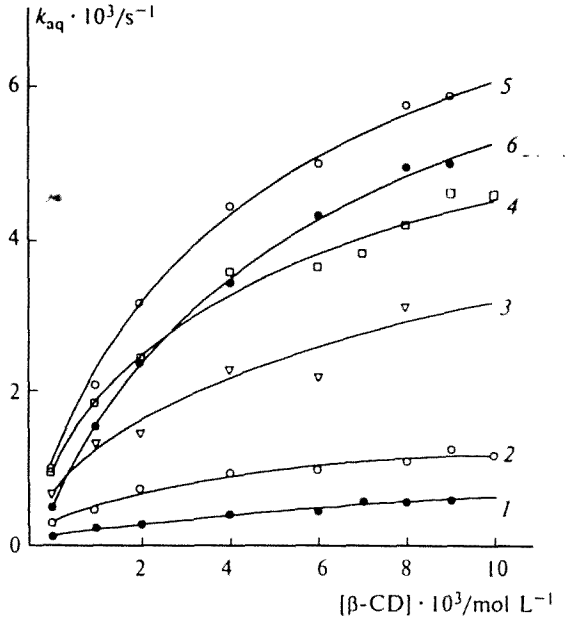


Fig. 2. Dependences of the observed rate constant of "aqueous" hydrolysis of **1a** on the concentration of β-CD at pH 8.0 (*1*), 8.5 (*2*), 9.0 (*3*), 9.5 (*4*), and 10.0 (*5*). Curve *6*, a solution of D_2O, pD = 10.4.

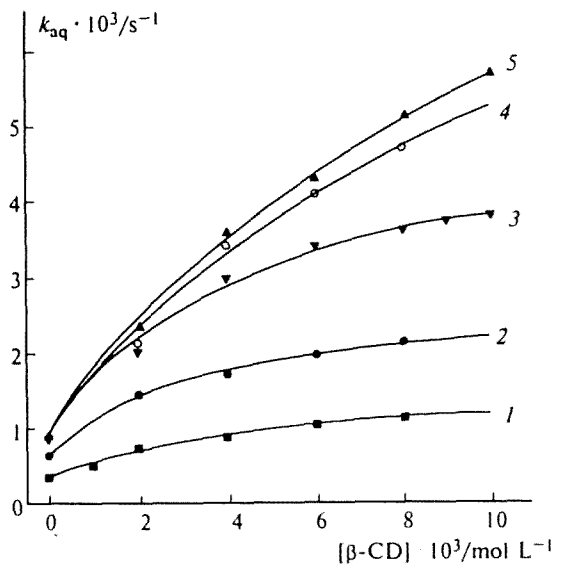


Fig. 3. Dependences of the observed rate constant of "aqueous" hydrolysis of **1b** on the concentration of β-CD at pH 8.5 (*1*); 9.0 (*2*); 9.5 (*3*); 10.0 (*4*), and 10.5 (*5*).

β-CD, and K_S is the observed binding constant. All these parameters depend on pH according to Eqs. (4)—(6), which are obtained from Schemes 1 and 2:

$$k_0 = k_0'/(1 + [H^+]/K_a^0), \quad (4)$$

$$k_c = k_c'/(1 + [H^+]/K_a^c), \quad (5)$$

$$K_S = K_S'(K_a^c + [H^+])/(K_a^0 + [H^+]), \quad (6)$$

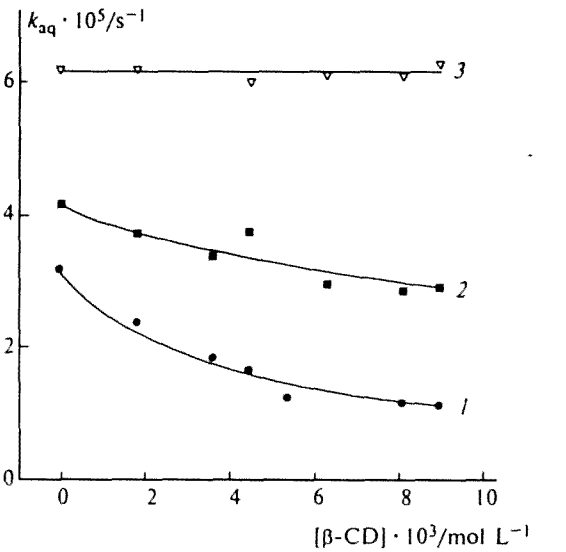


Fig. 4. Dependences of the observed rate constant of "aqueous" hydrolysis of **1c** on the concentration of β-CD at pH 9.6 (*1*); 10.1 (*2*), and 10.6 (*3*).

where k_0' and k_c' are the pH-independent rate constants of hydrolysis of free and bound substrates, K_a^0 and K_a^c is the acidic dissociation constants of free and bound substrates, and K_S' are the binding constant of non-dissociated forms of substrates.

The kinetic and equilibrium parameters determined for different pH are presented in Table 1, and the corresponding pH-independent constants are listed in Table 2. Since ester **1c** is hydrolyzed very slowly, its constants of binding with cyclodextrin at different pH were also determined by spectrophotometry (see Experimental and Table 3). As can be seen from Table 3, the parameters obtained by different methods are in good concordance.

It can be seen from the data presented in Table 1 that β-CD accelerates considerably the hydrolysis of nitrophenyl esters **1a,b**, but inhibits or exerts no effect on the hydrolysis of **1c**. These results agree with the fact previously discussed in the literature[11—14] that the effect of a catalyst on the hydrolysis of esters with a good leaving group is greater than on the hydrolysis of esters with a bad leaving group. A possible explanation for this difference is that the hydroxyl groups of cyclodextrin cannot compete with the more basic alkoxide leaving groups, but they easily expel the less basic aromatic phenoxide leaving groups from the tetrahedral intermediate. However, when it is taken into account that esters **1a—c** are hydrolyzed through the mechanism of general base catalysis (Scheme 1) and this mechanism is retained for a substrate bound with cyclodextrin, the hydroxyl group of cyclodextrin should not participate in hydrolysis.

The existence of the deacylation stage in hydrolysis of the bound ester was analyzed to elucidate whether the hydroxyl group of cyclodextrin takes part in the hydroly-

Table 1. Observed rate constants of hydrolysis of free substrates (k_0) and substrates bound with β-CD (k_c), the observed binding constant with β-CD (K_S), the rate constant of deacylation of acyl-CD (k_{deac}) for esters **1a—c** and **2a,b** (25°C; relative experimental error ±(10—20)%)

Run	Compound	pH	$k_0 \cdot 10^4$ /s^{-1}	$k_c \cdot 10^3$ /s^{-1}	K_S /L mol^{-1}	k_{deac}/s^{-1}
1	**1a**[a]	8.0	1.3	1.1	110	
2		8.5	2.5	1.6	200	
3		9.0	6.8	4.0	230	
4		9.5	8.9	6.1	230	
5		10.0	10.5	8.5	210	$7.2 \cdot 10^{-5}$
6		10.0[b]	5.2	8.3	150	
7		10.6				$1.0 \cdot 10^{-4}$
8		11.0				$9.2 \cdot 10^{-5}$
9	**1b**[c]	8.5	3.3	1.6	205	
10		9.0	6.5	3.7	190	
11		9.5	8.2	5.5	195	
12		10.0	8.2	11.0	80	$5.2 \cdot 10^{-5}$
13		10.5	8.3	12.0	80	
14		10.6				$1.3 \cdot 10^{-4}$
15	**1c**[d]	9.6	0.315	0.0033	280	
16		10.1	0.42	0.015	110	
17		10.6	0.60	β-CD exerts no effect on the reaction rate		
18		11.0	0.67	β-CD exerts no effect on the reaction rate		
19	**2a**[c]	9.5	1.8	0.90	220	
20		10.0	5.7	3.0	140	
21	**2b**[e]	10.6	15.0	39.0	180	

[a] 3% MeCN. [b] In D_2O, pD = 10.4. [c] 5% MeCN. [d] 1% MeCN. [e] See Ref. 12.

Table 2. Acidic dissociation constants of free esters **1a—c** (pK_a^0) and esters **1a—c** bound with cyclodextrin (pK_a^c), pH-independent rate constants of hydrolysis and the Smiles rearrangement (k_0' and k_c' for free substrates and substrates bound with β-CD, respectively), and binding constants of nondissociated forms (K_S') of esters **1a—c** with β-CD

Compound	Reaction*	pK_a^0	pK_a^c	$k_0' \cdot 10^4$ /s^{-1}	$k_c' \cdot 10^3$ /s^{-1}	K_S' /L mol^{-1}
1a	H	9.0±0.1	9.1±0.1	11.2±0.3	8.7±0.4	200±40
	S	9.0±0.1	9.1±0.1	11±1	6.3±0.6	240±160
1b	H	8.8±0.1	9.4±0.1	9.6±0.8	13±1	330±40
1c	H	9.6±0.1	10.3±0.1	0.64±0.06		510±50

* H is hydrolysis, S is the Smiles rearrangement.

Table 3. Observed binding constants of **1c** with β-CD at different pH values (25°C; relative experimental error ±(10—20)%)

pH	K_S/L mol^{-1}	
	Spectrophotometric data	Kinetic data
9.6	340	280
9.75	230	
9.8	240	180
9.9	250	
10.1	130	110

sis. For this purpose, we used a procedure presented in Ref. 10 involving spectrophotometric monitoring of the deacylation stage in the UV spectral region after the complete formation of the phenoxide anion. Using this procedure for esters **1a,b**, the existence of the deacylation stage with the corresponding rate constants of deacylation k_{deac} (Table 1) was confirmed. As should be expected, the deacylation constant was the same for both esters. This experiment confirmed the existence of acyl-β-cyclodextrins, which cannot be formed in hydrolysis *via* the mechanism of intramolecular general base catalysis and appear due to the nucleophilic attack of the hydroxyl group of β-CD at the functional group of a substrate. To be sure that the mechanism changes when the functional group is inserted into the cyclodextrin cavity, the isotopic effect of the hydrolysis of **1a** was measured under the conditions when the ester is completely deprotonated (Fig. 2). As follows from the kinetic parameters obtained for a solution of D_2O (Table 1, run 6), the isotopic effect k_H/k_D for the free substrate is equal to 2.0, and that for the bound substrate is equal to 1.02. These results also confirmed that the general base mechanism of the reaction changes to a nucleophilic mechanism. A small isotopic effect K_H/K_D = 1.40, which is difficult to interpret, was observed for the binding constants. Perhaps, this result reflects a change in the free energy of **1a** in H_2O and D_2O, because the transfer of nonpolar compounds from H_2O into D_2O is accompanied by a small and difficult to predict change in the free energy.[15]

Cyclodextrin exerts no effect on the hydrolysis of compound **1c** (see Table 1, runs 17 and 18) at pH higher than pK_a of the bound substrate (Table 2). As can be seen from Table 3, the binding constant of the dissociated form of **1c** is considerably lower than the binding constant of the nondissociated form of the substrate. Weakening of the binding as pH increases is also confirmed by the fact (see Eq. (6)) that for **1c** $pK_a^c > pK_a^0$ (Table 2). The following conclusion can be drawn concerning the observed rate of hydrolysis of **1c** in the presence of cyclodextrin at pH < pK_a: the binding constant of the deprotonated form of **1c** calculated using the data of Table 2 is equal to 100 L mol^{-1}, which means that at the maximum concentration of β-CD used, equal to 0.01 mol L^{-1}, ~50% of the total concentration of deprotonated **1c** should bind with cyclodextrin. This amount would be sufficient for detecting even small changes in the hydrolysis rate caused by the presence of cyclodextrin. Therefore, β-CD has no effect on the hydrolysis of the deprotonated form of methyl salicylate, and the observed decrease in the rate at pH < pK_a is likely due to an increase in pK_a of the substrate in the presence of cyclodextrin.

Despite the changes in the mechanism of hydrolysis of esters **1a,b** upon binding with cyclodextrin, the pH dependences of the rates of the hydrolysis of the free and bound substrates are similar (see Eqs. (4) and (5)). As can be seen from Table 2, for **1b** $pK_a^c > pK_a^0$. This is a quite reasonable result, because pK_a of phenols usually increases for binding with cyclodextrins due to the relative stabilization of their neutral form by the nonpolar cavity of cyclodextrin.[16] However, in the case of **1a**, both forms (free and bound) exhibit the same value of pK_a within the experimental accuracy (Table 2). These results point to the difference between inclusion complexes for *meta*- and *para*-substituted esters. It should be mentioned in this connection that the differences between the methods of incorporation of *meta*- and *para*-nitrophenyl acetates into the cavity of β-cyclodextrin during its hydrolysis have been demonstrated recently.[17,18] It is assumed that hydrolysis of the *para*-substituted ester, contrary to that of the *meta*-substituted ester, occurs without inclusion of the aryl group into the cyclodextrin cavity. Probably a molecule of **1a** is incorporated into a polar region of the cyclodextrin cavity.

Based on the pH dependences obtained and taking into account the formation of the intermediate acyl-β-CD, two mechanisms of hydrolysis can be suggested for esters **1a,b** incorporated into the cyclodextrin cavity (Scheme 3).

Scheme 3

$$\text{CD—OH} + \text{S—OH} \overset{K_S'}{\rightleftharpoons} (\text{CD—OH S—OH}) \rightleftharpoons \overset{K_a^c}{\rightleftharpoons} (\text{CD—OH S—O}^-) + \text{H}^+ \xrightarrow{k_{ac}} \text{acyl—CD} \xrightarrow{k_{deac}} \text{Products}, \quad (7)$$

$$\text{CD—OH} + \text{S—OH} \overset{K_S'}{\rightleftharpoons} (\text{CD—OH S—OH}) \rightleftharpoons \overset{K_a^{CD}}{\rightleftharpoons} (\text{CD—O}^- \text{ S—OH}) + \text{H}^+ \xrightarrow{k_{ac}} \text{acyl—CD} \xrightarrow{k_{deac}} \text{Products}, \quad (8)$$

where CD—OH and S—OH designate β-CD and the corresponding ester, and K_a^{CD} is the acidic dissociation constant of β-CD.

According to mechanism (7), acyl-CD forms when the deprotonated substrate reacts with the hydroxyl group of β-CD. This mechanism implies the general base assistance of the deprotonated *ortho*-hydroxyl group of esters **1a,b** in the attack of the secondary group of cyclodextrin at the carbonyl group of the ester and should result in a considerable isotopic effect. The absence of this effect excludes mechanism (7).

Reaction (8) is a commonly accepted mechanism of the cyclodextrin-catalyzed[11,12] hydrolysis of esters with a good leaving group and it is a nucleophilic attack by the deprotonated hydroxyl group of cyclodextrin on a neutral substrate. Therefore, the absence of an isotopic effect can be explained only by the fact that the *ortho*-hydroxyl group of the ester is not involved in this reaction in any way. Then it can be expected that the rate constant of acylation k_{ac} for esters **1a,b** should be close to the corresponding constant for the esters that contain no *ortho*-hydroxyl groups, *i.e.*, benzoates **2a,b.** The observed rate constants of hydrolysis for these esters are presented in Table 1 (runs 19—21). According to mechanism (8), the rate constant of acylation k_{ac} of a substrate that has no ionogenic groups is expressed in the following form:

$$k_{ac} = k_c [H^+]/K_a^{CD}, \quad (9)$$

where K_a^{CD} is the acidic dissociation constant of β-CD in its complex with a substrate. This parameter is unknown, and the pK_a value for free cyclodextrin used in the calculations was $pK_a^{CD} = 12.2$.[19] Using Eq. (9), $k_{ac} = 0.47\ s^{-1}$ for **2a** and $k_{ac} = 1.5\ s^{-1}$ for **2b** were obtained. According to mechanism (8), the rate constants of acylation for substrates **1a,b** are expressed by Eq. (10), which is obtained when two approximations are used: the complex of the deprotonated substrate with deprotonated β-CD is not taken into account and it is assumed that $K_a^c/K_a^{CD} >> 1$:

$$k_{ac} = k_c' K_a^c / K_a^{CD}. \quad (10)$$

Using the data of Table 2 and pK_a^{CD} presented above, we obtain $k_{ac} = 11\ s^{-1}$ for **1a** and $k_{ac} = 8.2\ s^{-1}$ for **1b**. A comparison of the constants obtained for benzoates and salicylates shows the difference in the behavior of *meta*- and *para*-nitrophenyl esters. Rate constants of the same order of magnitude were obtained for esters **1b** and **2b**, however, the rate constant of acylation for **1a** is much greater than that for **2a**. Apparently, there is some small assistance from the neutral hydroxyl group of the ester. Since the absence of an isotopic effect excludes any participation of this group in the proton transfer, this fact can be explained by the specific structure of the inclusion complex, which in the case of **1a** allows the hydroxyl group of the substrate to react with the hydroxyl groups of β-CD and, as a consequence, makes it possible to fix the substrate in a position favorable for nucleophilic attack.

An analog of mechanism (8) for the case of aqueous hydrolysis of salicylates in the absence of β-CD is the reaction of a neutral ester with the hydroxyl ion. The kinetics of this mechanism is equivalent to that of the general base mechanism presented in Scheme 1. However, its contribution is minimum when intramolecular general base catalysis is present. The incorporation of a molecule of ester into the cyclodextrin cavity suppresses the general base mechanism in favor of the nucleophilic mechanism.

Effect of cyclodextrin on borate-catalyzed hydrolysis of esters 1a,b. Aqueous hydrolysis of both esters **1a,b** is

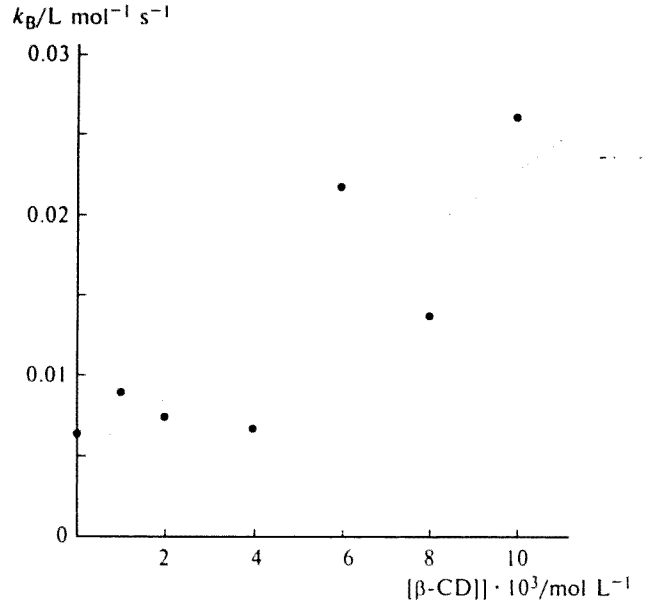


Fig. 5. Dependences of the observed rate constant of borate-catalyzed hydrolysis of **1a** on the concentration of β-CD at pH 10.0.

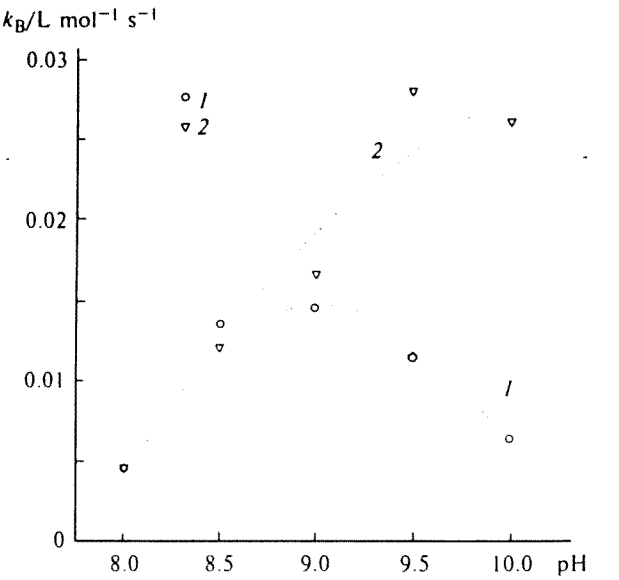


Fig. 6. Dependences of the observed rate constant of borate-catalyzed hydrolysis of **1a** on pH of the medium at concentrations of β-CD of 0 (*1*) and 0.01 mol L^{-1} (*2*).

catalyzed by boric acid.[8] Therefore it was of interest to study the influence of cyclodextrin on the mechanism and efficiency of borate catalysis. However, the poor reproducibility of k_B in the presence of β-CD (Fig. 5) did not allow us to perform quantitative analysis of the results, and the experimental data can be described only qualitatively. Some acceleration of the borate catalysis of β-CD for ester **1a** was obtained at pH 9.5 and 10, while β-CD has almost no effect on k_B in the region of pH < 9.

The pH-dependences of k_B in an aqueous medium in the presence of β-CD (0.01 mol L^{-1}) are presented in Fig. 6. The k_B values obtained at lower concentrations of cyclodextrin are arranged between these extreme points with a great scatter. For ester **1b**, no noticeable effect of β-CD on k_B was observed at all pH studied. Perhaps the difference in the behavior of k_B for both esters is also explained by the fact that the inclusion complexes of *para*- and *meta*-nitrophenyl esters are different.

According to Scheme 1, k_B is expressed in the following form:

$$k'_B = \frac{k_B K_B [H^+]}{([H^+] + K_a^B)([H^+] + K_a^0)}, \qquad (11)$$

where K_a^B is the dissociation constant of boric acid. According to Eq. (11), the dependence of k_B on the pH of the medium has a maximum at pH = $(pK_a^B + pK_a^0)/2$. In the absence of cyclodextrin, a maximum should be observed at pH 9, which is obtained from the experimental data (Fig. 6). Since the pK_a^B and pK_a^0 do not change in the presence of cyclodextrin ($pK_a^0 = pK_a^c$ (see Table 2) and β-CD does not react with boric acid[20]), it is reasonable to assume that the position of the maximum also remains unchanged when the mechanism of borate catalysis is retained in the presence of β-CD. Therefore, we assume that the changes observed for the dependence of k_B on the pH of the medium reflect a change in the mechanism of borate assistance involving the deprotonated hydroxyl group of cyclodextrin in the mechanism of hydrolysis of the ester. In other words, we assume that binding **1a** with β-CD results in changes in the mechanism of borate catalysis that are similar to those observed for aqueous hydrolysis, *i.e.*, the intramolecular attack is changed to nucleophilic attack of the deprotonated hydroxyl group of cyclodextrin.

The borate catalysis of the nucleophilic attack of the deprotonated hydroxyl group of β-CD can be presented as follows. As has been shown in the previous Section, the cleavage of the **1a** molecule bound to β-CD occurs through mechanism (8) and is the reaction of the deprotonated hydroxyl group of β-CD with the neutral molecule of the substrate. The existence of a substrate with a deprotonated *ortho*-hydroxyl group in the cavity of cyclodextrin is rather improbable, because it would strongly inhibit the reaction due to the electron-releasing effect and Coulomb repulsion. However, when a dissociated hydroxyl group of the substrate reacts with boric acid, delocalization of the charge occurs (see Scheme 1), and the electron density on this group decreases, which allows the incorporation of a substrate molecule into the cavity of cyclodextrin.

Effect of cyclodextrin on the Smiles rearrangement of ester 1a. The dependences of k_{Sml} on the concentration of β-CD at different pH values are presented in Fig. 7. These dependences were processed by Eq. (3). The

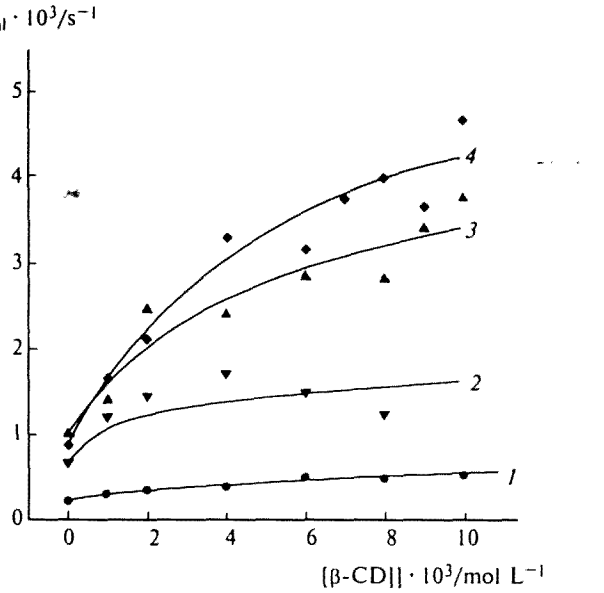


Fig. 7. Dependences of the observed rate constant of the Smiles rearrangement of **1a** on the concentration of β-CD at pH 8.5 (*1*); 9.0 (*2*); 9.5 (*3*), and 10.0 (*4*).

calculated rate constants of free (k_{Sml}^0) and bound (k_{Sml}^c) substrates and the equilibrium constants (K_S^{Sml}) are collected in Table 4. The corresponding pH-independent constants calculated by Eqs. (4)—(6) are presented in Table 2. It is noteworthy that the experimental errors for the determination of k_{Sml} are considerably higher than those for the determination of k_{aq}. As should be expected, no isotopic effect was observed either in the presence or in the absence of β-CD (see Table 4).

It is evident that β-CD accelerates the Smiles rearrangement of ester **1a**. As indicated above, this reaction proceeds *via* the mechanism of intramolecular nucleophilic aromatic substitution. The acceleration of electrophilic aromatic substitution has recently been mentioned.[21] Taking into account this fact, inhibition rather than acceleration by cyclodextrin should be expected in the case of nucleophilic aromatic substitution. However, in our case, the result obtained can be explained by the fact that the substrate in the initial state exists in the anionic form with the negative charge localized on the *ortho*-hydroxyl group of the substrate, and in the transition state this charge is delocalized on the nitroaromatic ring. This type of reaction should be accelerated on going from water to a less polar medium, in particular, when a substrate is incorporated into the hydrophobic cavity of cyclodextrin. In fact, we established that a threefold increase in k_{Sml} and an almost complete disappearance of cyclodextrin catalysis is observed in a 30% solution of acetonitrile.

Table 4. Observed rate constants of the Smiles rearrangement of free substrates (k_{Sml}^0) and substrates bound with β-CD (k_{Sml}^c) and the observed binding constant with β-CD (K_S^{Sml}) for ester **1a** (25°C, 3% MeCN). Relative error is 10—20%

pH	$k_{Sml}^0 \cdot 10^3/s^{-1}$	$k_{Sml}^c \cdot 10^3/s^{-1}$	K_S^{Sml}/L mol^{-1}
8.5	0.22	0.8	120
9.0	0.67	2.2	530
9.5	0.87	6.4	150
10.0	1.0	4.6	180
10.0[a]	1.0	5.5	360

[a] In D_2O, pD = 10.4.

* * *

"Host" molecules can induce some strains and/or restrictions on the internal rotation of an incorporated "guest" molecule. When a molecule undergoes intramolecular transformation, its incorporation into the cavity of a "host" molecule can change the rate of the chemical reaction in the same manner as the introduction of an additional alkyl group into the substrate. This group usually favors an increase in rates of the reactions occurring *via* a nucleophilic mechanism and exerts a smaller effect on the general acid mechanism.[1] The same conclusions seem also valid for the effect of cyclodextrins on intramolecular routes: β-CD considerably accelerates lactonization of the *ortho*-carboxyl group in phenolphthalein,[5] but, as our results show, β-CD has no effect on the rate of hydrolysis of salicylates *via* the mechanism of intramolecular general base catalysis involving the *ortho*-hydroxyl group of the substrate. Our results also agree with the accepted opinion that the relative efficiency of intramolecular nucleophilic reactions is higher than the efficiency of intramolecular processes involving proton transfer. It is evident that the predominant route of hydrolysis of salycilates **1a,b** with good leaving groups in solution is an attack by water with intramolecular general base assistance by the dissociated *ortho*-hydroxyl group of the substrate. However, in a complex with β-CD, when another nucleophilic route of hydrolysis also becomes intramolecular, the latter is preferable.

Experimental

Esters **1a,b** and **2a** were synthesized by a known procedure.[22] The purity of the products was determined by elemental analysis and from the elimination of *para*- and *meta*-nitrophenoxide anions in a strongly alkaline medium. The melting points of the compounds synthesized were in good correspondence with the published data: for *p*-nitrophenyl salicylate, 150°C (151—153 °C);[8b] for *m*-nitrophenyl salicylate, 102°C (105°C);[8b] and for *p*-nitrophenyl benzoate, 140°C (142.5 °C).[8a] Ester **1c**, β-CD, and the other reagents were obtained from Aldrich.

Reaction rates were measured at 25°C on a Hitachi 50-21 UV-VIS spectrophotometer with a thermostated cell section. The pseudo-first order rate constants (k_{obs}) were calculated by the overall equation for the rate of the first-order reaction. The k_{aq} and k_B values at each pH value and the concentration of

β-CD were obtained by Eqs. (1) and (2) from the dependence of k_{obs} on the concentration of the borate buffer. Hydrolysis of esters **1a,b** and **2a** was monitored by the appearance of 4-nitrophenoxide or 3-nitrophenoxide anions at 405 and 400 nm, respectively. Hydrolysis of **1c** was observed by the elimination of the salicylate anion at 335 nm.

The kinetics of the deacylation of acyl-β-CD in the reactions of β-CD with esters **1a,b** was monitored according to the procedure suggested in Ref. 12. When the 4- and 3-nitrophenoxide anions were eliminated, the reaction was monitored at 325 nm. The spectral changes resembled the changes observed during hydrolysis of **1c**.

Determination of the binding constant of 1c with β-CD. The optical density of equilibrium solutions of **1c** ($1 \cdot 10^{-4}$ mol L^{-1}) and β-CD of different concentrations (0.001 to 0.01 mol L^{-1}) were measured as a function of the concentration of β-CD at different pH values. The binding constants were calculated at at least four points using the equation

$$A/[\mathbf{1c}] = (\varepsilon_0 + \varepsilon_c K_S[\beta\text{-CD}])/(1+K_S[\beta\text{-CD}]),$$

where ε_0 and ε_c are the extinction coefficients of free and bound compound **1c**, respectively.

The concentrations of esters in solution usually were 10^{-5} mol L^{-1} for **1a,b** and **2a** and 10^{-4} mol L^{-1} for **1c**. The ionic strength of 0.1 mol L^{-1} was maintained by a solution of NaCl. Acetonitrile (1—5 vol.%) was added to the reaction mixture to improve the solubility of the esters. Phosphate, borate, and carbonate buffers were used to maintain the constant pH value in the corresponding ranges.

References

1. A. J. Kirby, in *Adv. Phys. Org. Chem.*, Eds. V. Gold and D. Bethell, 1980, **17**, 183.
2. W. P. Jenks, *Catalysis in Chemistry and Enzymology*, Dover Publ., New York, 1987.
3. A. J. Kerby and N. H. Williams, *J. Chem. Soc., Chem. Commun.*, 1991, 1643.
4. F. M. Menger and K. Gabrielson, *J. Am. Chem. Soc.*, 1992, **114**, 3574.
5. (a) K. Taguchi, *J. Am. Chem. Soc.*, 1986, **108**, 2705; (b) N. Yoshida, T. Shirai, and M. Fujimoto, *Carbohydr. Res.*, 1989, **192**, 291; (c) K. Tagushi, *J. Chem. Soc., Perkin Trans. 2*, 1992, 17.
6. M. Barra, J. J. Cosa, and R. H. deRossi, *J. Org. Chem.*, 1990, **55**, 5850.
7. D. W. Griffith and M. L. Bender, *J. Am. Chem. Soc.*, 1973, **95**, 1679.
8. (a) M. L. Bender, F. J. Kezdy, and B. Zerner, *J. Am. Chem. Soc.*, 1963, **85**, 3017; (b) B. Capon and B. C. Ghosh, *J. Chem. Soc. B*, 1966, 472; (c) M. N. Khan, *J. Chem. Soc., Perkin Trans. 2*, 1990, 675; (d) A. K. Yatsimirsky, K. Yu. Bezsoudnova, and I. K. Sakodinskaia, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 635; (e) M. N. Khan, *J. Mol. Catal.*, 1987, **40**, 195.
9. B. T. Tozer and S. Smiles, *J. Chem. Soc.*, 1938, 1897.
10. Y. Kurono, H. Fukatsu, T. Yotsuyanagi, and K. Ikeda, *Chem. Pharm. Bull.*, 1979, **27**, 963.
11. M. L. Bender and M. Komiyama, *Cyclodextrin Chemistry*, Springer-Verlag, New York, 1978.
12. R. L. VanEtten, G. A. Gloves, J. F. Sebastian, and M. L. Bender, *J. Am. Chem. Soc.*, 1967, **89**, 3253.
13. F. M. Menger and M. Ladika, *J. Am. Chem. Soc.*, 1987, **109**, 3145.
14. R. Breslow and S. Chung, *Tetrahedron Lett.*, 1990, **31**, 631.
15. N. Muller, *J. Solution Chem.*, 1991, **20**, 669.
16. A. Buvari and L. Barcza, *J. Chem. Soc., Perkin Trans. 2*, 1988, 543.
17. O. S. Tee, M. Bozzi, J. J. Hoeven, and T. A. Gadosy, *J. Am. Chem. Soc.*, 1993, **115**, 8990.
18. O. S. Tee and J. J. Hoeven, *J. Am. Chem. Soc.*, 1989, **111**, 8318.
19. R. I. Gelb, L. M. Schwarts, and D. A. Lauger, *Bioorg. Chem.*, 1982, **11**, 274.
20. T. L. Paal and J. Szejtli, *Acta Chim. Acad. Sci. Hung.*, 1981, **106**, 9.
21. H. Ye, D. Rong, and V. T. D'Souza, *Tetrahedron Lett.*, 1991, **32**, 5231.
22. T. H. Fife and D. M. McMahon, *J. Am. Chem. Soc.*, 1969, **91**, 7481.

Received June 27, 1995
in revised form October 4, 1996