[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

Evidence for General Base Catalysis in an Ester Hydrolysis. II. Hydrolysis of an Aminoalkyl Acetylsalicylate[1]

BY EDWARD R. GARRETT

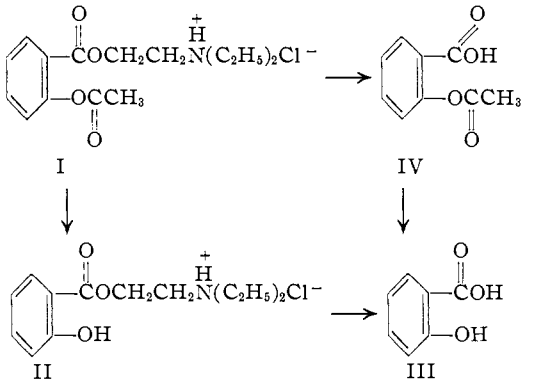
RECEIVED FEBRUARY 24, 1958

The protonated salicylate di-ester, diethylaminoethyl acetylsalicylate hydrochloride (I), hydrolyzes in acid solutions to diethylaminoethyl salicylate hydrochloride (II), which is highly resistant to hydrogen ion catalyzed hydrolysis. The compound I is susceptible to general base catalysis as by water and acetate ions to II. Hydrolysis to II by undissociated acetic acid catalysis is also indicated. The diester I is also hydrolyzed by hydroxyl and acetate ions to salicylic acid (III) possibly *via* an aspirin intermediate. The hydrolysis of II to III is only hydroxyl ion catalyzed. The ultimate product of the hydrolysis of I is III with increasing yields of II at the lower *p*H values.

The general base catalyzed hydrolysis of esters has been observed recently.[2,3]

The effect of a protonated amine substituted carboxyl in a salicylate diester, such as in an alkyl aminoacetyl salicylate,[3] was to inhibit hydrogen ion catalysis and promote acetate ion, water and hydroxyl ion catalysis in the hydrolysis of the phenyl carboxylate ester. The introduction of a protonated group such as ammonium ion in the alkyl rather than the acyl ester group of salicylic acid would permit an interesting comparison of kinetic dependence, magnitude of rate and possible mechanism.

In this light the kinetics of transformation of diethylaminoethyl acetylsalicylate hydrochloride (I) were studied in various buffer concentrations at *p*H values less than neutrality. The possible products were diethylaminoethyl salicylate hydrochloride (II), acetylsalicylic acid (aspirin) (IV) and salicylic acid (III).



Experimental

Potentiometric Titration of Diethylaminoethyl Acetylsalicylate Hydrochloride[4] (I).—Titration of this material in water with 0.1000 *N* NaOH gave a pK_a' of 8.68 and an equivalent weight of 290 (theoretical 316). Precipitation was noted at *p*H 9.0, about three-fourths of the stoichiometric titration. The solution cleared again after the addition of stoichiometric titer at *p*H 10.6 indicating hydrolysis to the acids. Titration in aqueous alcohol gave a pK_a' of 8.30 in 42% ethanol and an equivalent weight of 309 (theoretical 316). The sample did not precipitate during the titration but did precipitate on standing afterwards, again indicating complete hydrolysis to the acids where the salt of the one (probably sodium salicylate) exceeded its solubility in the aqueous ethanol.

Potentiometric Titrations of Diethylaminoethyl Salicylate Hydrochloride[4] (II).—Titration with standard alkali, 0.1000 *N* NaOH, in aqueous alcohol gave a pK'_a of 8.05 in 42% ethanol and an estimated equivalent weight of 278 (theoretical 274). Precipitation began at *p*H 7.5 and the sample started to redissolve at *ca.* *p*H 10.0. This indicated precipitation of the free amine ethyl salicylate and subsequent redissolution of some of the sodium salicylate that resulted from hydrolysis.

Preliminary Rate Studies on the Aqueous Hydrolysis of Diethylaminoethyl Acetylsalicylate Hydrochloride (I) **and Identification of Products.**—Sufficient I was weighed out to make up 10×10^{-4} *M* solutions in an acid buffer (buffer A) of *p*H *ca.* 1.0 (0.1304 *M* HCl and 0.0625 *M* KCl), solution A, and in a neutral buffer (buffer B) of *p*H *ca.* 6.0 (0.1275 *M* acetic acid and 0.1225 *M* NaOH), solution B. These solutions were maintained in a constant temperature bath at 30.3°. Five ml. of solution A was diluted to 25 ml. with buffer A and read (2×10^{-4} *M*) at various intervals at 212–360 mμ on the Cary recording spectrophotometer, model 11, against buffer A as the blank. Five ml. of solution A was added to 15 ml. of buffer B and 5 ml. of 0.1 *N* NaOH to approximate the composition of buffer B and this solution (2×10^{-4} *M*) was run spectrophotometrically against buffer B as the blank.

Five ml. of solution B was diluted to 25 ml. with buffer B and run spectrophotometrically (2×10^{-4} *M*) against buffer B as the blank. Five ml. of solution B was added to 15 ml. of buffer A and 5 ml. of 0.23 *M* HCl to approximate the composition of buffer A and this solution (2×10^{-4} *M*) was run spectrophotometrically against buffer A as the blank.

The spectra of 2×10^{-4} *M* diethylaminoethyl salicylate hydrochloride (II) and 2×10^{-4} *M* salicylic acid (III) were also run in buffers A and B.

No shift in the spectra of the hydrolysis products of I hydrolyzed at *p*H 1.0, was observed when aliquots were read at *p*H 1.0 or 6.0. The spectra were coincident with the spectra of II and it can be concluded that under acid hydrolysis of I, II is the product and not salicylic acid (III) (Fig. 1).

The spectra of the hydrolysis products of I hydrolyzed at *p*H 6.0 do shift for aliquots read at *p*H 1.0 and 6.0. The spectra are coincident with the spectra of salicylic acid at those *p*H's (Fig. 1). It can be concluded that under neutral hydrolysis of I, salicylic acid (III) is the end product.

Calculations of Amounts of Products in the Hydrolyses of Diethylaminoethyl Acetylsalicylate Hydrochloride (I) **and Diethylaminoethyl Salicylate Hydrochloride** (II).—An isoabsorptivity point is 300 mμ for the two products of diethylaminoethyl acetylsalicylate hydrochloride (I) hydrolysis, *i.e.*, diethylaminoethyl salicylate hydrochloride (II) and salicylic acid (III) at *p*H values *ca.* 6.0. This is for the salt forms of both of these hydrolytic products. A wave length at 320 mμ may be chosen for the maximum difference in absorptivities of I and II (see Fig. 1). Equations may be established for the calculations of concentrations in the hydrolysis of diethylaminoethyl acetylsalicylate hydrochloride, determined spectrophotometrically at *p*H *ca.* 6.0 where

$A\lambda$ = absorbance at a wave length λ in mμ for an initial concentration of diethylaminoethyl acetylsalicylate hydrochloride $[I]_0$ in the *p*H 6.0 spectrophotometrically analyzed aliquot.

(1) Presented before the 133rd National Meeting of The American Chemical Society, San Francisco, Calif., April, 1958.

(2) (a) T. C. Bruice and G. L. Schmir, THIS JOURNAL, **79**, 1663 (1957); (b) M. L. Bender and B. W. Turnquest, *ibid.*, **79**, 1652, 1656 (1957).

(3) E. R. Garrett, *ibid.*, **79**, 5206 (1957).

(4) The synthesis and characterization of these compounds will be covered by F. Kagan and R. D. Birkenmeyer in a paper submitted to *J. Org. Chem.*

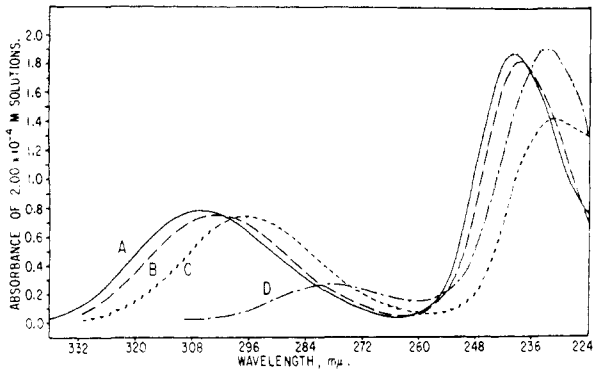


Fig. 1.—Spectra of diethylaminoethyl acetylsalicylate hydrochloride and its hydrolysis products (2×10^{-4} M): A, diethylaminoethyl salicylate hydrochloride (II) at pH 1.0 and 6.0; completely hydrolyzed diethylaminoethyl acetylsalicylate hydrochloride (I) at pH 1.0 and 6.0 (from hydrolysis carried out at pH 1.0). B, Salicylic acid (III) at pH 1.0; completely hydrolyzed I and II at pH 1.0 (from hydrolysis carried out at pH 6.0). C, Salicylic acid (III) (sodium salt) at pH 6.0; completely hydrolyzed I and II at pH 6.0 (from hydrolysis carried out at pH 6.0). D, Aspirin (IV) at pH 1.0 and diethylaminoethyl acetylsalicylate hydrochloride at pH 1.0 and 6.0.

[I] = concentration of diethylaminoethyl acetylsalicylate hydrochloride (I) in the aliquot.
[II] = concentration of diethylaminoethyl salicylate hydrochloride (II) in the aliquot.
[III] = concentration of salicylic acid (III) in the aliquot.
$\epsilon\lambda^{I}$, $\epsilon\lambda^{II}$, $\epsilon\lambda^{(II+III)}$, $\epsilon\lambda^{III}$ = absorptivities of the materials at the designated wave lengths

The equations are based on the relations

$$A_{300} = \epsilon_{300}^{(II+III)}\,[[II] + [III]] + \epsilon_{300}^{I}\,[I] \quad (1)$$
$$A_{320} = \epsilon_{320}^{II}\,[II] + \epsilon_{320}^{III}\,[III] \quad (2)$$
$$[I]_0 = [[II] + [III]] + [I] \quad (3)$$

The equations are

$$[[II] + [III]] = (A_{300} - \epsilon_{300}^{I}[I]_0)/(\epsilon_{300}^{(II+III)} - \epsilon_{300}^{I}) \quad (4)$$
$$[III] = (\epsilon_{320}^{II}\,[[II] + [III]] - A_{320})/(\epsilon_{320}^{II} - \epsilon_{320}^{III}) \quad (5)$$
$$[II] = (A_{320} - \epsilon_{320}^{III}\,[[II] + [III]])/(\epsilon_{320}^{II} - \epsilon_{320}^{III}) \quad (6)$$
$$[I] = [I]_0 - [[II] + [III]] \quad (7)$$

Molar absorptivity values are $\epsilon_{320}^{II} = 2200$, $\epsilon_{320}^{III} = 600$, $\epsilon_{300}^{I} = 115$, $\epsilon_{300}^{(II+III)} = 3515$.

The equation for calculation of diethylaminoethyl salicylate hydrochloride (II) and salicylic acid (III) in pH 6.0 spectrophotometrically analyzed aliquots of the hydrolysis of II is based on the relations

$$A_{320} = \epsilon_{320}^{III}\,[III] + \epsilon_{320}^{II}\,[II] \quad (8)$$
$$[II]_0 = [III] + [II] \quad (9)$$

where $[II]_0$ is the initial concentration of diethylaminoethyl salicylate hydrochloride in the pH 6.0 spectrophotometrically analyzed aliquot. The equation is

$$[III] = (A_{320} - \epsilon_{320}^{II}\,[II]_0)/(\epsilon_{320}^{III} - \epsilon_{320}^{II}) \quad (10)$$

Rates of Hydrolysis as Functions of pH and Buffer Concentrations.—The hydrolysis studies of I were conducted at 10.00×10^{-4} M in the given buffer system given in Table I. Aliquots at various times were diluted to 2.00×10^{-4} M with acetate buffers and NaOH so that the resultant pH was 5.5 and the aliquots then were read spectrophotometrically. The first-order rate plots of log [I] *vs.* time, of which typical examples are plotted in Fig. 2, were based on the concentrations of [I] calculated from the above equations. The derived rate constants (k'_1) are given in Table I.

The hydrolysis studies of [II] were conducted at 4.00×10^{-4} and 8.00×10^{-4} M in the given buffer systems presented in Table II. Aliquots at various times were diluted with acetate buffers and NaOH so that the resultant pH was 5.5 and the aliquots were then read spectrophotometrically.

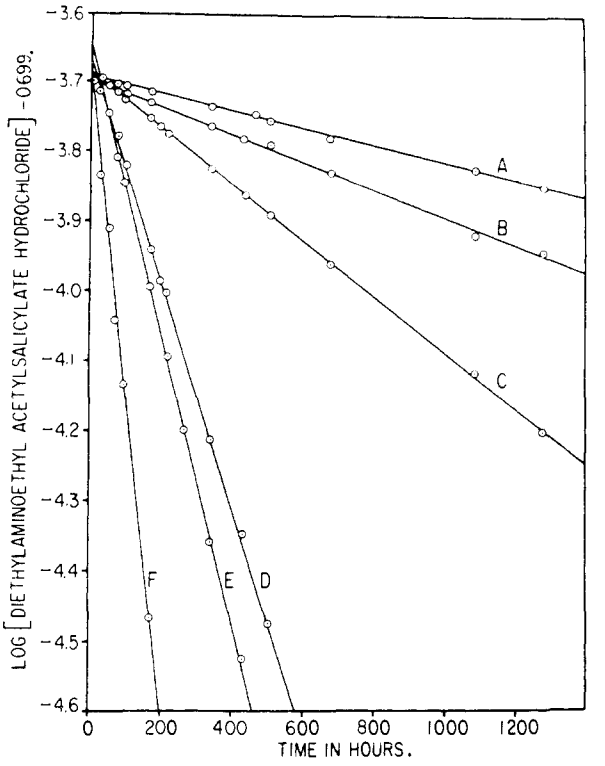


Fig. 2.—Typical first-order rate plots for the hydrolysis of 10×10^{-4} M diethylaminoethyl acetylsalicylate hydrochloride (I) at 30.3°.

Curve	A	B	C	D	E	F
pH	3.00	4.08	5.08	6.15	6.23	0.90
Item in Table I	5	13	21	30	31	1

The first-order rate plots of log [II] *vs.* time, of which typical examples are plotted in Fig. 3, were based on the concentrations of [II] calculated from the above equations. The derived rate constants (k_3) are given in Table II.

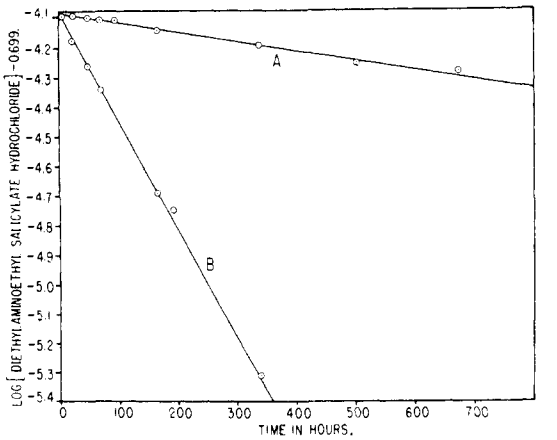


Fig. 3.—Typical first-order rate plots for the hydrolysis of 4 x 10^{-4} M diethylaminoethyl salicylate hydrochloride (II) at 30.3° (see Table II); curve A at pH 5.07 and curve B at pH 6.15.

Calculations and Results

Rates of Disappearance of Diethylaminoethyl Acetylsalicylate Hydrochloride (I).—The observed pseudo-first order rate constants (k'_1 in sec.$^{-1}$) for the transformation of I under various conditions

TABLE I

OBSERVED AND CALCULATED RATE CONSTANTS (k IN SEC.$^{-1}$) FOR THE SPECTROPHOTOMETRICALLY DETERMINED HYDROLYSIS OF 10.00×10^{-4} M DIETHYLAMINOETHYL ACETYLSALICYLATE HYDROCHLORIDE (I) AT 30.3°

Run	pH	Buffer composition [HCl]	[CH$_3$COOH]	[CH$_3$COO$^-$]	[KCl] / [NaCl]	10^5k_0[a]	Total rate $10^5k'_1$ Obsd.	Calcd.[b]	$100R$[d]	10^5k_1[e]	10^5k_{0-2}[f]
1	0.90	0.1304			0.0625	296	296	296			
2	1.79	0.0167			0.0500	37.0	37.0	38.1			
		[CH$_3$COOH]	[CH$_3$COO$^-$]		[NaCl]						
3	2.40	0.57				12.5	14.5	15.8			
4	2.98	.057				7.13	7.34	7.9			
5	3.00	.057				7.28	7.49	7.9			
6	3.53	.176	0.012			6.58	8.69	8.9			
7	4.00	.060	.015		0.085	6.55	8.61	8.6	87.6	7.5	0.7
8	4.00	.120	.030		.070	6.6	10.7	10.7	88.3	9.5	.6
9	4.00	.200	.050		.050	6.7	13.6	13.4	88.3	12.0	.4
10	4.02 (4.00)	.260	.065		.035	7.2	16.1	15.5	87.0	14.0	.6
11	4.02	.320	.080		.020	6.5	17.5	17.5	89.0	15.6	.2
12	3.99	.400	.100		.000	7.3	21.0	20.2	87.0	18.3	.4
13	4.08	.133	.033			7.8	12.3	11.1	87.7	10.8	.7
14	4.52	.080	.060			9.1	16.7	15.4	77.6	13.0	2.3
15	4.62	.015	.015		.085	8.7	10.6	10.2	72.9	7.8	2.5
16	4.62	.030	.030		.070	8.7	12.5	12.1	75.2	9.4	2.4
17	4.61 (4.62)	.050	.050		.050	8.7	15.0	14.5	79.1	11.9	1.9
18	4.63	.065	.065		.035	8.9	17.1	16.5	79.1	13.5	2.1
19	4.64	.080	.080		.020	8.9	18.4	18.5	80.0	14.8	1.8
20	5.03	.033	.084			14.7	25.1	22.6	73.0	18.3	4.9
21	5.08	.033	.084			15.4	25.8	23.4	68.2	17.6	6.3
22	5.20	.010	.040		.160	16.3	21.2	20.2	49.3	10.4	9.9
23	5.19	.020	.080		.120	15.8	25.7	24.9	53.9	13.9	12.0
24	5.21 (5.21)	.030	.120		.080	15.5	30.3	30.3	59.9	18.1	9.4
25	5.24	.040	.160		.040	15.8	35.6	35.8	62.7	22.3	9.6
26	5.22	.050	.200		.000	16.0	40.7	40.4	62.6	25.5	10.6
27	5.63	.0094	.0953			35.8	47.5	43.0	38	18.1	27.2
28	5.96	.0040	.0980			60.0	72.0	72.2	28	20.2	49.5
29	5.83	.0270	.4865			27.8	87.6	96.0[c]	63	55.3	21.1
30	6.15	.0050	.1225			86	101	105	30	30	69
31	6.23	.0050	.1225			112	127	123	24	30	97

[a] $k_0 = k'_1 - (k_{Ac}[CH_3COO^-] + k_{HAc}[CH_3COOH])$ where $k_{Ac} = 1.227 \times 10^{-3}$ l./mole/sec. and $k_{HAc} = 3.61 \times 10^{-6}$ l./mole/sec. [b] Based on the derived expression: $k_1 = k_{OH^-}[OH^-] + k_{H_2O} + k_{Ac}[CH_3COO^-] + k_{HAc}[CH_3COOH] + k_{H^+}[H^+]$ where $k_{OH^-} = 40.6$ l./mole/sec., $k_{H_2O} = 5.7 \times 10^{-6}$ sec.$^{-1}$ and $k_{H^+} = 2.0 \times 10^{-5}$ l./mole/sec. [c] If k_{Ac} were corrected for ionic strength, the calculated $k'_1 = 85.4 \times 10^{-6}$ when $\log k_{Ac} = \log (k_{Ac})_0 - \sqrt{\mu} + 0.5\ \mu$. [d] $R = [II]/[II']$ at any time t, where $[II]'$ is the appearance of II calculated on the premise of no aspirin intermediate and [II] is the experimental amount at that time t. [e] $k_1 = k'_1R$. [f] $k_2 = k'_1(1 - R)$ and $k_{0-2} = k_{OH}[OH^-] = k_2 - k_{Ac-2}[CH_3COO^-]$ where $k_{Ac-2} = 0.23 \times 10^{-6}$ l./mole/sec.

TABLE II

RATE CONSTANTS (k_3 IN SEC.$^{-1}$) FOR THE SPECTROPHOTOMETRICALLY DETERMINED HYDROLYSIS OF DIETHYLAMINOETHYL SALICYLATE HYDROCHLORIDE (II) AT 30.3°

Run[a]	pH[b]	[CH$_3$COOH]	[CH$_3$COO$^-$]	10^5k_3	k'_{OH^-}, l./mole/sec.[c]
32	5.07	0.033	0.084	0.217	125
33	6.10	.0013	.0306	2.02	109
34	6.13	.0025	.0613	2.03	102
35	6.15	.0039	.0918	1.88	90
36	6.15	.0050	.1225	2.03	97
37	6.15	.0050	.1225	2.25	108

[a] Runs 32 and 37 were 4.00×10^{-4} M and runs 33–36 were 8.00×10^{-4} M in II. [b] No change in spectra was observed at pH 3.0 for a two-month period and negligible change at pH 4.0. The estimated change in the latter case was 5% in three months. [c] $k'_{OH^-} = k_3/[OH^-]$ where $[OH^-] = 10^{-(pK_w - pH)}$ where $pK_w = 13.83$ at 30.3°.

are listed in Table I. The rate constants are based on plots, examples of which are given in Fig. 2, which conform to the classical first-order equation

$$\log [I] = -k'_1t + \log [I]_0 \qquad (11)$$

The rate constant, k'_1, on the assumption of general acid–base catalysis may be defined by

$$k'_1 = k_{OH^-}[OH^-] + k_{H_2O} + k_{Ac}[CH_3COO^-] + k_{HAc}[CH_3COOH] + k_{H^+}[H^+] \qquad (12)$$

The more elegant equation should correct the right-hand side of equation (12) by $1/(1 + K'_{a_I}/[H^+])$ where K'_{a_I} is the dissociation constant of I.[3] However, since these studies were conducted below pH 6.2 and the pK'_a of I is 8.68, there is negligible reduction in the amount of non-protonated I due to dissociation and this correction factor is unity for all practical purposes.

At constant pH, equation 12 reduces to

$$k'_1 = k_{Ac}[CH_3COO^-] + k_{HAc}[CH_3COOH] + k_0 \qquad (13a)$$
$$= [k_{Ac} + (k_{HAc}/K'_a)\ [H^+]\}\ [CH_3COO^-] + k_0 \qquad (13b)$$
$$= k'_{Ac}[CH_3COO^-] + k_0 \qquad (13c)$$

where the K'_a is the dissociation constant of acetic acid.

Figure 4 plots some of the observed rate constants, k'_1 in sec.$^{-1}$, of Table I against acetate ion concentration, $[CH_3COO^-]$, for three different pH values. Ionic strength was maintained constant

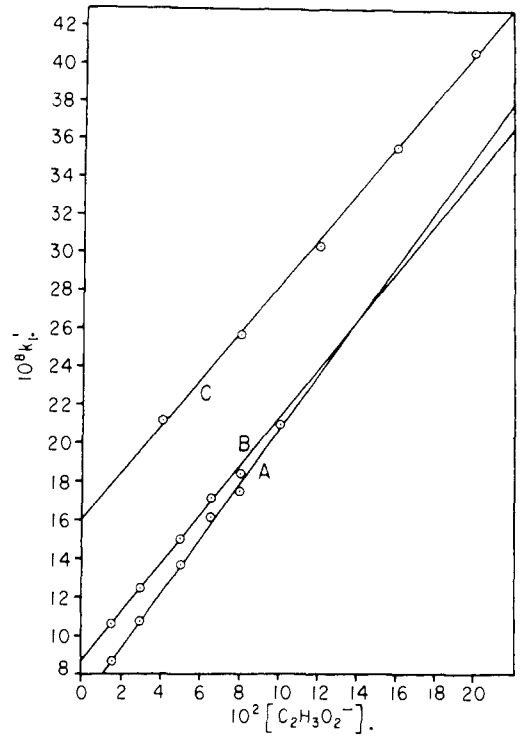


Fig. 4.—Effect of varying acetate ion concentration at constant ionic strength, μ, at several pH values on the first-order rate constants (k_1' in sec.$^{-1}$) of hydrolyses of 10×10^{-4} M diethylaminoethyl acetylsalicylate hydrochloride (I) at 30.3°: A, pH 4.00, μ 0.100; B, pH 4.62, μ 0.100; C, pH 5.21, μ 0.200.

for a given pH. The linearity of the plots confirmed the expectations of equation 13c, that the observed first-order rate constant, k'_1, depends on acetate concentration. The slopes, k'_{Ac}, and intercepts, k_0, of such plots are given in Table III.

TABLE III

DEPENDENCE OF PSEUDO FIRST-ORDER RATE CONSTANTS (k'_1 IN SEC.$^{-1}$) OF DIETHYLAMINOETHYL ACETYLSALICYLATE HYDROCHLORIDE HYDROLYSIS AT 30.3° ON ACETATE ION[a]

pH	Ionic strength, μ	Based on items in Table I	$10^3 k'_{Ac}$	$10^3 k_0$	$10^6[H^+]$[b]
4.00	0.1	7–12	1.435	6.45	100
4.62	.1	15–19	1.273	8.67	24
5.21	.2	22–26	1.241	15.80	6.2

[a] See Fig. 4. [b] $[H^+] = 10^{-pH}$.

The k'_{Ac} values of Table III indicate an apparent variation of the catalytic rate constant for acetate ion with pH. This variation is not solely a function of the ionic strength, μ; and the only other variable to consider is the concentration of undissociated acetic acid, [CH_3OOH], which only indirectly is a function of hydrogen and acetate ions, as is shown in equations 13a and 13b.

Thus the observed acetate ion catalytic constants, k'_{Ac}, and the hydrogen ion concentrations, $[H^+] = 10^{-pH}$, for the two cases at constant ionic strength, $\mu = 0.1$, given in Table III permit the evaluation of k_{HAc}/K_a', and k_{Ac} by equation 14 at 30.3°

$$k'_{Ac} = (k_{HAc}/K'_a)[H^+] + k_{Ac} = 2.06 \times 10^{-3}\,[H^+] + 1.227 \times 10^{-6} \quad (14)$$

where $k_{Ac} = 1.227 \times 10^{-6}$ l./mole/sec.; $k_{HAc} = 3.61 \times 10^{-8}$ l./mole/sec. and $K'_a = 1.75 \times 10^{-5}$.

The rate effects of acetic acid–acetate buffer system may be calculated for every study in Table I and subtracted from the over-all rate, k'_1, to permit estimation of the hydroxyl ion, hydrogen ion and "spontaneous" catalytic effect where from equations 12 and 13

$$k_0 = k_{OH^-}[OH^-] + k_{H_2O} + k_{H^+}[H^+] \quad (15)$$

The k_0 (in sec.$^{-1}$) values as calculated from equations 13c and 14 are listed in Table I. Inspection of these values indicates that the $k_{H^+}[H^+]$ contribution to k_0 is negligible above pH 4 so that a plot of k_0 for items 13–31 against the hydroxyl ion concentration, $[OH^-] = 10^{-(pK_w - pH)}$, as shown in Fig. 5, permits the evaluation of the slope, k_{OH^-},

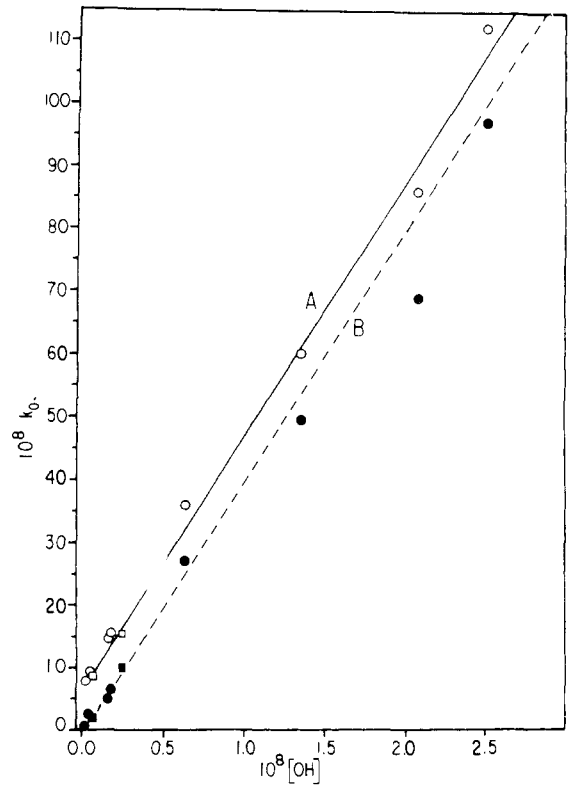


Fig. 5.—Effect of hydroxyl ion concentration on the first-order rate constants (k_0 and k_{0-2} in sec.$^{-1}$) for the hydrolysis of diethylaminoethyl acetylsalicylate hydrochloride (I) after correction for acetic acid–acetate buffer effects. Curve A is for k_0 derived from the total hydrolysis, k_1', of I. Curve B is for k_{0-2} derived from the hydrolysis rates of I which do not involve diethylaminoethyl salicylate hydrochloride (II) as an intermediate. The squares represent 5 to 6 separate values.

and the intercept k_{H_2O}. The pK_w of water at 30.3° is 13.83. This treatment of the data gives $k_{OH^-} = 40.6$ l./mole/sec. and $k_{H_2O} \sim 6.0 \times 10^{-8}$ sec.$^{-1}$.

Assignment of $k_{H_2O} = 5.7 \times 10^{-8}$ sec.$^{-1}$ permits estimates of $k_{H^+} = (k_0 - k_{H_2O})/[H^+]$ where $[H^+] = 10^{-pH}$. The values of k_{H^+} (l./mole/sec.) for runs 1, 2 and 3 (Table I) are 2.30×10^{-5}, 1.93×10^{-5} and 1.72×10^{-5}, respectively, with a mean value for $k_{H^+} = 2.0 \times 10^{-5}$ l./mole/sec.

The evaluated constants may be inserted in equation 12 to permit the calculation of k'_1 in sec.$^{-1}$ values at 30.3° for all the runs in Table I as

$$k'_1 = 40.6\,[OH^-] + 5.7 \times 10^{-6} + 1.23 \times 10^{-6}\,[CH_3COO^-] + 3.61 \times 10^{-6}\,[CH_3COOH] + 2.0 \times 10^{-5}\,[H^+] \quad (16)$$

The rate constants, k'_1, calculated from equation 16 and listed in Table I agree with the observed values listed therein to confirm the proposed kinetic dependencies. Correction for ionic strength[3] as by

$$\log k_{Ac} = \log (k_{Ac})_0 - \sqrt{\mu} + f(\mu) \quad (17)$$

does not significantly improve or lessen the agreement of observed and calculated k'_1 values except in the one extreme case of very high acetate ion concentration, item 29 in Table I where $f(\mu)$ was estimated at 0.5 μ.

Rates of Disappearance of Diethylaminoethyl Salicylate Hydrochloride (II).—The observed pseudo-first-order rate constants (k_3 in sec.$^{-1}$) for the transformation of II to salicylic acid (III) under various conditions are listed in Table II.

The rate constants are based on plots, examples of which are given in Fig. 3, which conform to the classical first-order equation

$$\log [II] = -k_3 t + \log [II]_0 \quad (18)$$

Inspection of Table II shows no significant dependence on acetate ion concentration (runs 33–37) and thus no significant general base catalysis. No "spontaneous" hydrolysis was apparent. If specific hydroxyl ion catalysis of II is the mechanism

$$k'_{OH^-} = k_3/[OH^-] = 1.0 \times 10^2 \quad (19)$$

where $[OH^-] = 10^{-(pK_w - pH)}$ and $pK_w = 13.83$ at 30.3°.

Comparison of Theoretical and Actual Rates of Appearance of Intermediates in the Hydrolysis of Diethylaminoethyl Acetylsalicylate Hydrochloride.—If the hydrolysis products of diethylaminoethyl acetylsalicylate hydrochloride (I) are only diethylaminoethyl salicylate hydrochloride (II) and salicylic acid (III), and no acetylsalicylic acid (aspirin) (IV) occurs, then the concentration of II (*i. e.*, [II]′) may be calculated from the expression[5]

$$[II]' = [I_0]\,\frac{k'_1}{k_3 - k'_1}\,(e^{-k'_1 t} - e^{-k_3 t}) \quad (20)$$

where $[I]_0$ is the initial concentration of diethylaminoethyl acetylsalicylate hydrochloride, and [II]′ is [II] on the presumption that the sole route of hydrolysis is

$$I \xrightarrow{k'_1} II \xrightarrow{k_3} III \quad (21)$$

Typical examples of the calculated amounts of II, *i. e.*, [II]′, as a function of time calculated on the basis of equation 20 on the presumption of the route in (21) are plotted in Figs. 6 and 7 as the curve A. The actual amounts of II, *i. e.*, [II], as derived from the spectrophotometric data are plotted as curve B. It is apparent that less II appears on hydrolysis than should be expected by the proposed route 21. It now is possible that a simultaneous route

$$I \xrightarrow{k_2} IV \xrightarrow{k_4} III \quad (22)$$

through aspirin (IV) exists. The spectra of dissociated aspirin at *p*H 5.5 are negligible at the wave lengths used in equations 1–6 and would not inter-

(5) S. Glasstone, "Textbook of Physical Chemistry," D. Van Nostrand Co., Inc., New York, N. Y., 2nd ed., 1946, p. 1075.

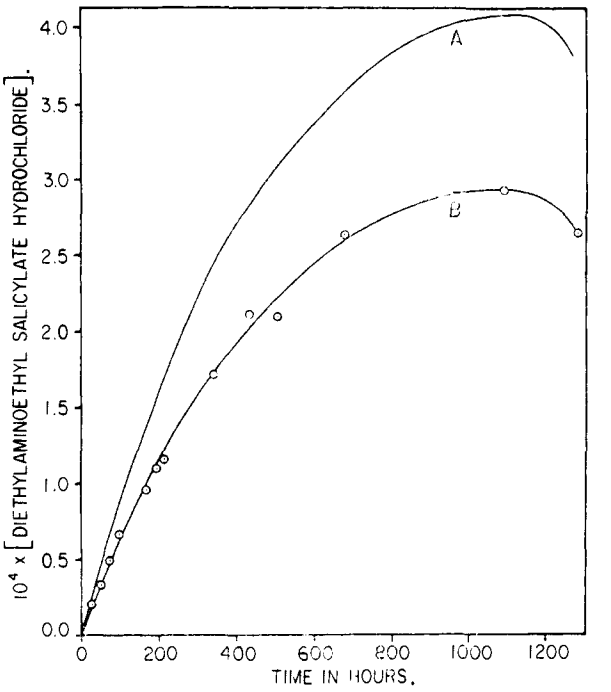


Fig. 6.—Amounts of diethylaminoethyl salicylate hydrochloride (II) *vs.* time from the hydrolysis of diethylaminoethyl acetylsalicylate hydrochloride (I). Curve A is the amount of II calculated on the assumption that the only route of hydrolysis is through II. Curve B is the experimental plot of II *vs.* time. The original conditions were 10.2 $\times 10^{-4}$ *M* in I, *p*H 5.08 at 30.3°, $[CH_3COOH] = 0.033$ and $[CH_3COO^-] = 0.084$.

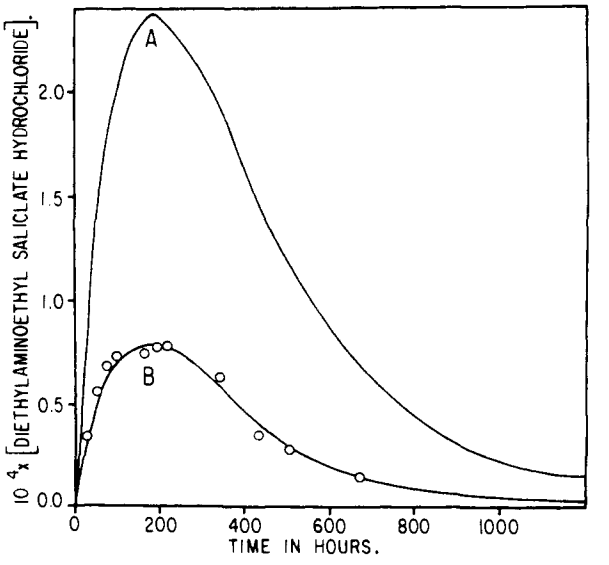
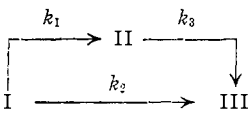


Fig. 7.—Amounts of II *vs.* time from the hydrolysis of I. Curve A is the amount of II calculated on the assumption that the only route of hydrolysis is through II. Curve B is the experimental plot of II *vs.* time. The original conditions were 10.1 $\times 10^{-4}$ *M* in I, *p*H 6.15 at 30.3°, $[CH_3COOH] = 0.0050$ and $[CH_3COO^-] = 0.1225$.

fere with the calculations of the quantities of II and III. However, the presence of finite amounts of aspirin should cause deviation in the first-order plots of I disappearance as based on equation 7. Figure 2 shows no such deviations from first-order which implies that no finite amount of aspirin (IV) appears during the hydrolysis.

This may be expected below *p*H 5.7 when I is hydrolyzed to IV and thence to III since k_4 is of the magnitude of 10^{-5} sec.$^{-1}$ at *p*H 5.0 which is 20–50 times greater than the other rates for the hydrolysis of I through II.

Thus, a scheme should be postulated as in (23) wherein there is no storage in the form of aspirin, (IV) and the spectrophotometric measurements of [II] and [III] are assumed to account for all of the hydrolyzed I



(23)

where $k'_1 = k_1 + k_2$, and

$$-d[I]/dt = k'_1[I] = [k_1 + k_2][I] \quad (24)$$

so that

$$[I] = [I]_0 e^{-k'_1 t} = [I]_0 e^{-(k_1+k_2)t} \quad (25)$$

$$d[III]/dt = k_3[II] + k_2[I] \quad (26)$$

$$d[II]/dt = k_1[I] - k_3[II] \quad (27)$$

and substituting equation 25 into 27

$$d[II]/dt = k_1[I]_0 e^{-(k_1+k_2)t} - k_3[II] \quad (28)$$

The integrating factor is $e^{\int k_3 dt} = e^{k_3 t}$ and since at $t = 0$, [II] = 0

$$[II] = [I]_0 \frac{k_1}{k_3 - k_1 - k_2}(e^{-(k_1+k_2)t} - e^{-k_3 t})$$

$$= [I]_0 \frac{k_1}{k_3 - k'_1}(e^{-k'_1 t} - e^{-k_3 t}) \quad (29)$$

Thus the values calculated by equations 29 and 20 form a constant ratio, R, independent of time, t, so that

$$k_1 = k'_1[II]/[II]' = k'_1 R \quad (30)$$

where

$$k_2 = k'_1(1 - R) \quad (31)$$

This signifies that the ratio, R, of the experimental amount [II] to the [II]′ calculated on the premise of no aspirin intermediate will be constant and equal for all specified times. Thus k_1 and k_2 can be calculated separately and are given in Table I. Figures 6 and 7 are examples of this procedure and show that the curves calculated by such procedures should be of the same shape and of constant proportionality at any given time.

Kinetic Dependence of the Alternate Routes of Hydrolysis of Diethylaminoethyl Acetylsalicylate Hydrochloride.—The values of R and k_1 are given in Table I for each study. The R values were obtained from the averaging of the constant ratios of [II]/[II]′ at several specific times where the numerator was plotted on an X–Y plotter using an analog computer with the appropriate k'_1 and k_3 values as per equation 20 and the denominator was obtained from the spectrophotometric analysis. The k_1 and k_2 values were calculated from the observed k'_1 and R values also given in Table I by equations 30 and 31.

On the preliminary assumption that k_1 and k_2 are subject to the same general acid–base catalysis as k'_1 in equation 12, plots of k_1 and k_2 against acetate ion concentration are given in Fig. 8 in accordance with the expected relationship similar to equation 13c. The respective slopes, k'_{Ac-1} and k'_{Ac-2}, in l./mole/sec. and intercepts, k_{0-1} and k_{0-2} in sec.$^{-1}$, are given in Table IV.

TABLE IV

DEPENDENCE OF PSEUDO-FIRST-ORDER RATE CONSTANTS (k_1 AND k_2 IN SEC.$^{-1}$) OF DIETHYLAMINOETHYL ACETYLSALICYLATE HYDROCHLORIDE HYDROLYSIS AT 30.3° ON ACETATE ION[b]

*p*H	Ionic strength, μ	Based on items in Table I	$10^5 k'_{Ac-1}$	$10^5 k_{0-1}$	$10^5 k'_{Ac-2}$	$10^5 k_{0-2}$
4.00	0.1	7–12	1.25	5.7	0.22	0.6
4.62	.1	15–19	1.10	6.0	..[a]	2.3
5.21	.2	22–26	1.01	5.8	0.25	9.8

[a] The variation among the data does not permit a good estimate of k'_{Ac-2} in this case. However, the same slope for the *p*H 4.62 studies as for the *p*H 4.00 studies is not inconsistent. [b] See Fig. 8 and Table III.

The k_{Ac-2} values are small so that no significant variation with hydrogen ion concentration and thus undissociated acetic acid catalysis as explained by equation 13 can be observed in the k_2 route, *i. e.*, $k_{HAc-2} = 0$ and $k'_{Ac-2} = k_{Ac-2} = 0.23 \times 10^{-6}$ l./mole/sec. The k_{0-2} values vary greatly with *p*H and are of the order of magnitude to account for all the hydroxyl ion catalyzed hydrolysis of I. No water or "spontaneous" hydrolysis is apparent in the k_2 route.

The k'_{Ac-1} values vary at constant ionic strength (*e. g.*, $\mu = 0.1$) for different *p*H values. Equations 13a and 13b are applicable here and by the same arguments given previously for k'_1 and equation 14

$$k'_{Ac-1} = (k_{HAc-1}/K'_a)[H^+] + k_{Ac-1}$$
$$= 2.0 \cdot 10^{-3}[H^+] + 1.04 \times 10^{-6} \quad (32)$$

where $k_{Ac-1} = 1.04 \times 10^{-6}$ l./mole/sec. and $k_{HAc-1} = 3.5 \times 10^{-8}$ l./mole/sec. The k_{0-1} values are reasonably constant. The catalysis in the k_1 route is as follows: $k_{0-1} \sim 6 \times 10^{-8}$ sec.$^{-1}$, by acetate ion k_{Ac-1} [CH_3COO^-], by acetic acid k_{HAc-1} [CH_3COOH] and by hydrogen ion $k_{H^+}[H^+]$ since the sole product in strong acid solutions is II. No significant hydroxyl ion catalysis can be assigned to the k_1 route from the studies summarized in Table IV.

Further proof of the non-involvement of hydroxyl ion catalysis in the k_1 route and complete accounting for this effect by the k_2 route is given by calculating k_{0-2} values for the studies in Table I from

$$k_{0-2} = k_2 - k_{Ac-2}[CH_3COO^-] = k_{OH^-}[OH^-] \quad (33)$$

where

$k_{Ac-2} = 0.23 \times 10^{-6}$ l./mole/sec. and

$$[OH^-] = 10^{-(pK_w - pH)}$$

The validity of equation 33 may be checked by plotting the derived k_{0-2} values (as given in Table I) against the hydroxyl ion concentration (see Fig. 5). The same slope, $k_{OH^-} = 40.6$ l./mole/sec., as for the hydroxyl ion dependency of the k_0 derived from the total reaction rate k'_1 and the zero intercept supports these statements.

Discussion

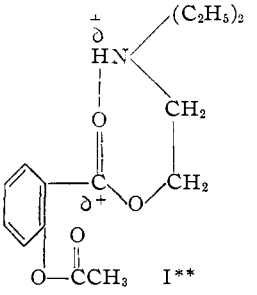
Diethylaminoethyl acetylsalicylate hydrochloride (I) undergoes hydrolysis by two routes: the one through diethylaminoethyl salicylate hydrochloride (II) to salicylic acid (III) and the other, either through an aspirin (IV), intermediate or directly to salicylic acid (III). The complete equations for the dependencies of the pseudo-first-order rate constant, k'_1 in sec.$^{-1}$, at 30.3°, for the hydrolysis of I are

$$k'_1 = \underbrace{(k_{H_2O} + k_{Ac-1}[CH_3COO^-] + k_{HAc}[CH_3COOH] + k_{H^+}[H^+])}_{k_1} + \underbrace{(k_{Ac-2}[CH_3COO^-] + k_{OH^-}[OH^-])}_{k_2}$$

$$= \underbrace{(5.7 \times 10^{-6} + 1.04 \times 10^{-6}\,[CH_3COO^-] + 3.5 \times 10^{-6}\,[CH_3COOH] + 2.0 \times 10^{-5}\,[H^+])}_{k_1} + \underbrace{(0.23 \times 10^{-6}\,[CH_3COO^-] + 40.6[OH^-])}_{k_2} \qquad (34)$$

The k_1 route involves hydrolysis of the acetoxy group of I while the diethylaminoethyl ester remains intact. Hydrogen ion catalysis, I to Ia to II in Chart I, is most probably classical in nature[6] and is of the same numerical magnitude as the hydrogen ion catalyzed hydrolysis of undissociated aspirin.[7]

It is possible that water or acetate ion directly attacks the acetoxy group without the assistance of the positive charge in the adjacent ester. However, it is more probable that the positive charge is involved and a plausible mechanism is to postulate the activation of the acetyl carbonyl *via* the proton of the protonated nitrogen which activates the phenylcarbonyl either by direct transfer as in I*, Chart I, or by adjacency, I**



I**

to give a cyclic intermediate similar to those previously suggested for acylsalicylate hydrolysis.[7]

Subsequent nucleophilic attack by acetate ion or water on the acetylcarbonyl carbon may be the rate-determining step (I* to Ib or Ic and then to II in Chart I).

Of course, the classical charge transfer of general base catalysis could also occur to give an uncharged reactive intermediate without directly involving a nucleophile, but the work of Bender and Turnquest[2b] and Bruice and Schmir[2a] indicates that this may be less probable.

(6) M. L. Bender, THIS JOURNAL, **73**, 1626 (1951).
(7) E. R. Garrett, *ibid.*, **79**, 3401 (1957).

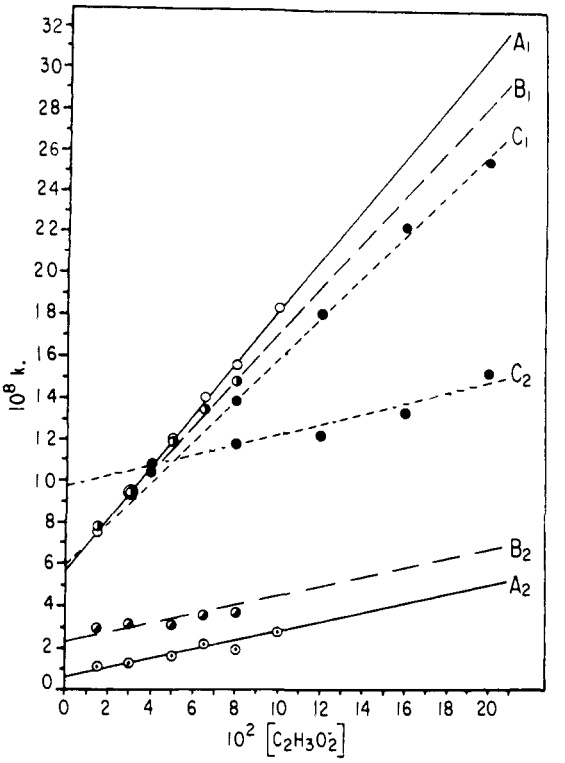


Fig. 8.—Effect of varying acetate ion concentration at constant ionic strength, μ, at several pH values on the simultaneous first-order rate constants of the hydrolyses to diethylaminoethyl salicylate hydrochloride (II) (*i. e.*, k_1) and to salicylic acid (III) (*i. e.*, k_2) of 10 × 10^{-4} *M* diethylaminoethyl acetylsalicylate hydrochloride (I) at 30.3°. The subscripts refer to the appropriate rate constant in sec.$^{-1}$.

Code	Curve	pH	μ
○	A	4.00	0.100
◑	B	4.62	0.100
●	C	5.21	0.200

The kinetics of equation 34 also indicates a catalytic dependence on undissociated acetic acid. The mechanism could be similar to the route I* to Ic, Chart I

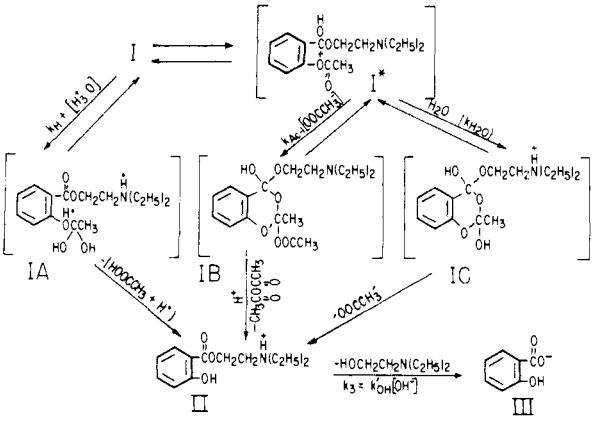
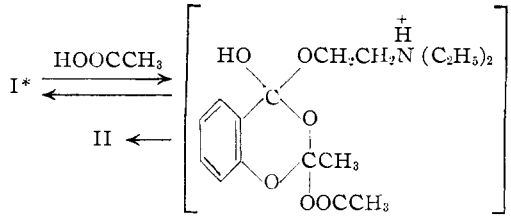


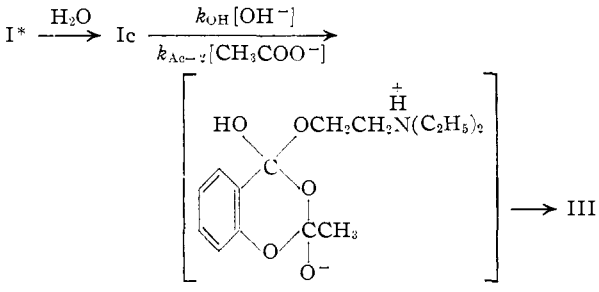
Chart I.—The hydrolysis of diethylaminoethyl acetylsalicylate hydrochloride (I) to salicylic acid (III) through a diethylaminoethyl salicylate hydrochloride intermediate II; the k_1 route.



The k_2 route involves hydrolysis of both ester groups in I to give salicylic acid (III). An unobserved aspirin intermediate IV may occur, although some question may be raised because of the adherence to first-order kinetics of the spectrophotometrically observed hydrolysis of I at high *p*H values, *ca.* 6.0, where the over-all hydrolysis rate, k_1, approaches the hydrolysis rate of aspirin.[7]

Hydroxyl ion catalysis, I* to Id to IV to III in Chart II, is most probably classical.[6] Acetate ion catalysis is of low magnitude compared to the k_1 route but may form an activated adduct Ie which may directly produce aspirin (IV) or a very quickly hydrolyzable mixed anhydride intermediate If prior to IV and thence to III.

An argument against Ie is that an anhydride intermediate for general base catalysis by acetate ion has been postulated by Bender and Turnquest.[2] This route appears to be of importance only for esters containing an alcohol that is a reasonably strong acid, *i. e.*, $pK_a' < 11$. However, the fact of a protonated group in the alcohol may modify this consideration. Of course, the direct route to salicylic acid may result from activation of a cyclic intermediate by charge transfer as per classical general base catalysis as



The major differences in the hydrolysis of an alkyl aminoacetylsalicylate and an aminoalkyl acetylsalicylate appear to be the ready hydrolysis of both esters in the latter and only the aminoacetyl group in the former. Both protonated groups resist hydrogen ion catalyzed hydrolysis and both are susceptible to nucleophilic attack or general base catalysis, although only the latter appears to induce susceptibility into the non-protonated vicinal ester.

Water, acetate ion and hydroxyl ion catalyzed hydrolysis of methyl pyrrolidylacetylsalicylate hydrochloride is one hundred times that of the comparable hydrolysis of diethylaminoethyl acetylsalicylate hydrochloride. This may indicate that

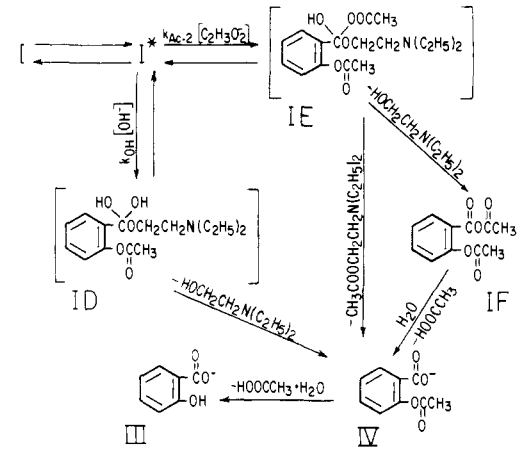


Chart II.—The hydrolysis of diethylaminoethyl acetylsalicylate hydrochloride (I) to salicylic acid (III) through an acetylsalicylate (aspirin) intermediate IV; the k_2 route.

the nucleophilic attack on the protonated group in the former case is the more direct than in the latter, that the electrophilicity of the protonated appendage in the latter case must, in general, be transferred to the non-protonated as by the cyclic intermediates proposed.[8]

Acknowledgment.—Grateful appreciation is given to Dr. Fred Kagan and R. D. Birkenmeyer for the synthesis of the esters, to Miss Susan Theal for some of the potentiometric titrations, to Mrs. Kathryn Polzin and Mrs. Lillian Snyder for excellent technical assistance, and to Mr. Clayton Alway for construction and instruction on the analog computer.

KALAMAZOO, MICH.

(8) It is easy to understand why the hydroxyl ion may cleave the phenyl ester link in methyl pyrrolidylacetylsalicylate hydrochloride[3] with the large bimolecular rate constant of 10^3 l. mole^{-1} sec.$^{-1}$ since the attack can be directly upon the protonated carbonyl-containing ester group. Since recent work[2] has indicated that general base catalysis may be expected in the hydrolysis of a dialkylaminoacetylphenate, the concept of hydroxyl ion attack through a cyclic mechanism is less attractive in this case.

However, the apparent failure of hydroxyl ion to react with a similar phenyl ester linkage in diethylaminoethyl acetylsalicylate hydrochloride (I), whereas the weaker base, acetate ion, is effective possibly through a proposed cyclic mechanism may need further explanation.

In these studies, acetate ion concentration is of the magnitude of 10^{-2} and at the highest *p*H, *i.e.*, 6, the hydroxyl ion concentration is 10^{-8}. The bimolecular rate constant of hydroxyl ion attack on the acetylphenate link would have to exceed 10 l. mole^{-1} sec.$^{-1}$ for its contribution to the total rate to have been barely observed at a *p*H of 6. For observation of such a contribution below this *p*H, the rate constant would have had to be even higher. The literature value[9] for hydroxyl ion attack on acetylphenate is of the magnitude 0.5 l. mole^{-1} sec.$^{-1}$.

A possible mechanistic explanation would be that even if hydroxyl ion attacked I*, Chart I, to produce a non-protonated Ic, the more stable configuration of Ic would be Id of Chart II, leading to an aspirin product. This may imply that whereas Id is more stable than non-protonated Ic, Ib is more stable than Ie. The experimental facts, *i.e.*, more II than IV from acetate ion catalysis tend to substantiate this statement.

(9) "Tables of Chemical Kinetics: Homogeneous Reactions," National Bureau of Standards Circular 510, U. S. Department of Commerce, Washington, D. C., 1951, p. 129.