# Base Promotion and Intramolecular Catalysis in Acetal Hydrolysis. Reaction of o-Hydroxybenzaldehyde Diethyl Acetal

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The existence of three different routes of hydrolysis has been demonstrated for the reactions of o-hydroxybenzaldehyde diethyl acetal. In the first route, the specifically hydronium ion-catalyzed decomposition prevails if the acid concentration is relatively high (pH about 6 or lower). In the second route, the decomposition proceeds mainly by the intramolecular catalysis of the phenolic hydroxy group if the pH varies between 7.9 and 8.6. In the third route, the base-promoted hydrolysis takes place if the solution is relatively basic. Especially, if the sodium hydroxide concentration is higher than 0.15 M, the observed first-order rate coefficients remain constant. The formal kinetics of these different routes has been described. The dissociation constant of the phenol has been estimated from the kinetic data.

The hydrolysis of acetals has been the object of intensive studies. Although the pre-equilibrium protonation and the subsequent unimolecular decomposition of the protonated substrate (an A-1 reaction) has been accepted as the general mechanism of acetal hydrolysis,[1] it has recently been shown that in many cases the proton transfer occurs in the rate-determining stage of the reaction.[2] It is by no means justified to assume that only these two routes could exist in the hydrolytic decomposition of acetals. For instance, the reactions of acetals in basic solutions have not been studied in detail. Although it is well-known [1b] that acetals are generally stable in basic solutions, it is reasonable to assume that in particular cases, for instance in the case of o-hydroxybenzaldehyde diethyl acetal (I), the structure of the acetal may favor the hydrolytic decomposition in basic solutions.

(I)
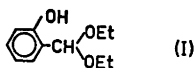
In solutions of strong bases the proton in the hydroxyl group is dissociated, and the structure of the anion thus formed can be assumed to favor a unimolecular heterolysis of the substrate as the negative charge of the phenolate ion will be easily distributed to the possible leaving group, the alkoxide ion. Moreover, (I) is an excellent model compound to study the possible intramolecular catalysis by a hydroxyl group. This phenomenon may especially appear in the hydrolysis of glycosides.

EXPERIMENTAL

Materials. o-Hydroxybenzaldehyde diethyl acetal was prepared from o-hydroxybenzaldehyde, triethyl orthoformate, and absolute ethanol using the method described previously by Pauly and Buttlar.[3] The product was purified by distillation. B.p. 98 °C/4 Torr. NMR spectrum: 6 H at δ 1.32 ppm, 4 H at δ 3.49 ppm, 1 H at δ 5.43 ppm, 5 H at δ 6.5 − 7.2 ppm, and 1 H at δ 7.75 ppm. Other signals were not observed.

Kinetic measurements. Kinetic measurements were performed in dilute perchloric acid solutions, in sodium hydroxide solutions, and in the following buffer systems: potassium dihydrogen phosphate-disodium hydrogen phosphate, boric acid-sodium dihydrogen borate, sodium hydrogen carbonate-sodium carbonate, and acetic acid-sodium acetate. Ordinary water was usually employed as solvent in the measurements. Some experiments were also performed in heavy water. The temperatures were between 25 and 80 °C.

The progress of the reaction was followed spectrophotometrically on a Unicam SP 800 (absorption of salicylaldehyde at 255 − 275 nm). The temperature of the cell housing block was adjusted with water circulation from a electronically controlled Lauda thermostat. The concentration of the substrate was about 3×10^{-5} M. First-order kinetics was strictly obeyed in all cases.

The pH values of the reaction mixtures were measured with a Radiometer apparatus. These determinations were performed at 70 °C.

RESULTS AND DISCUSSION

Specific hydronium ion catalysis. To study the nature of the catalysis in the hydrolysis of salicylaldehyde diethyl acetal some measurements were performed in relatively high hydronium ion concentrations (higher than 10^{-7} M) in acetic acid-sodium acetate buffers at 25 °C (Table 1). The kinetic data in 1/2 buffer reveal that the observed rate coefficients are independent of the concentration of the undissociated acid. This observation is in accordance with the A-1 mechanism of acetal hydrolysis (eqn. 1).

$$(1)$$
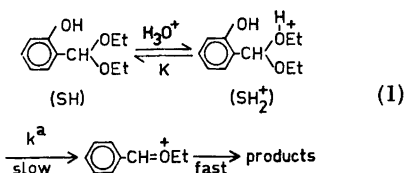
The rate of reaction (1) can be expressed by eqn. (2)

$$\text{rate} = k^a\, K_{eq}[H_3O^+][SH] = k_2^a\,[H_3O^+][SH] = k_1^a\,[SH] \tag{2}$$

where k_1^a is the measured first-order rate coefficient and k_2^a the corresponding second-order rate coefficient. The calculated second-order rate coefficients were found to be independent of the hydronium ion concentration of the solution, which is in accordance with eqn. (2). For instance, the second-order rate coefficients measured in 1/10, 1/2, and 1/1 acetic acid-sodium acetate buffers are equal within the limits of experimental error. Dilute perchloric acid solutions were also employed in some measurements (Table 2); the second-order rate coefficients were found to be in good agreement with those measured in buffer solutions. This reveals that the contribution of uncatalyzed reactions must be negligible under the above mentioned conditions. Some additional measurements were also performed in potassium dihydrogen phosphate-disodium hydrogen phosphate buffers (Table 1). If only the hydronium ion-catalyzed reaction occurred in these solutions, the ratio of the rate coefficients would correlate with the buffer ratio (HA)/(A⁻). It is found that the rate coefficients measured in 19/1 and 9/1 buffers have a ratio of 19/9.6, which is only a little lower than is expected and the rate coefficients measured in 7/3 and 1/1 buffers are, on the contrary, markedly higher than is expected on the basis of the buffer ratios. Thus it is evident that at hydronium ion concentrations lower than 10^{-6} M (19/1 buffer) some additional route must be taken into account.

The acid-catalyzed hydrolysis of salicylaldehyde diethyl acetal was also studied at different

Table 1. Kinetic data for the acid-catalyzed hydrolysis of *o*-hydroxybenzaldehyde diethyl acetal in buffer solutions at 25 °C. HA denotes the more acidic component of the buffer system.

HA	$\dfrac{[HA]}{[A^-]}$	[HA]	No. of runs	$10^2 k$ s⁻¹	$[H_3O^+]^b$ M	$10^2 k$ M⁻¹s⁻¹
CH₃COOH	1/1	0.100	4	2.385	4.17×10^{-5}	5.72
CH₃COOH	1/2	0.05	1	1.350	2.087×10^{-5}	6.47
CH₃COOH	1/2	0.0375^a	1	1.319	2.087×10^{-5}	6.32
CH₃COOH	1/2	0.0250^a	1	1.309	2.087×10^{-5}	6.27
CH₃COOH	1/2	0.0125^a	1	1.311	2.087×10^{-5}	6.28
CH₃COOH	1/10	0.0100^a	2	0.2221	4.17×10^{-6}	5.33
H₂PO₄⁻	19/1	0.0633	1	0.265		
H₂PO₄⁻	9/1	0.0600	2	0.1335		
H₂PO₄⁻	7/3	0.0467	1	0.0458		
H₂PO₄⁻	1/1	0.0333	1	0.0269		
H₂PO₄⁻	1/9	0.00667	1	0.01155		
H₂PO₄⁻	1/19	0.00333	1	0.01220		

[a] The ionic strength was adjusted at 0.1 M with sodium chloride.
[b] The hydronium ion concentration of the buffer solutions was determined kinetically by the method described previously.[4]

Table 2. Kinetic data for the hydronium ion-catalyzed hydrolysis of *o*-hydroxybenzaldehyde diethyl acetal in aqueous solutions at different temperatures. Perchloric acid was employed as the catalyst. $[H_3O^+]^a = 4.179 \times 10^{-5}$ M; No. of runs: 2.

t °C	k $M^{-1}s^{-1}$	$\Delta H^{\ddagger}_{298}$ kcal mol^{-1}	$\Delta G^{\ddagger}_{298}$ kcal mol^{-1}	$\Delta S^{\ddagger}_{298}$ cal K^{-1}mol^{-1}
6.6	121.1			
11.4	178.9			
16.2	259.0	12.6 ± 0.2	13.75 ± 0.01	-3.9 ± 0.6
21.2	394.2			
26.0	560.4			

[a] The hydronium ion concentration of the perchloric acid solution was determined kinetically by the medthod described previously.[4]

Table 3. First-order rate coefficients for the hydrolysis of *o*-hydroxybenzaldehyde diethyl acetal in aqueous buffer solutions at 70 °C. HA denotes the more acidic component of the buffer system.

$\dfrac{[HA]}{[A^-]}$	[HA] M	No. of runs	10^3k s^{-1}
HA = $H_2PO_4^-$; pK_a^{25} 7.20 (Ref. 7)			
9/1	0.0600	2	34.8
7/3	0.0467	2	16.6
1/1	0.0333	2	12.84
4/6	0.0267	2	11.6
3/7	0.0200	5	9.48
2/8	0.0133	4	9.16
1/9	0.00667	8	7.98
1/19	0.00333	2	7.82
HA = H_3BO_3; pK_a^{25} 9.23 (Ref. 7)			
5/1	0.100	6	8.41
5/2	0.100	3	7.82
10/7	0.100	2	7.31
1/1	0.100	4	6.66
3/5	0.0600	2	5.76
2/5	0.0400	2	4.86
2/10	0.0200	2	3.69
1/10	0.0100	2	2.75
HA = HCO_3^-; pK_a^{25} 10.33 (Ref. 7)			
1/1	0.100	2	3.35
3/5	0.0600	1	2.58
3/7	0.0429	1	2.09
3/17	0.0176	1	1.462
1/19	0.01111	1	1.162
HA = $D_2PO_4^{-a}$			
1/19	0.00333	2	5.35

[a] In deuterium oxide.

temperatures (Table 2). The parameters of the Arrhenius equation were calculated from the plot log k *versus* $1/T$ by the method of least squares. The activation entropy, $\Delta S^{\ddagger} = -3.9$ cal K^{-1} mol^{-1}, is found to be of the magnitude expected for the *A*-1 hydrolysis of acetals.[5]

Intramolecular catalysis. As mentioned above, an alternative route must exist in hydronium ion concentrations lower than 10^{-6} M. Further kinetic data are, however, required especially at low hydronium ion concentrations to get information on this mechanistical anomaly. The sensitivity of the studied compound to hydrolytic decomposition is relatively low under these conditions and therefore a higher temperature, 70 °C, was generally employed for the kinetic
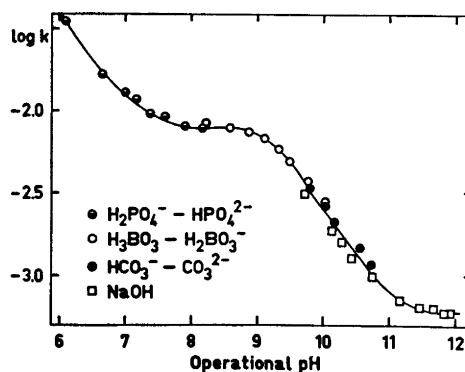

Fig. 1. The logarithms of the first-order rate coefficients of the hydrolysis of *o*-hydroxybenzaldehyde diethyl acetal in water as a function of the operational pH value of the solution. Temperature 70 °C.

measurements. First-order rate coefficients determined in different buffer systems at 70 °C are collected in Table 3. To get an illustration of the variation of the rate coefficients with the hydronium ion concentration of the solution the logarithms of the rate coefficients were plotted against the measured pH values of the reaction mixtures (Fig. 1). Although the pH values are only operative and do not give exact hydronium ion concentrations of the solutions it is reasonable to assume that they are satisfactorily in correlation with the hydronium ion concentrations of the solutions. From this plot it can be seen that in solutions with pH 7.9 − 8.6 the hydrolytic decomposition is actually independent of the hydronium ion concentration of the solution. This situation can best be explained in terms of an intramolecular general acid catalysis (eqn. 3). Although the intramolecular catalysis by a carboxy group has been realized in the hydrolysis of acetals [6] the related intramolecular cataly-

$$\text{(TS)}_\text{int} \qquad (3)$$
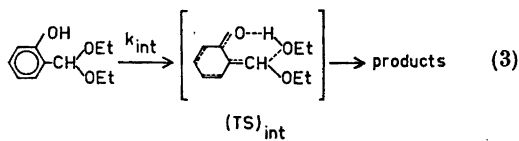
sis by a hydroxy group has not been observed in previous studies. In this particular case, however, structural effects can be assumed to favor the intramolecular catalysis. First, the phenolic hydroxyl group is at a position which enables the hydrogen bond formation with the etheral oxygen atom in the transition state of the reaction. Second, the quinone type structure of the transition state is energetically favorable. The rate of reaction (3) may be expressed by eqn. (4).

$$\text{rate} = k_\text{int}[\text{SH}] \qquad (4)$$

Naturally the rate of this particular reaction is independent of the hydronium ion concentration of the solution. The contribution of k_int decreases with increasing hydronium ion concentration of the solution as shown in eqn. (5).

$$\text{rate} = (k_2^\text{a}[\text{H}_3\text{O}^+] + k_\text{int}) \, [\text{SH}] = k_\text{obs}[\text{SH}] \qquad (5)$$

Thus k_int can be neglected along with the hydronium ion-catalyzed reaction at sufficiently high acid concentrations. As mentioned above this is really the case at hydronium ion

concentrations higher than 10^{-6} M. Eqn. (5) also reveals that at low hydronium ion concentrations the contribution of the term $k_2^\text{a}[\text{H}_3\text{O}]^+$ becomes negligible as compared with k_int. From the kinetic data in Table 2 a value of 9.6×10^3 $\text{M}^{-1}\text{s}^{-1}$ can be estimated for k_2^a at 70 °C. If the hydronium ion concentration is 10^{-8} M the term $k_2^\text{a}[\text{H}_3\text{O}^+]$ is $9.6 \times 10^{-5}\text{s}^{-1}$ and is thus only about one per cent of the observed rate coefficient. Hence, it is reasonable to assume that in the pH range 7.9 − 8.8 the contribution of the hydronium ion-catalyzed reaction is negligible and consequently the rate coefficients measured under these conditions give directly the value for k_int, thus, a value of $(8.01 \pm 0.14) \times 10^{-3}$ s^{-1} is obtained from the data in Table 3.
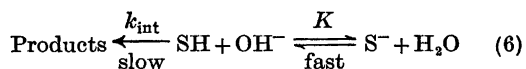
To get additional evidence for the change in the mechanism discussed above some measurements were performed in heavy water. The rate coefficients in 1/19 phosphate buffer give a k_D/k_H value of 0.68 (Table 3). As in the A-1 hydrolysis of acetals this ratio is generally of the magnitude 2 − 3,[1b] the remarkable difference cannot be explained without assuming a change in the reaction mechanism. On the contrary, deuterium solvent isotope effects of unity or lower reflect a general acid catalysis as shown by the kinetic data presented recently for the A-$S_\text{E}2$ hydrolysis of acetals.[2] Thus the measured k_D/k_H value is in accordance with the proposed intramolecular general acid catalysis.

To get information on the temperature dependence of the intramolecular OH-catalyzed reaction some measurements were performed in boric acid-sodium borate and potassium dihydrogen phosphate-disodium hydrogen phosphate buffers at different temperatures (Table 4). The rate coefficients measured in these buffers are equal within the limits of experimental error. If the measured activation entropy is compared with that of the hydronium ion-catalyzed hydrolysis only a small difference is found. This result is not surprising since in the case of A-1 and A-$S_\text{E}2$ reactions the activation entropies have been found to be of the same magnitude.[5]

As mentioned above the rate of the intramolecular OH-catalyzed reaction should be independent of the hydronium ion concentration of the solution. However, if a partial neutralization of the substrate took place, the total rate would be retarded due to the acid-base equilibrium described in eqn. (6).

Table 4. Kinetic data for the hydrolysis of o-hydroxybenzaldehyde diethyl acetal at different temperatures in boric acid-sodium borate buffer ($[HA] = 0.1$ M, $[A^-] = 0.1$ M), in potassium dihydrogen phosphate-disodium hydrogen phosphate buffer ($[HA] = 0.00333$ M, $[A^-] = 0.0633$ M) and in 0.2 M sodium hydroxide in water.

t °C	10^3k s^{-1}	$\Delta H^{\ddagger}_{298}$ kcal mol^{-1}	$\Delta G^{\ddagger}_{298}$ kcal mol^{-1}	$\Delta S^{\ddagger}_{298}$ cal K^{-1}mol^{-1}
$H_2PO_4^- $-$HPO_4^{2-}$				
25.0	0.1219			
40.6	0.571			
50.6	1.403	18.3 ± 0.3	22.81 ± 0.02	-15.0 ± 0.8
59.6	3.42			
69.8	7.82			
H_3BO_3-$H_2BO_3^-$				
40.6	0.583			
50.0	1.493			
59.6	3.56	18.9 ± 0.2	22.83 ± 0.02	-13.1 ± 0.5
69.8	8.41			
NaOH				
50.0	0.0802			
59.5	0.224			
69.5	0.601	22.0 ± 0.1	24.78 ± 0.02	-9.5 ± 0.4
80.0	1.591			

$$\text{Products} \xleftarrow[\text{slow}]{k_{\text{int}}} \text{SH} + \text{OH}^- \underset{\text{fast}}{\overset{K}{\rightleftharpoons}} \text{S}^- + \text{H}_2\text{O} \qquad (6)$$

Here the acid-base equilibrium can be assumed to be a diffusion-controlled reaction as a relatively strong acid will be neutralized with a strong base. When the acid-base equilibrium is taken into account the total rate of the reaction can be expressed with eqn. (7).

$$\text{rate} = \frac{k_{\text{int}}}{1 + K[\text{OH}^-]} [\text{SH}]_{\text{total}} = k_{\text{obs}}[\text{SH}]_{\text{total}} \qquad (7)$$

The form of this equation reveals that the difference between k_{int} and k_{obs} will be increased with increasing hydroxide-ion concentration of the solution, since the term $1 + K[\text{OH}^-]$ will deviate more and more from unity. Of course, the value of the equilibrium constant K determines in which pH region the difference between k_{obs} and k_{int} becomes observable. The kinetic data (see Fig. 1) reveal that this occurs when the pH value of the solution is higher than 8.6. As the pH measurements were performed at 70 °C, the hydroxide ion concentration of the solution is of the magnitude 10^{-4} M (pK_w is 12.80 at 70 °C [7]).

The equilibrium constant of reaction (6) is $K = K_a/K_w$, where K_a is the dissociation con-

stant of the acid and K_w is the ionic product of water. From the pK_a values of different phenols it can be concluded that in this case K_a is of the magnitude $10^{-9} - 10^{-10}$ (Ref. 8). As K_w is of the magnitude 10^{-13} at 70 °C the equilibrium constant K can be assumed to be between 10^3 and 10^4. Thus eqn. (7) can be reduced to eqn. (8) if the hydroxide
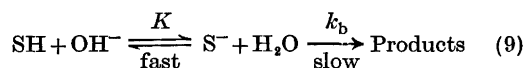
$$k_{\text{obs}} = k_{\text{int}}/K[\text{OH}^-] \qquad (8)$$

ion concentration of the solution is higher than 10^{-2} M when $K[\text{OH}^-] \gg 1$. Thus eqn. (8) should be valid especially at relatively high hydroxide ion concentrations. When this is the case it is at first sight surprising that at the highest hydroxide ion concentrations employed in this work (Table 5) the observed rate coefficients remain constant although the hydroxide ion concentration of the solutions is varied (see also Fig. 1). This situation is, however, understandable if a third reaction route is followed in the most basic solutions.

Base-promoted hydrolysis. In basic solutions the hydrolysis of salicylaldehyde diethyl acetal may also take place through the anionic form of the substrate as described in eqn. (9). The rate of this reaction is given by eqn. (10). In

Table 5. Kinetic data for the hydrolysis of *o*-hydroxybenzaldehyde diethyl acetal at 70 °C in sodium hydroxide solutions of different concentrations. The equilibrium constants of reaction (6) collected in the table have been calculated from the kinetic data using eqn. (13).

[NaOH] M	No. of runs	$10^3 k$ s^{-1}	$10^{-3} K$ M^{-1}
Solvent: H_2O			
0.00100	3	3.07	2.00
0.00250	2	1.838	1.99
0.00350	2	1.575	1.88
0.00500	3	1.255	2.05
0.0100	1	0.980	1.84
0.0250	1	0.692	(3.08)
0.0500	2	0.642	(3.27)
0.100	2	0.623	—
0.150	1	0.593	—
0.200	2	0.601	—
Solvent: D_2O			
0.096	2	0.292	—

$$SH + OH^- \underset{fast}{\overset{K}{\rightleftharpoons}} S^- + H_2O \overset{k_b}{\underset{slow}{\longrightarrow}} Products \quad (9)$$

$$rate = \frac{k_b K [OH^-]}{1 + K[OH^-]} [SH]_{total} \quad (10)$$

extreme cases, $K[OH^-] \gg 1$, eqn. (10) is reduced to form (11).

$$rate = k_b [SH]_{total} \quad (11)$$

This expression shows that although the rate of reaction (9) depends on the hydroxide ion concentration of the solution under relatively mild conditions, the rate of the base-promoted reaction is independent of $[OH^-]$ at sufficiently high hydroxide ion concentrations. The kinetic data in Fig. 1 show that this is really the case in solutions in which the hydroxide ion concentration is higher than 0.1 M. Thus the value of k_b can be calculated from the kinetic data in 0.15 and 0.2 M sodium hydroxide solutions and a value of 5.97×10^{-4} s^{-1} is obtained.

In the formal kinetics discussed above it was not taken into account that in reality reactions (6) and (9) can take place simultaneously. The rate coefficient of this total reaction is expressed by eqn. (12). It is easy to find out that eqn. (10) is only a particular case of this expression, as in

$$k_{obs} = (k_{int} + k_b K[OH^-])/(1 + K[OH^-]) \quad (12)$$

the numerator k_{int} was disregarded in comparison with the term $k_b K [OH^-]$. This is naturally the case when the hydroxide ion concentration is sufficiently high. However, in the pH range 8.6 – 11.5 all the terms in eqn. (12) must be taken into account.

Eqn. (12) enables also the determinations of the equilibrium constant K in eqn. (6) in water solutions. From the rate coefficients $k_{int} = 8.01 \times 10^{-3}$ s^{-1} and $k_b = 0.597 \times 10^{-3}$ s^{-1} and from the first-order rate coefficients measured in sodium hydroxide solutions of different concentrations (Table 5) a value for the equilibrium constant can be obtained using eqn. (13).

$$K = (k_{int} - k_{obs})/(k_{obs} - k_b)[OH^-] \quad (13)$$

The results are collected in Table 5. When the equilibrium constant $(1.95 \pm 0.04) \times 10^3$ was calculated, the rate coefficients measured in 0.025 and 0.05 M sodium hydroxide solutions were omitted as the term $(k_{obs} - k_b)$ becomes indeterminate within the limits of experimental error.

In the determination of the dissociation constants of salicylaldehyde diethyl acetal potentiometric titration cannot be applied. First, the acid is relatively weak and consequently the accuracy of the measurements may be low. Second, the substrate undergoes hydrolytic decomposition both in acid and neutral solutions. The dissociation constant K_a can, however, be calculated from the kinetic data. The dissociation constant $K_a = K \times K_w$ and thus a value of $K_a = (3.09 \pm 0.06) \times 10^{-10}$ is obtained at 70 °C from the ionic product of water and from the kinetic value of K. Thus pK_a of the acid is 9.51 ± 0.01 at 70 °C. This pK_a value is found to be a little lower than that of the unsubstituted phenol. This difference is expected as the electronegative diethoxymethyl group in the aromatic ring may increase the acid strength of the substrate.

The hydrolysis of salicylaldehyde diethyl acetal in 0.2 M sodium hydroxide was studied also at different temperatures (Table 4). The activation entropy of this reaction, -9.5 cal K^{-1}mol^{-1}, is only slightly negative and therefore it seems probable that a water molecule has not taken part in the transition state of the reaction. Some additional measurements were performed in 0.1 M sodium hydroxide using different

Table 6. Salt effects in the hydrolysis of *o*-hydroxybenzaldehyde diethyl acetal at 0.1 M sodium hydroxide in water at 70 °C.

Salt	[Salt] M	10^3k s^{-1}
—	0	0.630
NaCl	0.100	0.639
	0.250	0.666
	0.500	0.654
	0.750	0.669
Na_2CO_3	0.100	0.610
	0.300	0.614
Na_3PO_4	0.100	0.636

amounts of added electrolytes (Table 6); the rate coefficients are seen to be equal within the limits of experimental error. Solvent deuterium isotope effect was also studied in basic solutions (Table 5). The ratio k_D/k_H was found to be 0.469.

Although the formal kinetics of the hydrolysis of salicylaldehyde diethyl acetal reveals that in relatively basic solutions the hydrolysis of the compound proceeds through the anionic form of the substrate, the transition state of this reaction cannot be deduced on the basis of the formal kinetics. It is, however, reasonable to assume that in the transition state of this route the negative charge of the phenolate ion will be distributed to the leaving alkoxide ion [structure $(TS)_b$]. The stability of this species can be
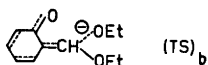
assumed to be relatively high and consequently the observed decomposition in basic solutions is understandable in this particular case, although this kind of reaction has not been observed in previous studies of acetal hydrolysis. All the kinetic data are also in accordance with this mechanism. First, the salt effects are expected to be negligible in this route as the initial state and the transition state differ only in the distribution of the negative charge. Second, the activation entropy of the reaction is in accordance with this mechanism as stated above. Third, the deuterium solvent isotope effect is not unexpected for this kind of unimolecular

decomposition. Naturally the mechanism in which the solvent, water, would act as a general acid cannot fully be excluded, but it seems less probable on the basis of the kinetic data. In accordance with this assumption the buffer experiments performed in sodium hydrogen carbonate-sodium carbonate and disodium hydrogen phosphate-sodium phosphate buffers did not give evidence for a general acid catalysis.

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