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THE KINETICS AND MECHANISM OF HYDROLYTIC CLEAVAGE OF PHENYL SALICYLATE UNDER HIGHLY ALKALINE MEDIUM

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Abstract—The kinetics of hydrolytic cleavage of phenyl salicylate within the hydroxide ion concentration range of 0.05–2.0M at 35° indicate rate constants are almost independent of $[OH^-]$ within the range of 0.05 M to 0.1 M and vary linearly, within the range of 0.1–2.0 M with rates attributable to intramolecular general base catalyzed neutral hydrolysis. The hydroxide ion catalyzed hydrolytic cleavage is ~ 10^4 times slower than the respective reaction of phenyl benzoate. The rate enhancement of pH independent rate of hydrolysis has been found to be solely due to favourable ΔS^*.

Since the cleavage of ester and amide bonds are involved in many biochemical reactions such as esterolysis by esterases[1] and proteinolysis by proteinases,[2] a special effort has been focussed, far last not more than three decades, by many investigators to explore the mechanistic details of such reactions. Bender *et al.*[3] studied the hydrolysis of various p-nitrophenyl salicylates and the aim of this study was to determine quantitatively the effect of neighbouring hydroxyl group on hydrolytic cleavage of ester bond. Capon and Ghosh[4] studied the hydrolysis of phenyl salicylate and its derivatives and discussed the probable mechanisms of these reactions. These authors, however, studied the mechanism in a weakly alkaline medium. It is well known from earlier studies[5] on various acyl transfer reactions that the mechanism of hydrolytic processes changes with the change in the alkalinity of the reaction medium and we decided to study the mechanism of hydrolysis of phenyl salicylates in a highly alkaline medium.

EXPERIMENTAL

Materials

Phenyl salicylate used was of reagent grade obtained from B.D.H. All other chemicals were also of reagent grade and were used without any further purification. All solutions for kinetic runs were prepared in deionized glass distilled water.

Kinetic measurements

Reaction mixtures containing all the reaction constituents except phenyl salicylate were prepared in a total volume of 48 ml and were temperature equilibrated in a thermostatic water bath at 35° for about 10–15 mins. The reaction was started by transferring 2 ml of concentrated solution of substrate (phenyl salicylate prepared in 96% ethanol water solvent) into temperature equilibrated reaction mixture. This procedure added 4% ethanol to reaction mixture. An aliquot equals to 2.5–3 ml was withdrawn from the reaction mixture and was transferred to a 3 ml quartz cuvette. The cuvette was then quickly placed into the cell compartment of Hitachi 100-50 double beam UV-Visible spectrophotometer. The absorbance of reaction mixture was recorded at a fixed wave length of 340 mm. There was always a maximum of ~30 sec lapse on the average between the time of removal of the aliquots and the time at which their absorbance was recorded. During this period, the error due to the drop in temperature of reaction mixture was considered to be negligible because the constant temperature (35°) for most of the kinetic runs was very close to ambient temperature (~30°). The kinetics were carried out by monitoring the decrease in absorbance due to disappearance of phenyl salicylate and in almost all kinetic runs, the absorbance changes were generally 0.5 absoobance units. Reactions were generally followed up to 80–98% completion with at least 10 readings as well as a reading after ~20 hrs. Sodium hydroxide ion concentrations were 10^2–10^4 times larger than that of substrate in all kinetics runs. The reactions under such conditions, were found to follow pseudo first-order kinetics. Rate constants (k_{obs}) were calculated from eqn (1) using a nonlinear

$$A_{obs} = X_0E_{app}\exp(-k_{obs}t) + A_\infty \qquad (1)$$

least squares technique. In eqn (1), A_{obs} is observed absorbance at any time t, X_0 is the initial concentration of substrate, E_{app} is an apparent extinction coefficient, and A_∞ is the absorbance at infinite time of reaction. A_∞, E_{app} and k_{obs} were considered as three unknown parameters in regression analysis.[6] Agreement between experimental and calculated data points was generally excellent as evident from a typical kinetic run (Fig. 1). Nearly all kinetic runs were carried out in duplicates and few in triplicate and average deviations between these rate constants were always less than 5%.

At the end of few kinetic runs, the UV spectra of reaction products were recorded and were compared with that of an authentic mixture of the expected products phenol and salicylic acid. Good agreement was always obtained.

RESULTS

A series of kinetic runs were carried out at 35° within the sodium hydroxide concentration range of 0.05–2.0 M at a constant ionic strength of 2.0 M maintained by either sodium nitrate or potassium chloride. The observed

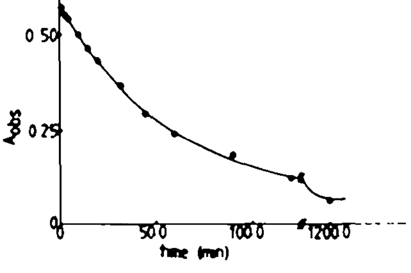


Fig. 1. Plot showing the variation of observed absorbance vs. time for a typical kinetic run containing 0.05 M NaOH and 1.2×10^{-4} M phenyl salicylate. The solid line is generated from eqn (1) with the calculated values of k_{obs}, A_∞ and E as 1.74×10^{-2} min^{-1}, 0.065 and 4291 M^{-1} cm^{-1}, respectively.

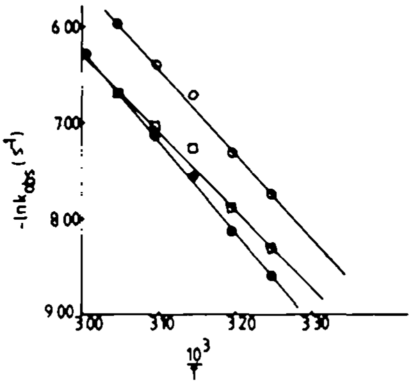


Fig. 2. *Plots showing the dependence of k_{obs} on temperature for k_2 step (●), $k_1 + k_2$ step (○) and k_2 step (□). The solid lines are drawn through the calculated values of rate constants.*

pseudo first-order rate constants, as shown in Table 1, were found to be well fitted to an empirical eqn (2) within the hydroxide ion concentration

$$k_{obs} = \frac{A_1[OH^-] + A_2[OH^-]^2}{1 + A_3[OH^-]} \qquad (2)$$

range of 0.05–2.0 M. The empirical adjustable parameters A_1, A_2 and A_3 were evaluated using nonlinear least squares regression technique[6] and the values thus obtained are $124.5 \pm 39.3\ M^{-1}\ min^{-1}$, $318.6 \pm 26.4\ M^{-2}\ min^{-1}$ and $10864 \pm 227\ M^{-1}$, respectively. The reproducibility of the observed data is evident from the Table 1.

In order to study the effect of ionic strength on hydrolysis the reaction kinetics were performed at different ionic strength ranging from 0.05–1.5 M at 50°. The observed results are summarized in Table 2. These results indicate that the rate constants are almost independent of ionic strength.

The effect of temperature on rate of hydrolysis was studied within the temperature range of 35°–60° at two different hydroxide ion concentrations 0.05 and 0.5 M. The observed pseudo first-order rate constants are shown graphically in Fig. 2. These rate constants were found to be well fitted to Arrhenius and Eyring equations 3 and 4, respectively.

Table 1. Effect of hydroxide ion concentrations on hydrolytic cleavage of Phenyl Salicylate[a]

$[OH^-]$ M	$10^2 k_{obs}$ min^{-1}	$10^2 k^c_{cal}$ min^{-1}
0.05	1.11 ± 0.18	1.29
0.07	1.31 ± 0.10	1.35
0.10	1.30 ± 0.02	1.44
0.20	1.50 ± 0.01	1.73
0.50	2.56 ± 0.02	2.61
0.70	3.24 ± 0.05	3.20
1.00	3.86 ± 0.14	4.08
1.20	4.82 ± 0.05	4.66
1.50	6.20 ± 0.24	5.54
2.00	6.58 ± 0.18	7.01

[a] Conditions: $[\text{Phenyl Salicylate}]_0 = 1.20 \times 10^{-4}$ M, temp = 35°, $\mu = 2 \cdot 0$ M, 4% ethanol in the reaction mixture.
[b] Error limits are standard deviations.
[c] Calculated from equation 2 with A_1, A_2, and A_3 listed in the text.

Table 2. Effect of ionic strength on hydrolytic cleavage of phenyl salicylate[a]

Ionic Strength [KCl]	$10^2 k_{obs}$ (min^{-1})	A_∞	A_{obs} at 120 min
0.05 M	4.46 ± 0.24[b]	0.038 ± 0.007[b]	0.044
0.50 M	4.75 ± 0.09	0.046 ± 0.002	0.049
1.00 M	4.34 ± 0.14	0.047 ± 0.004	0.054
1.50 M	3.55 ± 0.21	0.033 ± 0.010	0.057

[a] Conditions: 0.05 M NaOH, 1.24×10^{-4} M Phenyl salicylate, 50°.
[b] Error limits are standard deviations.
[c] At 90 min.

$$k_{obs} = A \exp(-Ea/RT) \qquad (3)$$

$$k_{obs} = (k_B T/h) \exp(-\Delta H^*/RT) \exp(\Delta S^*/R) \qquad (4)$$

All the symbols have their usual meanings. The activation parameters were obtained from equations (3) and (4) using the nonlinear least squares regression technique.[6] The results obtained are summarized in Table 3. The maximum and root mean squares deviations between

Table 3. Activation parameters of hydrolytic cleavage of phenyl salicylate[a]

Reaction step	ΔF^{*b} (kcal/mole)	ΔH^* (kcal/mole)	$-\Delta S^*$ (cal/deg.mole)	E_a (kcal/mole)	10^{-8} A (sec^{-1})	$10^5 R^c_{ms}$ (sec^{-1})	Max dev[d] (%)
k_2^{e}	23.36	17.66 ± 0.38[f]	18.2 ± 1.1[f]	18.29 ± 0.38[f]	18.7 ± 0.0[f]	3.76	9
$k_1 + k_2^{g}$	22.84	15.90 ± 1.02	22.2 ± 3.2	16.54 ± 1.02	2.58 ± 0.00	14.1	11
$k_2'^{h}$	23.18	13.25 ± 1.23	31.7 ± 3.8	13.88 ± 1.23	0.002 ± 0.000	9.67	25

[a] Conditions: 1.2×10^{-4} M phenyl salicylate, $\mu = 2.0$ M.
[b] ΔF^* was calculated from relationship $k = (K_B T/h) \exp(-\Delta F^*/RT)$ at 35°.
[c] $R_{ms} = \left(\sum_{i=1}^{N} (k_{obs}\ k\ calcd)^2/(n-2)\right)^{1/2}$.
[d] Maximum deviation between observed and calculated values of rate constants.
[e] At 0.05 M NaOH.
[f] Error limits are standard deviations;
[g] At 0.5 M NaOH.
[h] k_2' (sec^{-1}) was calculated from the relationship.
$k_2' = k_{obs}$ at 0.5 M NaOH $- K_{obs}$ at 0.05 M NaOH where $k_2' = k_2[\bar{O}H]$.

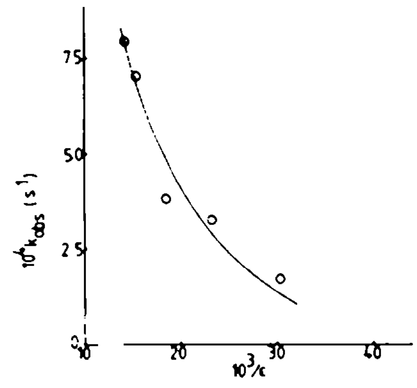


Fig. 3. Plot showing the dependence of k_{obs} on dielectric constant. The solid line is generated from Eq. 5 with $10^3 k_0 = 3.80$ sec^{-1} and $\beta = 111.2$.

observed and calculated values as mentioned in Table 3 represent the extent of reliability of the data fitting.

The effect of dielectric constant on hydrolysis was studied at 50° by using solvent containing different amount of ethanol (by volume). The ionic strength and hydroxide ion concentration were kept constant at 0.1 and 0.05 M, respectively. The observed pseudo first-order rate constants, as shown in Fig. 3, were reasonably fitted by an empirical eqn (5) which is similar to one

$$k_{obs} = k_0 \exp(-\beta/D) \qquad (5)$$

obtained[7] for reactions between ions of charge Z_A and Z_B with $\beta = Z_A Z_B e^2/K_B T r^*$ where r^* denotes the interionic distance of activated complex, e, k_B and T denote electronic charge, Boltzmann's constant and temperature (°K), respectively. The empirical constants k_0 and β were calculated from eqn (5) using the nonlinear least-squares technique and thus the obtained values are $(3.80 \pm 1.30)10^{-3}$ sec^{-1} and 111.2 ± 20.8, respectively.

DISCUSSION

An enhanced reactivity of phenyl salycylate in comparison to phenyl o-methoxysalicylate has been attributed to the presence of neighbouring hydroxyl group which is acting either as a general acid or a general base in the hydrolytic process. Although the correct mechanism has not been so far unambiguously confirmed, the preferred mechanism[4] is shown in Scheme 1. It is not clear from the studies by Capon and Ghosh whether the general base catalyzed nucleophilic water attack or expulsion of leaving group is rate determining step. However, viewing the earlier studies[8] on the hydrolytic cleavages of methyl o-(2-imidazolyl) benzoate (1) and trifluoroethyl o-(2-imidazolyl) benzoate (2), where the rate enhancement (of the order of 10^3) has been observed in (2) but not in (1), it seems that the rate enhancement depends upon the relative acidity of leaving group as well as nucleophiles; however, this comparison may not be justified since there is a nucleophilic reaction in this case. Similarly, Bender et al[5] observed a rate enhancement of the order of ~10^3 at pH 8 in the hydrolysis of p-nitrophenyl salicylate compared with p-nitrophenyl o-methoxybenzoate but no such enhanced reactivity was seen in the hydrolyses of ethyl esters. These studies indicate that, possibly, for esters having leaving groups with $pK_a < 13$, the nucleophilic attack is rate determining step while for those having leaving groups with $pK_a > 13$, the expulsion of leaving group is rate determining step and the rate enhancement could be seen only if nucleophilic attack is rate determing step provided neighbouring group is devoid of any property of stabilizing the tetrahedral intermediate. Thus these studies support a stepwise mechanism rather than a concerted one. Considering the earlier studies[3,4,8] and the one we carried out under highly alkaline medium, we are led to the following mechanism (Scheme II):

In the reaction Scheme II, the tetrahedral intermediates T_1 and T_2 are considered to be the transient species and hence applying the steady state assumption one gets the rate eqn (6).

$$k_{obs} = \frac{k_3 k_1 K_1'[OH^-][H_2O]}{(k_{-1} + k_3)(1 + K_1'[OH^-])} + \frac{k_4 k_2 K_1'[OH^-]^2}{(k_{-2} + k_4)(1 + K_1'[OH^-])}$$

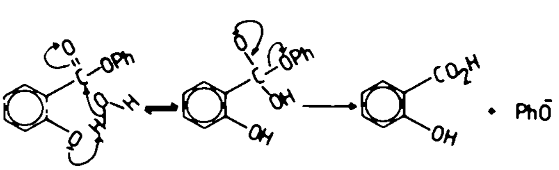
where

$$K_1' = \frac{K_1}{[H_2O]} = \frac{K_a}{K_w} \text{ with } K_a = a_H[S^-]/[SH]. \qquad (6)$$

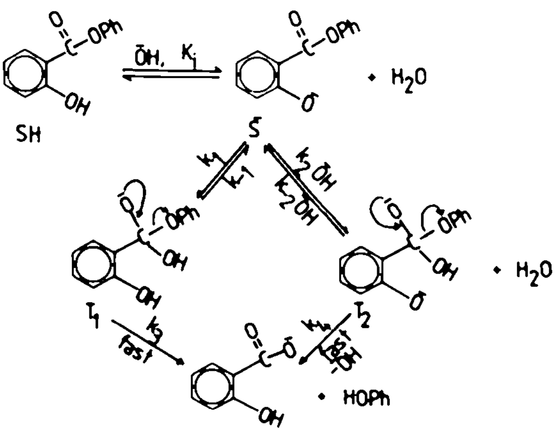
Since the phenoxide ion is a far better leaving group than hydroxide ion, therefore $k_{-1} \ll k_3$ and $k_{-2} \ll k_4$. Application of these conditions reduces eqn (6) and eqn (7).

$$k_{obs} = \frac{k_1 K_1'[H_2O][OH^-] + k_2 K_1'[OH^-]^2}{1 + K_1'[OH^-]}. \qquad (7)$$

Equation (7) is similar to the empirically observed rate eqn (2) with $A_1 = k_1 K_1'[H_2O]$, $A_2 = k_2 K_1'$ and $A_3 = K_1'$. The ratio A_1/A_3 ($= 3.47 \times 10^{-6}$ M^{-1} s^{-1}) gives the value of k_1. It may be shown that k_1 is ~10^2 and ~10^3 times larger than the rate constants for neutral hydrolyses of phenyl benzoate[8] and phenyl o-methoxybenzoate[4], respectively, under comparable conditions. The calculated value of k_2 ($= A_2/A_3$) is 4.89 10^{-4} M^{-1} sec^{-1} at 35°C which is ~10^4



Scheme 1.



Scheme 2.

times smaller than the bimolecular hydroxide ion catalyzed rate constant for hydrolysis of phenyl benzoate[9]. This observation could be attributed to (i) an extremely strong electron donating power of o-O^- which deactivates carbonyl carbon for any nucleophilic attack and (ii) an electrostatic repulsion between ionized ortho hydroxyl group of substrate and anionic nucleophile.

It is generally believed that much of the efficiency of intramolecular reactions results from relatively favourable ΔS^* values[10]. The activation parameters (Table 2) obtained at 0.05 M NaOH where k_2 step is believed to be relatively insignificant, are comparable with those obtained in various intramolecular nucleophilic reactions.[11] The comparison of these values with those obtained recently in neutral hydrolysis of phenyl benzoate,[9] shows that entire rate acceleration due to intramolecular general base catalyzed neutral hydrolytic cleavage of phenyl salicylate comes from favourable ΔS^* value while ΔH^* value is actually unfavourable compared with phenyl benzoate. The activation parameters, obtained at 0.05 M NaOH (Table 2) where both steps k_1 and k_2 are almost equally significant, reveal that increase in the contribution of k_2 step decreases the values of both ΔH^* and ΔS^*. The values of ΔH^* and ΔS^* were also obtained for only k_2 step (Table 2) and are comparable with those obtained in alkaline hydrolyses of di-n-butylphthalate[12a] and monomethylphthalate.[12b]

The dependence of k_{obs} on dielectric constant, exhibited by eqn (5), indicates that the critical transition state involves two ionic reacting species of similar charge[7] while the proposed mechanism, within the hydroxide ion concentration range of 0.05 M to 0.1 M, indicates the involvement of an ionic and a neutral species in rate determining step. Thus, the change in dielectric constant either changes the reaction mechanism or the exact nature of empirical constants k_0 and β is simply unknown. The relationship $\beta = Z_A Z_B e^2/K_B T R^{\neq}$ was used to calculate $r^{\neq}$ as 0.46 nm at 50° which is similar to those obtained at different temperatures in alkaline hydrolysis of monomethyl phthalate.[12b]

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