high-resolution mass spectrum, calcd for $C_7H_{11}OF$ m/z 130.0794, found m/z 130.0785.

***exo*-2-Fluoro-*anti*-bicyclo[2.2.1]heptan-7-ol (5c)**: mp 111-113 °C (hexane); IR (CCl_4) ν_{OH} 3610, 3420; ^1H NMR (CCl_4) δ 0.8-2.5 (m, 8 H), 3.5 (s, 1 H, OH), 4.2 (br s, 1 H, CHOH), 4.4 (2 unsym q, J_{HF} = 57 Hz, 1 H, CHF); ^{13}C NMR, see Table II; mass spectrum, m/z (relative intensity) 130 (M^+, traces), 110 (17), 79 (100); high resolution mass spectrum, calcd for $C_7H_{11}OF$ m/z 130.0794, found m/z 130.0789.

Reaction of *exo*-Norbornene Oxide with Triethylammonium Tris(hydrogen fluoride). To a stirred solution of 1 (2 mmol) in 5 mL of dry $CHCl_3$ was slowly added 0.6 mL of triethylammonium tris(hydrogen fluoride). After being stirred at 55 °C for 20 h, the reaction mixture was poured into a mixture of ice and concentrated ammonium hydroxide, extracted with ether, dried over anhydrous sodium sulfate, and analyzed by GLC, showing the products in the yields reported in Table I.

Registry No. 1, 3146-39-2; **2b**, 85551-24-2; **3b**, 31337-70-9; **3c**, 85507-31-9; **4b**, 85507-32-0; **5c**, 85507-33-1; PyHCl, 628-13-7; PyHI, 18820-83-2; HI, 10034-85-2; PVPHCl, 29323-87-3; $Py(HF)_x$, 62778-11-4; $Et_3N{\cdot}3HF$, 73602-61-6.

Structure-Reactivity Relationships and the Rate-Determining Step in the Nucleophilic Cleavage of Phenyl Salicylate with Primary and Secondary Amines

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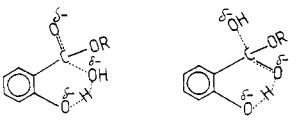
Received November 9, 1982

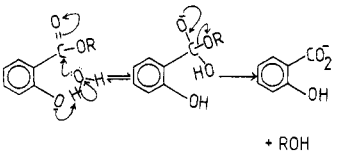
The kinetics of reactions of phenyl salicylate with piperidine, methylamine, morpholine, glycine, 1,2-diaminoethane, piperazine, and *N*-methylpiperazine have been studied at 30 °C. The respective values of bimolecular nucleophilic rate constants for the reactions of these amines with the ionized and nonionized forms of phenyl salicylate, k_1 and k_2, have been found to fit to the Brønsted equation with slopes, β_{nuc_1} and β_{nuc_2}, equal to 0.18 ± 0.02 and 0.82 ± 0.07, respectively. The low value of β_{nuc_1} is attributed to the intramolecular general-base-catalyzed nucleophilic attack as the rate-determining step while the high value of β_{nuc_2} is indicative of the expulsion of the leaving group as the rate-determining step. The extent of the enhanced reactivity produced by the intramolecular general-base catalysis depends upon the relative basicity of the nucleophiles and the phenolic group of the ester. The two Brønsted plots intersect each other at pK_a = 10.56. Thus, as the pK_a of the nucleophile decreases from 10.56, the ratio k_1/k_2 increases, while a decrease in k_1/k_2 takes place with an increase in the pK_a of the nucleophile from 10.56. The nonappearance of buffer catalysis in the cleavage of phenyl salicylate in buffer solutions of trimethylamine indicates that k_1 or k_1/k_2 should be very close to zero. Thus, the value of k_1/k_2 (0.38) for methylamine still displays an enhanced reactivity caused by intramolecular general-base catalysis. The buffer catalysis could not be detected in the nucleophilic cleavage of methyl salicylate in the presence of piperidine buffer solution. This observation has been ascribed to the expulsion of the leaving group as the rate-determining step for the cleavage of ionized methyl salicylate. The present study has supported our conclusion that the enhanced reactivity due to intramolecular general-base catalysis could be detected in such reactions only if the nucleophilic attack is the rate-determining step.

Intramolecular reactions and their mechanisms have become of immense importance since the awareness that intramolecular participation is one of the various factors which is responsible for the exceptionally high catalytic power of many enzymes.[1] Bender and his co-workers[2] have studied the hydrolytic cleavage of *p*-nitrophenyl salicylate and a few of its derivatives with the aim to find out quantitatively the rate facilitation produced by the neighboring hydroxyl group in the ester. They also attempted to differentiate between two kinetically indistinguishable probable mechanisms: (i) intramolecular general-base and (ii) general-acid catalysis involving transition states 1 and 2, respectively. But their deuterium



1 2

Scheme I



oxide solvent technique could not ultimately differentiate between these two. However, they preferred 1 over 2 because they could not detect any rate acceleration for the reactions between salicylate esters and nucleophiles having no transferable proton. In an attempt to clarify further the mechanism involved in the hydrolytic cleavage of salicylate esters, Capon and Ghosh[3] have studied the hydrolysis of phenyl salicylate and several of its derivatives, but their studies could not produce any better evidence than that produced by earlier studies[2] to show a preference for either of the two alternative mechanisms. Capon and Ghosh have proposed a mechanism as shown in Scheme I. All these studies could not produce any evidence to support whether nucleophilic attack or expulsion of the leaving group is the rate-determining step.

(1) Jencks, W. P. "Catalysis in Chemistry and Enzymology"; McGraw-Hill: New York, 1969. Bruice, T. C.; Benkovic, S. J. "Bioorganic Mechanisms"; W. A. Benjamin: New York, 1966. Fife, T. H. *Adv. Phys. Org. Chem.* **1975**, *11*, 1.

(2) Bender, M. L.; Kezdy, F. J.; Zerner, B. *J. Am. Chem. Soc.* **1963**, *85*, 3017.

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0022-3263/83/1948-2046$01.50/0

In the recent years, it has been well established that the Brønsted-type of plots for the reactions of primary, secondary, and tertiary amines with substituted phenyl acetates exhibit a change in slope from a large slope (β_{nuc} = 0.9 ± 0.1) for less basic amines to a small slope (β_{nuc} = 0.2 ± 0.2) for most basic amines compared with the basicity of the leaving group.[4] Similar results have been obtained in the nucleophilic cleavage of substituted diphenyl carbonates.[5] This kind of change in the slope of the Brønsted plot in these and related reactions is attributed to a change in the rate-determining step.[6,7] A small value of β_{nuc} (0.2) indicates that the nucleophilic attack is rate-determining step while a large value β_{nuc} (0.9) indicates the expulsion of the leaving as the rate-determining step. In our recent studies on hydrolysis of methyl salicylate,[8] we have concluded qualitatively that the enhanced reactivity due to intramolecular general-base catalysis could be seen only if the nucleophilic attack is the rate-determining step. To test this conclusion, we carried out the experiments described in this paper with an original belief that if it is valid, the Brønsted-type of plot for reactions between amines (primary and secondary) and ionized phenyl salicylate should display a small value of β_{nuc}.

Experimental Section

Materials. Anal. R grade chemicals such as glycine, morpholine, piperazine, 1,2-diaminoethane, methylammonium chloride, potassium chloride, hydrochloric acid, and phenyl salicylate were obtained from the BDH chemical company. Reagent grade *N*-methylpiperazine and piperidine were obtained from Fluka AG. Methyl salicylate was synthesized as described elsewhere.[8] All other chemicals used were also of reagent grade. Deionized, glass-distilled water was used throughout the kinetic studies.

Kinetic Measurements. The kinetics of aminolysis of phenyl salicylate was studied by monitoring either the disappearance of ester or the appearance of product, depending upon the pH of the reaction medium. Reaction mixtures having a total volume of 49 mL were prepared which contained the required amounts of buffer solutions of amine of desired pH and potassium chloride to maintain a constant ionic strength of 1.0 M. These reaction mixtures were kept in a thermostatic water bath at a constant temperature of 30 °C for about 10–15 min for temperature equilibration. All the amine buffer solutions were freshly prepared. The reaction was started by adding 1 mL of standard stock solution of phenyl salicylate prepared in absolute ethanol. This procedure thus added 2% ethanol into the reaction mixture. An aliquot of 2–3 mL of the reaction mixture was withdrawn periodically and was transferred quickly to a 3-mL quartz cuvette kept in the cell compartment of spectrophotometer whereby absorbance was recorded at the appropriate analytical wavelength. The process of transferring an aliquot from the reaction mixture to the cuvette in the cell holder and recording the absorbance generally took ~30 s. For the very fast reactions, a single aliquot was used for about 2 min to get a sufficient number of readings before the reaction approached its end. Any lowering of the temperature of reaction mixture in the cuvette was considered to be negligible because the constant temperature of reaction mixture (30 °C) was very close to the ambient temperature (~29 °C). The analytical wavelengths chosen were 340 nm for the disappearance of ester in the buffer solutions of pH 9.50–11.67, 320 nm for the disappearance of ester in morpholine buffer solutions of pH 8.41–9.29, 340 nm for the appearance of product in the pH range of 7.53–8.37 for the reaction of ester with 1,2-diaminoethane, and 310 nm for the disappearance of ester in its reaction with piperazine within the pH range of 6.15–8.25. The piperidinolysis of methyl salicylate was studied by monitoring the disappearance of ester at 340 nm. The spectrophotometer used in the present studies was a Cecil CE505 double-beam spectrophotometer modified characteristically for up to a 20× absorbance scale expansion. Measurements were taken for more than 6 half-lives in most of the kinetic runs. The pH values of all kinetic runs were obtained just before the start and at the end of the reaction by using a Philips digital pH meter, Model PW 9409. The pH values before the start and at the end of reaction were always found to be almost same in nearly all the kinetic runs.

The concentration of ester in the reaction mixtures was kept constant either at 1.8×10^{-4} M or less, depending upon the pH of the reaction mixture. Thus, under such conditions, the total buffer concentrations were always more than 100 times larger than that of the ester which satisfied very well the conditions for pseudo-first-order kinetics. The observed pseudo-first-order rate constants, k_{obsd}, were calculated from eq 1 for kinetic runs where

$$A_{obsd} = X_0 E_{app} \exp(-k_{obsd} t) + A_\infty \quad (1)$$

the disappearance of the ester was monitored as a function of time. In eq 1, X_0 is the initial concentration of ester, E_{app} is the apparent molar extinction coefficient, A_{obsd} is the absorbance value at any time t, and A_∞ is the absorbance at $t = \infty$. The nonlinear least-squares technique[9] was used to calculate the unknown parameters k_{obsd}, E_{app}, and A_∞. Equation 2 was used to calculate

$$A_{obsd} = X_0 E_{app} (1 - \exp(-k_{obsd} t)) + A_0 \quad (2)$$

k_{obsd} for those reactions where the appearance of product was monitored as a function of time. In eq 2, k_{obsd}, E_{app}, and A_0 (absorbance value at $t = 0$) were considered as three unknown parameters in the least-squares treatment. The observed data were found to fit to either eq 1 or 2 with maximum deviations between observed and calculated values of absorbance of not more than ~1% during several half-lives of the kinetic runs. Nearly eight kinetic runs were carried out at each pH of the buffer solutions for almost all the amines studied. The buffer concentration range of 0.02–0.5 M was maintained in most of the kinetic runs.

In order to check whether the products formed in piperazinolysis of phenyl salicylate within the pH ranges of 9.59–10.53 and 6.15–8.25 are the same, we carried out a test as follows. To about 2.5 mL of 0.2 M piperazine buffer of pH 10.21 were added a few drops of stock solution of phenyl salicylate. The reaction was found to be completed within a few minutes by monitoring at 340 nm. After the reaction was over, the wavelength was changed from 340 to 310 nm which changed A_∞ from 0.12 to 0.70. About 1 or 2 drops of ~10.7 M HCl was added to the cuvette containing the reaction products, and then very quickly the absorbance was recorded and was found to have dropped from 0.70 to 0.105. The value of A_∞ (0.105) thus obtained is similar to A_∞ obtained for kinetic runs carried out at 310 nm and at pH 6.15.

pK_a Determination. The values of pK_1 and pK_2 of piperazine and *N*-methylpiperazine were determined by the potentionmetric titration technique. The pH readings recorded from 0.15 to 0.85 mol and from 1.15 to 1.85 mol of HCl/mol of diamine were used for calculation of pK_2 and pK_1 from eq 3 and 4, respectively. A

$$pK_2 = pH + \log \frac{[H_2{}^+NR_2NH]\nu_{H_2{}^+NR_2NH}}{[HNR_2NH]} \quad (3)$$

$$pK_1 = pH + \log \frac{[H_2{}^+NR_2{}^+NH_2]\nu_{H_2{}^+NR_2{}^+NH_2}}{[H_2{}^+NR_2NH]\nu_{H_2{}^+NR_2NH}} \quad (4)$$

duplicate titration yielded nearly identical results, and these values, with their standard deviations, are as follows: pK_1 = 5.57 ± 0.02 (5.56 ± 0.01) and pK_2 = 9.83 ± 0.01 (9.81 ± 0.01) for piperazine and pK_1 = 4.62 ± 0.01 (4.71 ± 0.01) and pK_2 = 9.10 ± 0.02 (9.09 ± 0.01) for *N*-methylpiperazine. The activity coefficients, ν, for mono- and diprotonated diamines were calculated from Davies[10] eq 5, where μ is the ionic strength.

$$\log \nu = -0.5Z^2\left(\frac{\mu^{1/2}}{1 + \mu^{1/2}} - 0.2\mu\right) \quad (5)$$

(4) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622.
(5) Jencks, W. P.; Gresser, M. J. *J. Am. Chem. Soc.* **1977**, *99*, 6963.
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(7) Pohl, E. R.; Wu, D.; Hupe, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 2759.
(8) Khan, M. N.; Olagbemiro, T. O. *J. Org. Chem.* **1982**, *47*, 3695.
(9) A nonlinear least-squares program for three unknown parameters in BASIC was developed, and all the computations were carried out on a VAX-11 digital computer.

Table I. Apparent Second-Order Rate Constants for the Reaction of Amines with Phenyl Salicylate[a]

amine	pH	$10^3 k_n$, M^{-1} min^{-1}	$10^6 \sum_{i=1}^{N} d_i^2$,[b] min^{-1}
morpholine	8.41	289.1 ± 3.9[c]	59.03
	8.60	474.6 ± 3.5	53.93
	8.82	885.5 ± 18.4	1289
	9.10	1638 ± 8	238.0
	9.29	2371 ± 34	4181
glycine	9.52	482.2 ± 12.6	673.0
	9.70	433.1 ± 6.5	149.5
	9.97	853.1 ± 9.6	330.1
	10.13	718.9 ± 16.8	589.8
	10.91	1272 ± 10	389.1
methylamine	10.12	2288 ± 44	2522
	10.42	3043 ± 67	5849
	10.72	5711 ± 52	3482
	10.94	5837 ± 78	3476
piperidine	10.67	2975 ± 15	250.1
	10.77	3354 ± 17	1176
	11.00	4832 ± 86	4260
	11.20	6090 ± 80	8817
	11.46	8762 ± 155	10080
	11.67	11264 ± 157	23090
N-methylpiperazine	8.80	644.2 ± 15	805.1
	9.07	1367 ± 13	144.3
	9.11	1393 ± 24	2053
	9.30	1924 ± 23	1903
	9.60	4072 ± 43	1658
	9.82	5038 ± 84	4076
1,2-diaminoethane	7.53	52.22 ± 2.63	53.77
	7.74	76.60 ± 2.20	36.26
	7.91	99.65 ± 1.52	17.89
	8.12	185.2 ± 4.2	165.5
	8.37	268.6 ± 3.8	44.57
	8.76	2025 ± 37	4804
	9.90	1909 ± 26	2349
	10.11	2428 ± 49	8468
	10.18	2538 ± 27	2598
	10.64	2984 ± 33	6393
piperazine	6.15	1.673 ± 0.053	0.00846
	6.64	4.519 ± 0.075	0.0235
	6.99	9.685 ± 0.260	0.278
	8.25	149.1 ± 3.1	32.96
	9.59	4542 ± 37	779.6
	9.74	6548 ± 79	3560
	9.93	8183 ± 93	4941
	10.02	9684 ± 166	19290
	10.21	12610 ± 162	3748
	10.53	15079 ± 150	3230

[a] Temperature 30 °C; ionic strength 1.0 M. [b] $d_i = k_{obsd_i} - k_{calcd_i}$, and N is the total number of kinetic runs carried out at a constant pH. [c] Error limits are standard deviations.

The pK_a of phenyl salicylate was determined by the spectrophotometric technique. The buffer solutions (14) of pH ranging from 4.67 to 11.35 at 1 M ionic strength were kept in a thermostatic water bath at 30 °C for few minutes, and then an appropriate amount of 9×10^{-3} M phenyl salicylate solution was added to the buffer solution to give 1.2×10^{-4} M as the final ester concentration in the buffer. The absorbance values of buffer mixtures were quickly measured to avoid any possible hydrolysis. The acidity constant, K_a, of the ester was calculated from eq 6 by the nonlinear

$$A_{obsd} = \frac{A_{R^-}K_a + a_H A_{RH}}{a_H + K_a} \quad (6)$$

least-squares technique, considering K_a, A_{R^-}, and A_{RH} as three unknown parameters. In eq 6, A_{obsd} is the absorbance at any pH, and A_{R^-} and A_{RH} are the absorbance values of ionized and nonionized phenyl salicylate, respectively. The calculated values of K_a, A_{R^-}, and A_{RH} are $(5.67 \pm 0.41) \times 10^{-10}$ M, 0.791 ± 0.011, and 0.043 ± 0.007, respectively. The absorbance of 1.2×10^{-4} M phenyl salicylate was found to be 0.780 in 0.2 M NaOH and 0.034 in 0.08 M HCl. These values are comparable with the calculated values of A_{R^-} and A_{RH}.

Results and Discussion

The nucleophilic cleavage of phenyl salicylate was studied at various pHs with primary and secondary amines. An attempt was made to fit the observed pseudo-first-order rate constants, k_{obsd}, to eq 7, where k_0 and

$$k_{obsd} = k_0 + k_n[B]_T \quad (7)$$

k_n are the buffer-independent and -dependent rate constants for cleaage of phenyl salicylate and $[B]_T$ represents the total amine buffer concentration. A least-squares treatment gave the values of k_0 either negative or positive with standard deviations of more than 100% for almost all the amines studied. This analysis thus indicated that the k_0 term is statistically insignificant compared to the k_n term. However, k_0 could not be equated to zero as earlier studies on hydrolytic cleavage of phenyl salicylate[3] have revealed an enhanced reactivity due to intramolecular participation of a neighboring hydroxyl group. We, therefore, calculated k_0 at several pHs from eq 8, where

$$k_0 = \frac{k_1' K_a'}{a_H + K_a'} \quad (8)$$

(10) Davies, C. W. *J. Chem. Soc.* **1938**, 2093.

Table II. Second-Order Rate Constants for the Reactions of Amines with Ionized (k_1) and Unionized (k_2) Phenyl Salicylate at 30 °C and Ionic Strength 1.0 M

amine	pK_{amine}[a]	k_1, M^{-1} min^{-1}	k_2, M^{-1} min^{-1}
morpholine	8.60[b]	5.18 ± 0.03[c]	0.09[j]
		(4.66 ± 0.29)[d]	(0.158 ± 0.049[c])[d]
glycine	9.63[e]	1.18 ± 0.09	1.02[j]
methylamine	10.85[f]	12.26 ± 0.58	31.9[j]
piperidine	11.23[e]	13.84 ± 0.23	
N-methylpiperazine	9.10 (pK_2)	7.09 ± 0.18	
1,2-diaminoethane	10.18[g] (pK_2)	3.32 ± 0.48	0.333[j]
	7.53[g] (pK_1)	2.18 ± 0.24	(6.25 ± 0.81) × 10^{-2}
piperazine	9.83 (pK_2)	18.64 ± 0.27	
	5.57 (pK_1)	1.65 ± 0.02	(7.99 ± 0.032) × 10^{-4}
imidazole	7.05[h]		8.3 × 10^{-3}[i]

[a] The pK_a values of conjugate acids of amines. [b] Fife, T. H.; DeMark, B. R. *J. Am. Chem. Soc.* **1979**, *101*, 7379. [c] Error limits are standard deviations. [d] Calculated from eq 14 as described in the text. [e] Becker, A. R.; Richardson, D. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1977**, *99*, 5058. [f] Rogers, D. Z.; Bruice, T. C. *Ibid.* **1979**, *101*, 4713. [g] Bruice, T. C.; Willis, R. C. *Ibid.* **1965**, *87*, 531. [h] Fife, T. H.; DeMark, B. R. *Ibid.* **1977**, *99*, 3075. [i] Calculated from the reported value in ref 3. [j] These values are not very reliable.

K_a' (5.67×10^{-10}) is the acidity constant of phenyl salicylate and $k_1' = 0.01336$ min^{-1} (estimated from the reported value of Capon and Ghosh[3]). The values of k_n were calculated from eq 9 by the linear least-squares technique, and the

$$k^{corr} = k_n[B]_T \quad (9)$$

results obtained are summarized in Table I. In eq 9, $k^{corr} = k_{obsd} - k_0$. The fitting of observed data to eq 9 is evident from the sum of the squares of deviations between observed and calculated values of rate constants as shown in Table I. The general rate law for the cleavage of phenyl salicylate in the buffer solutions of amine may be given as

$$-d[PS]_T/dt = k_0[PS]_T + k_1[PS^-][B] + k_2[PSH][B] + k_3[PS^-][B][OH^-] + k_4[PSH][B][OH^-] + k_5[PS^-][BH^+] \quad (10)$$

where $[PS]_T$ represents the total concentration of phenyl salicylate. From eq 9 and 10, it follows that

$$k_nQa_H = k_3K_aK_a'K_w + (k_1K_aK_a' + k_4K_aK_w)a_H + (k_2K_a + k_5K_a')a_H^2 \quad (11)$$

where $Q = (a_H + K_a')(a_H + K_a)$ and K_a is the acidity constant of monoamine.

The cleavage of phenyl salicylate was studied with buffer solutions of morpholine of pH ranging from 8.41 to 9.29. The plot of k_nQa_H vs. a_H was found to be linear within the pH range of 8.60–9.29 as shown in Figure 1. The linearity of the plot could be explained by assuming that within this pH range $k_3K_aK_a'K_w + (k_1K_aK_a' + k_4K_aK_w)a_H \gg (k_2K_a + k_5K_a')a_H^2$. The application of this assumption reduced eq 11 to eq 12. The intercept ($k_3K_aK_a'K_w$) and slope ($k_1K_aK_a'$ + $k_4K_aK_w$) were calculated by the linear least-squares technique, and their respective values were found to be (17.79 ± 8.55) × 10^{-29} M^2 min^{-1} and (72.72 ± 0.55) × 10^{-19} M min^{-1}. The standard deviation of the intercept indicates that it is not statistically different from zero. The insignificant contribution of the k_3 term could be attributed to the fact that such a term has been observed in related reactions only with highly basic amines and where the general-base-catalyzed term ($k[B]^2[subs]$) has been found to contribute significantly to the rate law.[11-13] Thus, in the present case, $k_3K_aK_a'K_w + k_4K_aK_wa_H \ll k_1K_aK_a'a_H$. The application of this consideration reduces eq 12 to eq 13. The value of $k_1K_aK_a'$ as calculated by least squares

$$k_nQa_H = k_1K_aK_a'a_H \quad (13)$$

technique was found to be (73.72 ± 0.40) × 10^{-19} M min^{-1}. The value of k_1 was calculated from $k_1K_aK_a'$ with known values of K_a and K_a' and is shown in Table II.

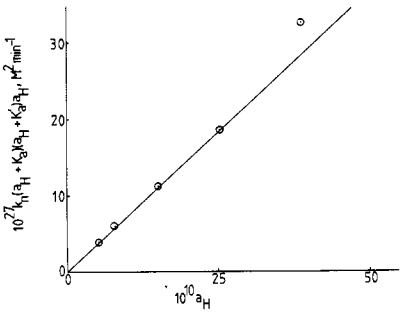

Figure 1. Plot of $k_n(a_H + K_a')(a_H + K_a)a_H$ vs. a_H for the reaction of morpholine with phenyl salicylate. The solid line is drawn through the least-squares-calculated points obtained by using eq 13 with $k_1K_aK_a' = 73.72 \times 10^{-19}$ M min^{-1}.

The observed point at pH 8.41 was found to be deviated ~11% from linearity (Figure 1). This indicates that the assumption that $(k_2K_a + k_5K_a')a_H^2 \ll k_1K_aK_a'a_H$ is no longer true at this pH. The value of $(k_2K_a + k_5K_a')a_H^2$ was evaluated at pH 8.41 from the observed value of k_nQa_H (3209×10^{-29} M^2 min^{-1}) and the calculated value of $k_1K_aK_a'$. The value thus obtained is 341.5×10^{-29} M^2 min^{-1}. Since for an amine like morpholine, the k_5 term is unlikely to exist, the value of k_2 as shown in Table II was calculated from known values of $k_2K_aa_H^2$ and K_a. The observed data within the pH range of 8.41–9.29 were also subjected to eq 14 and the calculated values of $k_1K_aK_a'$ and k_2K_a were

$$k_nQa_H = k_1K_aK_a'a_H + k_2K_aa_H^2 \quad (14)$$

found to be (66.37 ± 4.11) × 10^{-19} M min^{-1} and (0.3983 ± 0.1231) × 10^{-9} min^{-1}, respectively. These values were also used to calculate k_1 and k_2 as shown in Table II. The reactivity of glycine, methylamine, piperidine, and *N*-methylpiperazine with phenyl salicylate was studied at varying pH as shown in Table I. Equation 13 was found to be followed by the observed data within the pH range of 9.70–10.91 for glycinolysis, 10.42–10.92 for methylaminolysis, 10.67–11.67 for piperidinolysis, and 8.80–9.82 for *N*-methylpiperazinolysis of phenyl salicylate. The least-squares calculated values of $k_1K_aK_a'$ for the reactions of glycine, methylamine, piperidine, and *N*-methyl-

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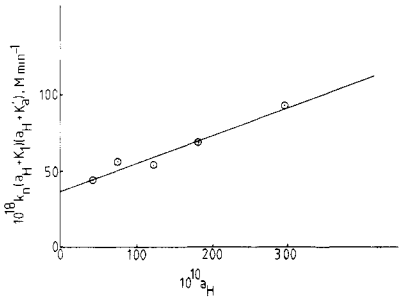


Figure 2. Plot showing the dependence of $k_n(a_H + K_a')(a_H + K_1)$ vs. a_H for the reaction of 1,2-diaminoethane with phenyl salicylate. The solid line is drawn through the least-squares-calculated points obtained by using eq 15 with $k_1K_1K_a' = 3.641 \times 10^{-17}$ M min^{-1} and $k_2K_1 = 1.844 \times 10^{-9}$ min^{-1}.

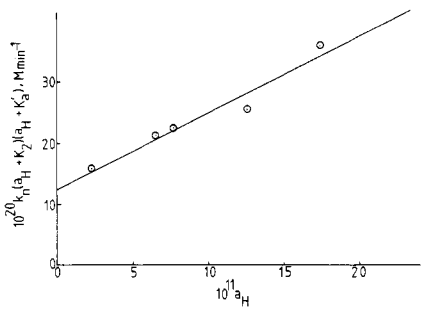


Figure 3. Plot of $k_n(a_H + K_2)(a_H + K_a')$ vs. a_H for the reaction of 1,2-diaminoethane with phenyl salicylate. The solid line is drawn trhough the least-squares-calculated points obtained by using eq 16 with $k_1K_2K_a' = 12.42 \times 10^{-20}$ M min^{-1} and $k_2K_2 + k_5K_a' = 1.258 \times 10^{-9}$ min^{-1}.

piperazine with phenyl salicylate were found to be (15.62 ± 1.20) × 10^{-20}, (9.817 ± 0.469) × 10^{-20}, (46.20 ± 0.76) × 10^{-21}, and (31.93 ± 0.83) × 10^{-19} M min^{-1}, respectively. These values were used to calculate k_1 as shown in Table II from known values of K_a and K_a'. The observed points at pH 9.52 for glycinolysis and at pH 10.12 for methylaminolysis of phenyl salicylate were found to be deviated ~30% and ~25%, respectively, from linearity as predicted by eq 13. These deviations revealed that the contribution due to the k_2 term could not be neglected compared with the k_1 term at these pH values. The observed values of k_nQa_H (678.8 × 10^{-31} and 1004 × 10^{-32} M^2 min^{-1}) and the calculated values of $k_1K_aK_a'$ at pH 9.52 and 10.12 were used to calculate k_2 as shown in Table II. However, these values of k_2 are not very reliable because they are obtained from a single observed point.

The nucleophilic cleavage of phenyl salicylate with 1,2-diaminoethane was studied at different pHs ranging from 7.53 to 10.64. The plot of k_nQ vs. a_H is shown in Figure 2. The plot appeared to be linear within the pH range of 7.53–8.37. Since the values of pK_1 and pK_2 of 1,2-diaminoethane are 7.53 and 10.18, respectively, it is unlikely for an unprotonated diamine to contribute significantly to the rate even at pH 8.37. Thus, within the pH range of 7.53–8.37, only the monoprotonated diamine was considered to be reacting with ester. The linearity of the plot (Figure 2) revealed that $k_3K_1K_a'[OH^-] \ll k_1K_1K_a' + k_4K_1K_w + (k_2K_1 + k_5K_a')a_H$. The k_3 and k_4 terms could be neglected compared to other terms simply because the general-base-catalyzed term was not observed in the rate law. Similarly, the k_5 term would be unlikely to exist for diprotonated 1,2-daiminoethane. Application of these considerations reduces eq 11 to eq 15. The values of

$$k_nQ = k_1K_1K_a' + k_2K_1a_H \quad (15)$$

$k_1K_1K_a'$ and k_2K_1 as calculated from eq 15 by the linear least-squares technique are (36.41 ± 4.03) × 10^{-18} M min^{-1} and (18.44 ± 2.38) × 10^{-10} min^{-1}, respectively. The respective values of $k_1K_1K_a'$ and k_2K_1 were used to calculate k_1 and k_2 which are shown in Table II.

The plot of k_nQ vs. a_H as shown in Figure 3 covered the pH range of 9.76–10.64. The plot is essentially linear, and this linearity could be explained by assuming that $k_3K_2K_a'[OH^-] + k_4K_2K_w \ll k_1K_2K_a' + (k_2K_2 + k_5K_a')a_H$. On application of these considerations, eq 11 was simplified to eq 16. The intercept ($k_1K_2K_a'$) and slope ($k_2K_2 + k_5K_a'$)

$$k_nQ = k_1K_2K_a' + (k_2K_2 + k_5K_a')a_H \quad (16)$$

were calculated from eq 16, and the values obtained are (12.42 ± 1.81) × 10^{-20} M min^{-1} and (12.58 ± 1.69) × 10^{-10} min^{-1}, respectively. The values of k_1 was calculated from intercept with known values of K_2 and K_a' and is shown in Table II. The value of k_2 was calculated from slope with known values of K_2, K_a', and k_5 (2.18 M^{-1} min^{-1}, as determined from the kinetic analysis carried out within the pH range of 7.53–8.37) and is shown in Table II. The relative values of k_2K_2 and k_5K_a' revealed that the contribution of the k_2 term compared with the k_5 term was ~2%.

Table III. Pseudo-First-Order Rate Constants for Piperidinolysis of Methyl Salicylate[a]

[piperidine]$_T$, M	10^3k_{obsd},[b] min^{-1}	E_{app},[b] M^{-1} cm^{-1}	A_∞[b]
0.05	7.015 ± 0.153	4572 ± 39	0.039 ± 0.010
0.10	7.119 ± 0.177	4564 ± 46	0.053 ± 0.012
0.15	6.939 ± 0.182	4423 ± 48	0.052 ± 0.013
0.20	6.656 ± 0.076	4608 ± 20	0.067 ± 0.005
0.25	6.664 ± 0.086	4594 ± 22	0.074 ± 0.006
0.35	6.823 ± 0.054	4594 ± 14	0.107 ± 0.004

[a] Conditions: [methyl salicylate]$_T$ = 2.47 × 10^{-4} M; temperature = 30 °C; μ = 1.0 M; 2% ethanol in the reaction mixture; the pH of piperidine buffer solution is 11.76. [b] The error limits are standard deviations.

The piperazinolysis of phenyl salicylate was studied at various pHs ranging from 6.15 to 10.53. The values of pK_1 (5.57 ± 0.01) and pK_2 (9.82 ± 0.01) revealed that the concentration of unprotonated amine would not be great enough to contribute significantly in the pH range of 6.15–8.25. Thus, the observed data were found to follow eq 15. The least-squares calculated values of $k_1K_1K_a'$ and k_2K_1 were found to be (25.23 ± 0.32) × 10^{-16} M min^{-1} and (2.150 ± 0.085) × 10^{-9} min^{-1}, respectively. The values of k_1 and k_2 calculated from the intercept and slope are shown in Table II.

The observed data within the pH range of 9.59–10.53 were found to follow eq 13. This observation could be explained by assuming that all the kinetic terms are neligible compared with the k_1 term in eq 11. Thus, the least-squares treatment of the observed data with eq 13 where K_a was replaced by K_2 gave the value of $k_1K_2K_a'$ as (1.563 ± 0.023) × 10^{-18} M min^{-1}. The rate constant k_1 was calculated from $k_1K_2K_a'$ and is shown in Table II.

The hydrolytic cleavage of methyl salicylate was also studied at pH 11.76 and at different total piperidine buffer concentrations ranging from 0.05 to 0.35 M. The observed pseudo-first-order rate constants E_{app} and A_∞ calculated from eq 1 are shown in Table III. The observed results revealed that there was no buffer catalysis for the cleavage of this ester.

Proposed Mechanism

The dependence of the bimolecular nucleophilic rate constant on the basicity of the attacking amine for ionized and nonionized forms of phenyl salicylate is shown in the

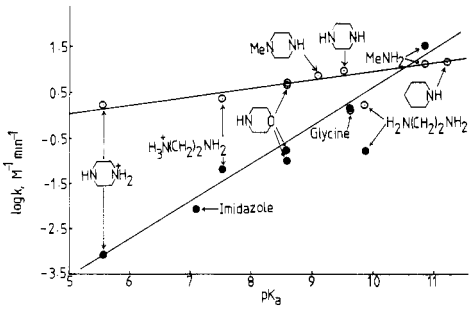


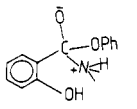
Figure 4. Dependence of the nucleophilic bimolecular rate constants for the reactions of ionized (⊙) and unionized (●) phenyl salicylate with primary and secondary amines on the pK of the conjugate acid of amines at 30 °C and an ionic strength 1.0 M. The solid lines are drawn through the least-squares-calculated points obtained by using eq 17 with $\beta_{nuc_1} = 0.18$ and $C_1 = -0.85$ M min^{-1} for (⊙) and eq 18 with $\beta_{nuc_2} = 0.82$ and $C_2 = -7.68$ M^{-1} min^{-1} for (●). In the calculation of β_{nuc_1}, the observed points at pK = 10.18 (pK_2 for 1,2-diaminoethane) and 9.63 (glycine) were not included. Similarly, in the calculation of β_{nuc_2}, the points at pK = 7.05 (imidazole) and 10.18 (pK_2 for 1,2-diaminoethane) were not included. Statistical corrections to pK_2, k_1, and k_2 for the reactivity of piperazine and 1,2-diaminoethane were made in the Brønsted plots.

Brønsted-type plots of Figure 4. The data for cleavage of the ionized and nonionized forms of phenyl salicylate were found to fit eq 17 and 18, respectively. The unknown

$$\log k_1 = \beta_{nuc_1} pK_a + C_1 \quad (17)$$

$$\log k_2 = \beta_{nuc_2} pK_a + C_2 \quad (18)$$

parameters β_{nuc_1}, β_{nuc_2}, C_1, and C_2 were calculated by the least-squares technique, and the values thus obtained are 0.18 ± 0.02, 0.82 ± 0.07, −0.85 ± 0.19, and −7.68 ± 0.60, respectively. The significantly different values of β_{nuc_1} and β_{nuc_2} clearly demonstrate the existence of two different types of transition states in the rate-determining steps.[11] A β_{nuc_2} value of 0.82 ± 0.07 is not very much different from the β_{nuc} values of 0.96,[12] 0.73,[13] and 1.05[14] obtained for nucleophilic attack by primary and secondary amines on phenyl quinoline-6-carboxylate[12] (Q-6) and phenyl acetate. A similar β_{nuc} value (0.95) was also obtained for the nucleophilic cleavage of 2,4-dinitrophenyl quinoline-6-carboxylate with tertiary amines.[15] In these studies the values of β_{nuc} have been attributed to the rate-determining step involved in the breakdown of the tetrahedral intermediate. It is well established as a result of the huge amount of research work carried out in the area of aminlysis and thiolysis of esters that a high value of β_{nuc} is an indication of the formation of a late transition state on the reaction coordinate in the critical rate-determining step where a large amount of bond formation between nucleophile and the electrophilic center has occurred before the leaving group has departed.[16] Thus, a β_{nuc_2} value of 0.82 ± 0.07 led us to propose that the rate-determining step in the nucleophilic cleavage of nonionized phenyl salicylate (PSH) is the breakdown of the tetrahedral intermediate **3**. The similarity of β_{nuc} values obtained for PSH, Q-6,



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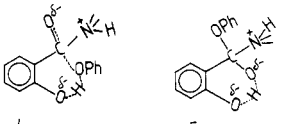
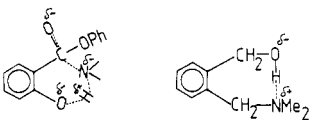
phenyl acetate, and phenyl quinoline-8-carboxylate (Q-8)[12] also rules out the possibility of the intramolecular general-acid-catalyzed cleavage of PSH involving a transition state of the type **4**, for such a type of participation should



4 **5**

increase the effective leaving ability of the departing group which in turn should result in a lower value of β_{nuc}. Furthermore, the acidity of PSH (pK_a = 9.25) is higher than that of phenol (pK_a = 9.99), and an intramolecular proton transfer from the neighboring hydroxyl group to the leaving phenol is therefore unlikely. An intramolecular general-acid catalysis should be more effective in the cleavage of methyl salicylate compared with that of PSH, but no such catalysis was observed in the piperidinolysis of methyl salicylate. However, an increase in the stability of **3** due to intramolecular hydrogen bonding as shown in **5** cannot be completely ruled out, for a similar type of intermediate has been proposed in the hydrolytic cleavage of methyl salicylate.[8] This kind of stabilization should increase the reactivity of PSH over phenyl *o*-methoxybenzoate (PhOMB). Capon and Ghosh[3] have observed an ~2-fold increase in the reactivity of imidazole with PSH compared with PhOMB. About a 2-fold decrease in the reactivity of PhOMB could partly be ascribed to the increase in steric hindrance caused by *o*-OMe compared with *o*-OH. The apparent significant negative deviation of the point (log k_2) for unprotonated 1, 2-diaminoethane from the Brønsted plot could be attributed to the uncertainty associated with its calculation. The value of k_2 was calculated from observed data where its contribution was only nearly 2%.

A considerably low value of β_{nuc_1} (0.18 ± 0.02) indicates very little bond formation between the attacking amine and the carbonyl carbon of PSH in the early transition state. This conclusion is based on Jencks' hypothesis that the Brønsted coeficient is a measure of the extent to which the reaction has progressed in the transition state.[16] Thus, we propose that the rate-determining step is the intramolecular general-base-catalyzed nucleophilic attack at the carbonyl carbon in ionized phenyl salicylate (PS^-). A transition state of the type **6** might be involved in the



6 **7**

rate-determining step. Although, according to Jencks' recent conclusion,[5] a change in rate-determining step from the breakdown to the formation of the tetrahedral intermediate should occur when the amine becomes more basic than the leaving group by 4–5 pK units; a change in the nature of the rate-determining step has occurred due to the presence of ionized and nonionized neighboring hydroxyl groups. In a transition state like **6**, an intramolecular hydrogen bonding between the ionized hydroxyl group and the hydrogen of the attacking amine increases the effective basicity of amine much more than its apparent basicity. Although it seems unlikely that the ionized neighboring hydroxyl group acts as an efficient catalyst by removing the proton from attacking amine even when the amine moiety is as much as 2 pK units stronger a base, it is an observed fact that the intramolecular hydrogen bonding exists in the free base form of *o*-[(di-

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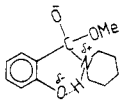
(15) Bruice, P. Y.; Bruice, T. C. *J. Am. Chem. Soc.* **1974**, *96*, 5523.
(16) Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451.

methylamino)methyl]benzyl alcohol (7) where the pK_a difference between the hydroxyl group and the dimethylamino group is ~5–6.[17] The reactivity of 7 was found to be more than 100-fold larger than that of *N,N*-dimethylbenzylamine for the attack on *p*-nitrophenyl acetate. Our recent conclusion that such a type of intramolecular hydrogen bonding in a nucleophile would result in exceptionally high reactivity only in those reactions where nucleophilic attack would be the rate-determining step is supported by the present study. This conclusion is further supported by the nonappearance of any kinetically detectable nucleophilic catalysis in piperidinolysis of methyl salicylate where breakdown of the tetrahedral intermediate 8 would most likely be the rate-determining



8

step. Since the pK_a of piperidine is nearly 2 pK units higher than that of PSH, the effective decrease in acidity of piperidine moiety in 8 is still not enough to make the methoxy group a better leaving group compared with piperidine.

An alternative stepwise mechanism[18] for the cleavage of anionic substrate is that the rate-determining step is amine attack but without catalysis. This is followed by proton transfer to the oxygen anion and breakdown of the intermediate in fast steps. This proton transfer need not be thermodynamically favorable in order to be effective. All that is needed is to remove the proton so that the intermediate does not revert to starting materials and can break down easily. This mechanism, however, suffers from the fact that the complete proton transfer from the attacking amine to the oxygen anion before the breakdown of the intermediate could not explain the nonappearance of any detectable nucleophilic catalysis in piperidinolysis of methyl salicylate.

The intersection of two Brønsted plots (Figure 4) has occurred at $pK_a = 10.56$, which reveals that for an amine having pK_a higher than 10.56, the reactivity toward PSH is higher than toward PS^-. This could be explained qualitatively by considering the location of the proton between the nitrogen of the amino group and the oxygen of the neighboring hydroxyl group which in turn gives a measure of the reduction with respect to both the positive charge developing on the attacking nitrogen and the unit negative charge of oxygen. Thus, as the pK_a of the attacking amine increases compared with the pK_a of PSH (9.25), the reduction with respect to both the developing positive charge and the unit negative charge decreases which in turn increases the electron-donating (deactivating effect) power of $o\text{-}O^-$ group and decreases the nucleophilicity of nucleophile. The rate constant k_2 could not be detected in the reaction of piperidine with PSH simply because the pH range of reaction mixtures was not sufficient to produce a large enough concentration of PSH to make the k_2 term significant compared with the k_1 term. The k_2 term was found to be significant in methylaminolysis of PSH only at pH 10.12 where its contribution was ~25%. For the amines having a pK_a lower than 10.56, the ratio k_1/k_2 increases from unity and reaches a value of the order of 10^4 for an amine of pK_a 5.57. About a 5-fold negative deviation of k_1 for glycine could be attributed to steric hindrance caused by the possible intermolecular electrostatic repulsion between the negatively charged ionized *o*-OH group and the carboxylate ion of glycine. A steric factor could be also responsible for a 4-fold decrease in the reactivity of unprotonated 1,2-diaminoethane. An intramolecular general-base-catalyzed rate accleration cannot be expected for tertiary amines acting as nucleophiles. In order to test this expectation, we have already started a kinetic study of the nucleophilic reactivity of tertiary amines with PSH. Trimethylamine has been found to show no nucleophilic reactivity with PSH. These observations thus indicate that the k_1 value is almost zero for tertiary amine. The nonappearance of the k_1 term gives a measure of the deactivating effect produced by the electron-donating power of $o\text{-}O^-$. The value of k_1/k_2 (0.38) obtained for methylamine thus displays a many-fold rate acceleration produced by intramolecular general-base catalysis.

Acknowledgment. I am very much grateful to the Research and Higher Degrees Committee of Bayero University for a research grant to purchase the UV–visible spectrophotometer.

Registry No. Phenyl salicylate, 118-55-8; phenyl salicylate anion, 61141-14-8; methyl salicylate, 119-36-8; morpholine, 110-91-8; glycine, 56-40-6; methylamine, 74-89-5; piperidine, 110-89-4; *N*-methylpiperazine, 109-01-3; 1,2-diaminoethane, 107-15-3; piperazine, 110-85-0; imidazole, 288-32-4.

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(18) I thank one of the referees for suggesting this alternative mechanism.