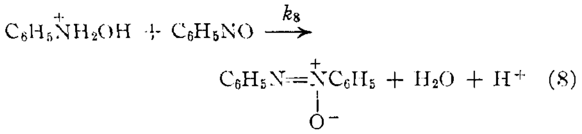
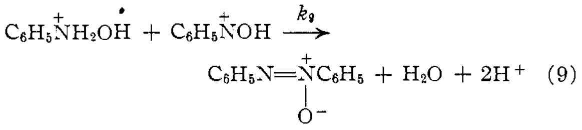
Furthermore, the possibilities of the other mechanisms will be discussed below. A rate-determining reaction of protonated phenylhydroxylamine with nitrosobenzene



$$C_6H_5\overset{+}{N}H_2OH + C_6H_5NO \xrightarrow{k_8} C_6H_5N{=}\underset{O^-}{\overset{+}{N}}C_6H_5 + H_2O + H^+ \quad (8)$$

or a rate-determining condensation of both pro-



$$C_6H_5\overset{+}{N}H_2OH + C_6H_5\overset{+}{N}OH \xrightarrow{k_9} C_6H_5N{=}\underset{O^-}{\overset{+}{N}}C_6H_5 + H_2O + 2H^+ \quad (9)$$

tonated reactants should lead to the rate constant expression

$$k = \frac{k_8K_1[H^+]}{(1 + K_1[H^+])(1 + K_4[H^+])}$$

or

$$k = \frac{k_9K_1K_4[H^+]^2}{(1 + K_1[H^+])(1 + K_4[H^+])}$$

respectively; hence neither mechanism alone or combined with equation 5, where

$$k = \frac{k_5K_4[H^+]}{(1 + K_1[H^+])(1 + K_4[H^+])}$$

agrees with the fact, since each k value should diminish to zero as the hydrogen ion concentration approaches zero. Also, equations 8 and 9 do not seem rational in the light of the electronic theory, since they involve the attack of a cation on the positive nitrogen of nitrosobenzene.

This electronic point of view can also be used to eliminate a mechanism involving the simultaneous reaction of equations 8 and 2, although the mechanism leads to a rate equation consistent with the experiment.

Acknowledgments.—The authors wish to thank Profs. R. Oda, S. Tanaka and M. Okano for their aid in performing these experiments.

KYOTO, JAPAN

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

The Kinetics of Solvolysis of Acyl Esters of Salicyclic Acid

BY EDWARD R. GARRETT

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The acid, neutral and alkaline hydrolysis of acetyl-, trimethylacetyl-, β-cyclopentylpropionyl- and diethylacetylsalicyclic acids were studied and the rate constants determined as functions of dissociation and of hydrogen and hydroxyl ion concentration. The Arrhenius parameters of entropy and heat of activation also were determined and mechanisms were considered in light of these values and the structures of the esters. Disagreement with values given in the literature was noted. An unusual increase in "spontaneous" rate was observed with increasing alcohol concentration whereas no such increase was noted with increasing dioxane content.

In order to determine the inhibition of hydrolysis of acyl salicylates by varying alkyl substitution on the acyl group, the acid and base hydrolysis of esters selectively chosen to scan substituent effects, acetyl-, trimethylacetyl-, β-cyclopentylpropionyl- and diethylacetyl salicylic acids were studied. A very complete study of the hydrolysis of acetyl salicylic acid (aspirin) had been made by Edwards.[1,2] However, since these papers had reported an unusually high alkaline hydrolysis heat of activation of 25 kcal./mole, whereas similar acyl phenates had activation energies of an order of magnitude of 12 kcal./mole,[3] the hydrolysis studies of aspirin were repeated and the Arrhenius parameters determined.

It was desired to carry out the hydrolysis studies in solutions as nearly aqueous as possible, but the inadequate water solubility of β-cyclopentylpropionyl- and diethylacetylsalicylic acids necessitated use of water–alcohol mixtures as solvents to maintain sufficient material in solution for spectrophotometric analysis. In order to place the hydrolysis studies of all these esters on comparative grounds, the hydrolysis of aspirin was studied in various water–alcohol mixtures. An unexpected increase in the hydrolysis rates of the anion in the *p*H-independent region was observed. This *p*H-independent hydrolysis of the completely ionized compound (as represented by the plateau of rate *vs.* *p*H at *p*H 5.5–9 in Fig. 1) had been ascribed by Edwards[1,2] to the water attack on the aspirin ion and would imply general acid–base catalysis.[4] In this light ethanol would have to be considered a more active base than water. However, Edwards[1] had also shown by studies in various concentrations of acetate buffers that the "spontaneous" hydrolysis was not subject to general acid–base catalysis.

The extraordinary magnitude of this "spontaneous" or water hydrolysis of aspirin has led to the formulation of cyclic mechanisms involving interaction of both carbonyls and their carbons in a rate-determining step.[5,6]

In order to clarify the anomalous enhancement of "spontaneous" hydrolysis with increasing alcohol content of the solvent and to determine if the rates were dependent on water content or were functions of dielectric constant, the "spontaneous" hydrolysis was studied in various dioxane–water mixtures. Surprisingly, there was small variation in hydrolysis rates.

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(1) L. J. Edwards, *Trans. Faraday Soc.*, **46**, 723 (1950).

(2) L. J. Edwards, *ibid.*, **48**, 696 (1952).

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

(4) J. L. Hockersmith and E. S. Amis, *Anal. Chim. Acta*, **9**, 101 (1953).

(5) J. D. Chanley, E. M. Gindler and H. Sobotka, THIS JOURNAL, **74**, 4347 (1952).

(6) D. Davidson and L. Auerbach, *ibid.*, **75**, 5984 (1953).

TABLE I

TABULATION OF RATE CONSTANTS (k IN SEC.$^{-1}$, k_1 IN L./MOLE/SEC.) FOR CALCULATION OF HYDROLYSIS OF ACYL ESTERS OF SALICYLIC ACID IN ACID AND NEUTRAL MEDIA[a]

Ester of salicylic acid	t, °C.	$10^6 k$[b] pH 1.10	$10^6 k$[c] pH 2.50	$10^6 k$[d] pH 5.05	$10^6 k_1$	$10^3 k_4$	$10^6 k_5 C_{H_2O}$
	25.0	2.24	0.562	3.63	25.0	1.02	3.72
Acetyl-	35.0	5.00	1.31	8.03	55.2	2.55	8.33
	50.3	20.5	4.83	35.3	237	7.13	36.3
	60.3	44.2	12.1	80.8	492	21.2	83.8
	25.0	0.113	0.0883	0.933	0.960	0.190	0.978
Trimethylacetyl-	35.0	0.273	.213	2.23	2.33	0.465	2.35
	50.3	1.13	.847	10.00	10.6	1.45	10.5
	60.3	2.77	2.02	25.5	27.8	2.80	26.8
		pH 1.10	pH 2.60	pH 5.30			
	25.0	0.922	0.207	3.62	10.3	1.80	3.95
β-Cyclopentylpropionyl-	35.0	2.15	0.462	8.05	24.3	3.97	8.80
	50.3	7.62	2.03	33.7	82.2	19.4	36.7
	60.3	17.8	5.12	80.0	188	51.6	87.5
	25.0	0.0262	0.0110	0.117	0.223	0.187	0.131
Diethylacetyl-	35.0	.0850	.0362	0.338	0.713	0.633	0.387
	50.3	.458	.215	1.64	3.53	4.00	1.82
	60.3	1.45	.662	4.38	11.2	12.5	4.92

[a] The acetyl- and trimethylacetylsalicylic acids were studied in 0.5% ethanol; the β-cyclopentylpropionyl- and diethylacetylsalicylic acids were studied in 20% ethanol by volume. [b] The solutions were 0.0978 M in HCl, 0.0469 M in KCl. [c] The solutions were 0.534 M in acetic acid. [d] The solutions were 0.1091 M in acetic acid, 0.0785 M in NaOH.

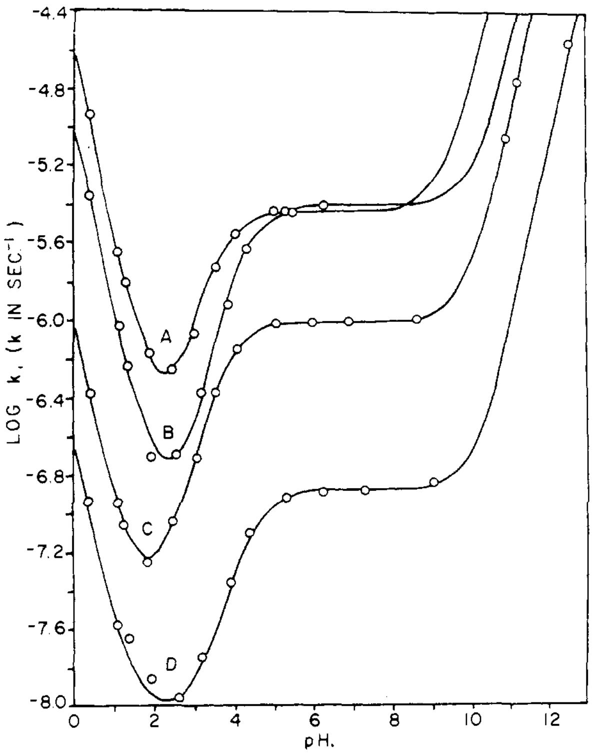

Fig. 1.—The pH profile of the logarithm of apparent first-order rate constants for hydrolysis. The points are experimental; the drawn lines are calculated.

Curve	Ester of salicylic acid
A	Acetyl-
B	β-Cyclopentylpropionyl-
C	Trimethylacetyl-
D	Diethylacetyl-

Calculations and Results

According to Edwards[1,2] the hydrolysis of aspirin, $C_6H_4(OOCCH_3)COOH$, may be expressed by

$$\begin{aligned} &d([C_6H_4(OOCCH_3)COOH] + [C_6H_4(OOCCH_3)COO^-])/dt \\ &= -k_1\,[H^+][C_6H_4(OOCCH_3)COOH] \\ &- (k_4[H^+] + k_5C_{H_2O} + k_6[OH^-])[C_6H_4(OOCCH_3)COO^-] \\ &= -k\,\{[C_6H_4(OOCCH_3)COOH] + \\ &\qquad [C_6H_4(OOCCH_3)COO^-]\} \quad (1) \end{aligned}$$

where

$$\begin{aligned} k &= k_1[H^+]/(1 + K'_a/[H^+]) \\ &+ (k_4[H^+] + k_2C_{H_2O} + k_6[OH^-])/(1 + [H^+]/K'_a) \quad (2) \end{aligned}$$

where K_a is the dissociation constant of aspirin and k is the pseudo first-order rate constant at a constant pH. The pseudo first-order rate constants obtained at pH values of 1.1, 2.5 and 5.1 and the determined K_a' values were used to calculate the k_1, k_4 and $k_5C_{H_2O}$ values for acetyl-, trimethylacetyl-, β-cyclopentylpropionyl- and diethylacetylsalicylic acids at 25.0°, 35.0°, 50.3° and 60.3°. These rate constants are given in Table I. The spectrophotometrically determined pK_a and pK_a' are given in Table II. Their relative significance is discussed in the Experimental section. The experimentally determined bimolecular rate constants, k_6, are in Table III.

TABLE II

DISSOCIATION CONSTANTS OF ESTERS OF SALICYLIC ACID

Ester of salicylic acid	% EtOH	pK'_a	pK_a	t, °C.	K_w H₂O	K_w 20% EtOH
	0.5	3.62	3.69	25	14.00	14.33
	20	3.97	4.15	35	13.68	14.00
Acetyl-	30	4.26	4.47	50	13.26	13.57
	40	4.71	4.94	60	13.02	13.32
Trimethylacetyl-	0.5	3.74	3.87			
β-Cyclopentylpropionyl-	20	4.26	4.36			
Diethylacetyl-	20	4.35	4.45			

Actually, in these equations 1 and 2, $k_1 = k_1'f_{H^+}$ and $k_4 = k_4'f_{H^+}$, where the k_i' are true specific rate constants and f_{H^+} is the activity coefficient of hydrogen ion. The values actually used for $[H^+]$ were

TABLE III

TABULATION OF BIMOLECULAR RATE CONSTANTS (k_6 IN L./MOLE/SEC.) FOR ALKALINE HYDROLYSIS[a] OF 5×10^{-4} *M* ACYL ESTERS OF SALICYLIC ACID AS DETERMINED AT VARIOUS INITIAL ALKALI CONCENTRATIONS, $[NaOH]_0$[b]

Ester of salicylic acid	*T*, °C., 25.3°		35.0°		50.3°		60.3°	
	$10^4[NaOH]_0$	10^2k_6	$10^4[NaOH]_0$	10^2k_6	$10^4[NaOH]_0$	10^2k_6	$10^4[NaOH]_0$	10^2k_6
	100	11.3	50	20.2	20	53.8	10	95.0
Acetyl-[d]	40	10.6	20	20.7	10	54.3	5	113[c]
	20	11.0						
	20	10.8						
Trimethylacetyl-	20	0.862	400	1.67	200	4.75	100	8.05
	10	0.867	200	1.66	100	4.50	50	7.70
β-Cyclopentylpropionyl-	200	4.03	100	8.05	50	14.7	30	26.8
	100	4.05	50	7.78	20	16.0	20	26.3
Diethylacetyl-	400	0.144	400	0.328	400	0.662	400	1.26
	200	0.139	200	0.297	200	0.638	200	1.18

[a] The acetyl- and trimethylacetylsalicylic acids were studied in 0.5% ethanol; the β-cyclopentylpropionyl- and diethylacetylsalicylic acids were studied in 20% ethanol. [b] The bimolecular rate constants were determined from pseudo first-order rate plots at $[NaOH]_0$ concentrations of 100×10^{-4} *M* and greater. [c] At this low concentration of alkali, it is expected that catalysis other than hydroxyl would be significant. Thus, the observed k_6 should be higher than the true k_6. [d] The apparent bimolecular rate constants (k_6) for alkaline hydrolysis were 0.116 and 0.114 l./mole/sec. in 20 and 40% ethanol by volume with 10×10^{-4} *M* [NaOH].

TABLE IV

OTHER ACID HYDROLYSIS[a] STUDIES OF ACYL ESTERS OF SALICYLIC ACID WITH ACTUAL *p*H[b] AND *p*H CALCULATED FROM $[H^+] = (k - k_4K_a)/k_1$; *k* IN SEC.$^{-1}$

Ester of salicylic acid	Acetyl-			Trimethylacetyl-			β-Cyclopentylpropionyl-			Diethylacetyl-		
T, °C.	10^5k	Actual *p*H	Calcd *p*H	10^6k	Actua *p*H	Calcd. *p*H	10^6k	Actual *p*H	Calcd. *p*H	10^6k	Actual *p*H	Calcd. *p*H
25.0	11.8	0.40[c]	0.34	0.415	0.32[c]	0.40	4.51	0.43[c]	0.36	0.116	0.50[c]	0.32
	1.57	1.30[d]	1.27	.0885	1.27[d]	1.23	0.593	1.33[d]	1.32	.0224	1.40[d]	1.29
35.0	6.88	0.86[e]	0.95	.347	0.93[e]	0.95	2.70	0.96[e]	0.99	.101	0.99[e]	1.00
50.3	26.9	.92[e]	.97	1.37	.95[e]	.98	9.40	1.03[e]	1.00	.556	.97[e]	0.97
60.3	199	.34[c]	.40	9.75	.34[c]	.48	28.2	0.67[f]	0.87	2.52	.71[f]	0.76

[a] The acetyl- and trimethylacetylsalicylic acids were studied in 0.5% ethanol; the β-cyclopentylpropionyl- and diethylacetylsalicylic acids were studied in 20% ethanol by volume. [b] *p*H was averaged from five samples taken at room temperature during the hydrolysis, the range in *p*H values was of the order of 0.1 *p*H. [c] 0.4708 *M* H_2SO_4. [d] 0.04708 *M* H_2SO_4. [e] 0.1178 *M* H_2SO_4. [f] 0.2354 *M* H_2SO_4.

the activities as related to the experimentally determined *p*H values. Anion and acid concentrations are defined in terms of K_a' experimentally derived from the spectrophotometric titrations. The rate constants k_5 and k_6 do not need activity corrections since they are based on anion concentrations similarly derived; the latter, k_6, is determined from hydroxyl concentration given in terms of molarity.

It should also be realized that Edwards' term, $k_4[H^+]$ [anion] is kinetically indistinguishable from $k_4K'_a$ [acid].

The logarithmic profiles of pseudo first-order rate constants against *p*H at 25° for these esters of salicylic acid as calculated from the derived k_1, k_4, $k_5C_{H_2O}$, k_6 and K_a' values are drawn in Fig. 1. The plotted points are experimentally determined rate constants at their determined *p*H values and confirm the derived values. Similar profiles may be constructed for other temperatures using the proper autoprotolysis constant, K_w, of the solvent. Such values may be estimated from the literature.[7,8]

Several acid hydrolysis studies were run at the various temperatures and *p*H values and pseudo first-order rate constants were determined (Table IV). The experimental rate constant data were used to calculate the theoretical *p*H values determined on the basis of the previously derived k_1 and k_4 values, $[H^+] = (k - k_4K_a)/k_1$; the agreement of the actual and calculated *p*H values lends support to the validity of the data and methods of calculation.

The Arrhenius plots of the logarithm of the rate constants against the reciprocal of the absolute temperature as per

$$\log k = -(\Delta H_a/2.303R)(1/T) + \log P = S/T + \log P \qquad (3)$$

are given in Fig. 2 for k_1, Fig. 3 for k_4, Fig. 4 for $k_5C_{H_2O}$ determined at *p*H 5.1 and Fig. 5 for k_6. The thermodynamic quantities derived from this function are given in Table V where $\Delta S^{\ddagger}$, the entropy of activation, is calculated from absolute reaction rate theory[9] as

$$\Delta S^{\ddagger} = 2.303R[\log P - \log (k_B\,T/h)] \qquad (4)$$

where k_B is Boltzmann and *h* is the Planck constant.

The pseudo first-order rate constants for the hydrolysis of aspirin in various percentages by volume of 95% ethanol and dioxane in water mixtures, as well as the apparent *p*H values are given in Table VI.

Experimental[10]

Spectrophotometric Determination of Dissociation Constants.—The dissociation constants given in Table II of

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(7) B. Gutbezahl and E. Grunwald, THIS JOURNAL, **75**, 565 (1953).

(8) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 2nd Ed., Reinhold Publishing Corp., New York, N. Y., 1950, p. 485.

(9) S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941.

(10) The esters of salicylic acid were supplied by Mr. Maxton F. Murray of the Chemistry Department, The Upjohn Co.

TABLE V

THERMODYNAMIC QUANTITIES[a] FOR THE HYDROLYSIS[b] OF ESTERS OF SALICYLIC ACID

Ester of salicylic acid	Acetyl-				β-Cyclopentylpropionyl-				Trimethylacetyl-				Diethylacetyl			
Rate constants	S	ΔH_a	log P	$\Delta S‡$	S	ΔH_a	log P	$\Delta S‡$	S	ΔH_a	log P	$\Delta S‡$	S	ΔH_a	log P	$\Delta S‡$
k at pH 1.10	3640	16.6	6.55	−28.8	3610	16.5	6.08	−30.7	3880	17.7	6.05	−31.2	4910	22.5	8.88	−17.9
k at pH 2.5	3700	17.0	6.17	−30.2	3880	17.8	6.40	−29.3	3860	17.7	5.90	−31.6	4980	22.8	8.74	−18.8
k_1	3690	16.7	7.78	−22.9	3560	16.3	6.93	−27.0	4130	18.9	7.80	−22.9	4710	21.6	9.16	−16.5
k_4	3590	16.4	9.05	−17.4	4150	19.0	11.14	− 7.8	3295	15.1	7.36	−24.7	5110	23.4	13.41	+ 2.7
$k_5C_{H_2O}$[c]	3840	17.6	7.45	−24.7	3820	17.5	7.40	−24.7	3980	18.2	7.34	−25.2	4420	20.2	7.95	−22.0
k_6	2730	12.5	8.18	−21.0	2480	11.3	6.89	−27.0	2730	12.5	7.08	−26.1	2700	12.4	6.21	−30.2

[a] The quantities are derived from the logarithmic form of the Arrhenius relation: $\log k = -(\Delta H_a/2.303R)(1/T) + \log P = -S/T + \log P$ where the k is in sec.$^{-1}$ and the k_1 in l./mole/sec., the ΔH_a is the heat of activation in kcal./mole, R is the gas constant in cal./degree and T is the absolute temperature. The $\Delta S‡$ entropy of activation is calculated from absolute reaction rate theory: $\Delta S‡ = 2.303R\,[\log P - \log (k_BT/h)]$ where k_B is the Boltzman constant and h is Planck's constant. [b] The acetyl- and trimethylacetylsalicylic acids were studied in 0.5% ethanol; the β-cyclopentylpropionyl- and diethylacetylsalicylic acids were studied in 20% ethanol by volume. [c] The values for $k_5C_{H_2O}$ are determined for the pseudo first-order rate constant of the presumed product in sec.$^{-1}$.

the various acyl esters of salicylic acid were determined at 26 ± 1° by a procedure similar to Edwards'[1] by the expression

$$pH = pK_a' - \log\{(a_{HA}C - A_t)/(A_t - a_{A}\text{-}C)\}$$
$$= pK_a - \log\{(a_{HA}C - A_t)/(A_t - a_A - C) + fZ_1Z_2\sqrt{\mu} \qquad (5)$$

where $a_{HA}C$ is the asymptotic absorbance in acid media, a_A-C is the asymptotic absorbance in alkaline media, a_{HA} and a_A- are the molar absorptivities, respectively, of the undissociated and dissociated acid, μ is the ionic strength, fZ_1Z_2 is the coefficient of the ionic strength correction in the simple Debye–Hückel equation,[11] C is the total concentration of acid, *i.e.*, $C = [HA] + [A^-]$, and A_t is the total absorbance at any pH, *i.e.*, $A_t = a_A\text{-}(C - [HA]) + a_{HA}[HA]$.

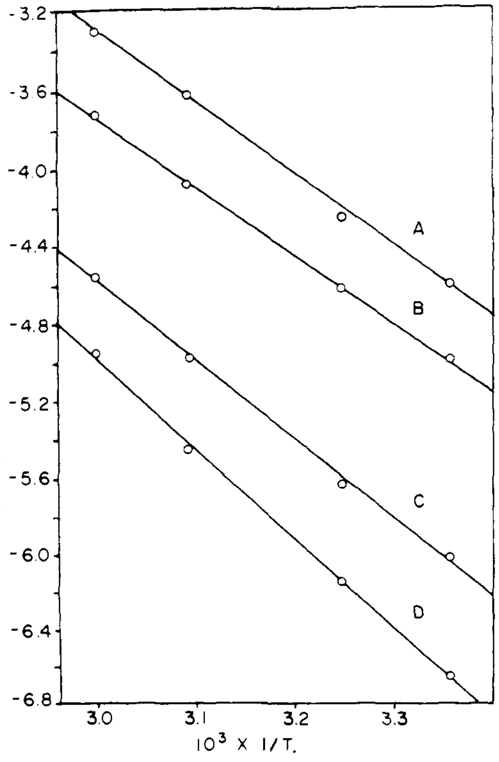

Fig. 2.—Arrhenius plots for acid hydrolysis of undissociated esters of salicylic acid (k_1 in l./mole/sec.).

Curve	Ester
A	Acetyl-
B	β-Cyclopentylpropionyl-
C	Trimethylacetyl-
D	Diethylacetyl-

The value of f in water is 0.51, but $f \propto 1/D^{3/2}$ where D is the dielectric constant so that $(D_{H_2O}/D_{\%\ \text{Ethanol}})^{3/2}\,0.51 = f_{\%\ \text{Ethanol}}$ where values of D for various percentages of ethanol at 25° are given in the literature.[12] The ionic strength of the acetate buffers in various ethanol concentrations also was calculated from the pK_a of acetic acid in aqueous alcohol.[13]

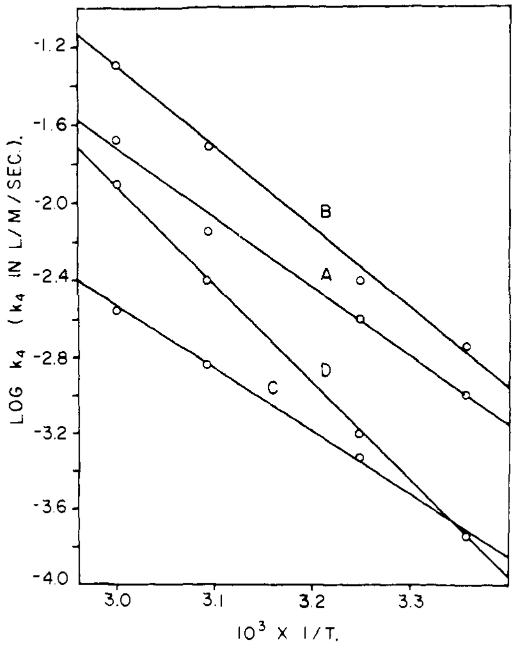

Fig. 3.—Arrhenius plots for acid hydrolysis of dissociated esters of salicylic acid (k_4 in l./mole/sec.).

Curve	Ester
A	Acetyl-
B	β-Cyclopentylpropionyl-
C	Trimethylacetyl-
D	Diethylacetyl-

Sufficient acyl ester of salicylic acid was weighed in volumetric flasks, dissolved in the appropriate amounts of eth-

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(11) F. H. Getman and F. Daniels, "Outlines of Physical Chemistry," 7th Ed., John Wiley and Sons, Inc., New York, N. Y., 1945, pp. 667–670.

(12) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 2nd Ed., Reinhold Publishing Corp., New York, N. Y., 1950, p. 118.

(13) J. M. Vandenbelt, C. H. Spurlock, M. Giffels and M. W. Bash, *Science*, **121**, 646 (1955).

TABLE VI

EFFECT OF OTHER SOLVENTS ON PSEUDO FIRST-ORDER RATE CONSTANTS (k IN SEC.$^{-1}$) OF ASPIRIN HYDROLYSIS AT 25°
(EACH COLUMN HAS THE SAME BUFFERS AND BUFFER CONCENTRATION.)

Volume % ethanol	10^6k	Apparent pH	10^6k	Apparent pH	10^6k	Apparent pH	10^6k	Apparent pH	10^6k	Apparent pH	10^6k	Apparent pH	10^6k	Apparent pH
0	(3.98)[a]	(8.65)	(3.69)[a]	(6.90)	3.62	6.00	0.560	2.45	0.672	1.90	2.24	1.10	1.18	0.40
20	5.19	8.42	5.02	7.28	4.86	6.25	.394	2.67	.536	1.94	1.94	1.19	2.71	1.04
40	9.54	8.83	9.10	7.74	9.10	6.71	.268	2.87	.395	2.07	1.60	1.21	1.98	1.21
60	14.4	9.36	14.1	8.19	14.4	7.91								
Volume % dioxane														
20	3.32	8.50	3.19	7.36	3.21	6.46								
40	3.42	9.15	3.34	8.00	3.41	7.11								
60	3.30	9.74	3.23	8.29	2.98	7.92								

[a] Estimated from Fig. 1

anol and diluted with water and concentrated buffer so that the final molarity in ester was 5×10^{-4} M at the desired alcohol concentration. The final buffer concentrations for dissociation constant determinations were similar to Edwards' first fourteen in his Table III.[1] The ester was dissolved in alcohol so that solubilization would be complete prior to the addition of buffer and the hydrolysis kept to a minimum before the immediate pH and spectrophotometric readings.

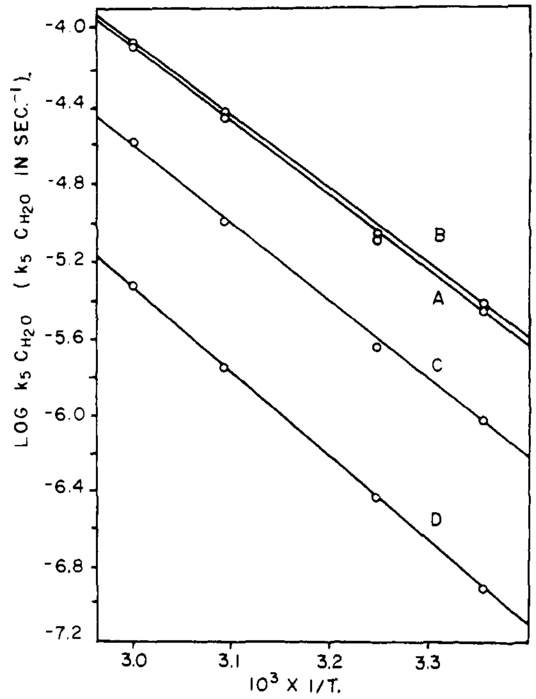

Fig. 4.—Arrhenius plots for so-called "spontaneous" hydrolysis of dissociated esters of salicylic acid ($k_5C_{H_2O}$ in sec.$^{-1}$).

Curve	Ester
A	Acetyl-
B	Cyclopentylpropionyl-
C	Trimethylacetyl-
D	Diethylacetyl-

The pK_a' and pK_a were calculated for all buffers at wave lengths of 268, 272, 276, 280 and 284 mμ by equation 5. The calculated values at a given wave length whose log $[(a_{HA}C - A_t)/(A_t - a_{A^-}C)]$ lay within ±1 limits (usually four) were averaged. The results for the several wave lengths were again averaged to give the pK_a' and pK_a estimates of Table II. The pH-independent isosbestic point of salicylic acid on the Cary model 11 recording spectrophotometer was 300 mμ.

Determination of Rates of Alkaline Hydrolysis.—One-tenth of a millimole of the ester of salicylic acid was dissolved in 100 ml. of nitrogen-purged water (or aqueous alcohol) and maintained at the desired temperature. Twice the desired final alkali concentration was maintained at the same temperature in 50 ml. of water. Two different alkali concentrations were used. Fifty ml. of the acyl ester salicylic acid solution were added to each solution of alkali so that the final solution was 5×10^{-4} M in the acyl ester of salicylic acid and $5–400 \times 10^{-4}$ M in alkali; 5-ml. aliquots of the solutions were taken out at appropriate times and quenched in 5 ml. of HCl of sufficient concentration to neutralize the initial alkali content of the aliquot and with sufficient alcohol content to keep the free acid of the ester in solution. The sampling schedule was adjusted to include at least 1.5 times the half-life of the hydrolysis. These acidified aliquots were read at 296.5 mμ on a Beckman DU spectrophotometer for the appearance of salicylic acid. This previously had been determined as the isosbestic point for salicylic acid with absorbance independent of pH for this

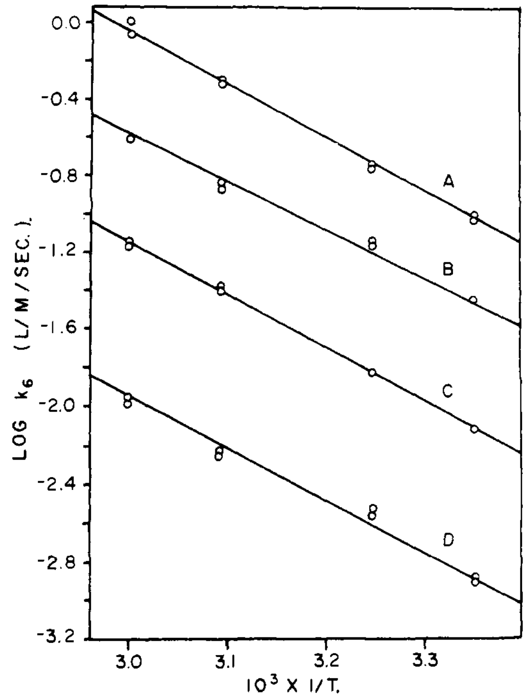

Fig. 5.—Arrhenius plots for alkaline hydrolysis of dissociated esters of salicylic acid (k_6 in l./mole/sec.).

Curve	Ester
A	Acetyl-
B	Cyclopentylpropionyl-
C	Trimethylacetyl-
D	Diethylacetyl-

machine. The molar absorptivity was 354. The rate constants were determined from the slopes of the pseudo first-order plots of log $(A_\infty - A)$ *vs.* time for alkali concentrations $[\text{NaOH}]_0$ over $100 \times 10^{-4} M$ where A_∞ is the absorbance of salicyclic acid at total hydrolysis and A is the absorbance at any time t and

$$\log (A_\infty - A) = -k't = -k[\text{NaOH}]_0 t/2.303 \quad (6)$$

where

$$k = 2.303k'/[\text{NaOH}]_0$$

For lower alkali concentrations, the slopes of bimolecular rate plots were used

$$\log ([\text{NaOH}]/[\text{Ester}]) = k''t + \text{constant} = k([\text{NaOH}]_0 - [\text{Ester}]_0) \times t/2.303 + \text{constant} \quad (7)$$

where

$$k = 2.303k''/([\text{NaOH}]_0 - [\text{Ester}]_0)$$

and

$$[\text{Ester}] = [(A_\infty - A)/A_\infty] \times [\text{Ester}]_0$$

and

$$[\text{NaOH}] = [\text{NaOH}]_0 - [\text{Ester}]$$

The resultant rate constants and the alkali concentrations used in their determination are given in Table III.

Determination of Rates in Neutral and Acid Media.—The same buffer solutions as used in the determination of pK_a values were used in the determination of pseudo first-order rate constants. The buffer concentrations were 94% of Edwards' concentrations.[1] The experimentally determined constants are given in Tables I and IV and plotted in Fig. 1; 100 ml. of solution, 5×10^{-4} *M* in ester, was used for each study. The rate constants were determined from the slopes of the first-order plots of the appearance of salicylic acid at the *p*H independent isosbestic point of the Beckman DU at 296.5 mμ as

$$\log (A_\infty - A) = -kt/2.303 + \text{constant} \quad (8)$$

The *p*H values were determined with the Cambridge *p*H meter using glass-saturated calomel electrodes at room temperature and are given as the average from five samples taken during an hydrolysis study. The range in *p*H values was of the order of 0.1 *p*H unit. Ten to fifteen aliquots were assayed for salicylic acid during the hydrolysis and were so chosen as to at least be equitably distributed throughout 1.5 times the half-life.

The pseudo first-order rate constants for aspirin hydrolysis in varying amounts of 95% ethanol and dioxane were run with the same buffers and are given in Table VI.

Discussion

Arrhenius Parameters of Basic and Acidic Hydrolysis.—The entropies of activation $\Delta S^{\ddagger}$ as listed in Table V in the alkaline hydrolysis (k_6) of the studied acyl esters of salicylic acid conform to normal expectation in that $\Delta S^{\ddagger}$ for acetyl- > β-cyclopentylpropionyl- ∼ trimethylacetyl- > diethylacetylsalicylic acid. The longer the alkyl chain and the greater its degree of branching, the greater should be the loss in degrees of freedom in formation of the activated state and thus the more negative $\Delta S^{\ddagger}$.[14]

The heats of activation ΔH_a for the alkaline hydrolysis of aspirin and the other acyl esters of salicylic acid are of the magnitude of 12 kcal./mole which is consistent with the hydrolysis of similar acyl phenates.[3] Thus the more than twice this value reported previously[2] must be an artifact of the method of study.

The assumption of a common intermediate for acid-catalyzed esterification and hydrolysis permits comparison of substituent effects from both reactions.

Loening, *et al.*,[15] have tabulated the Arrhenius parameters for the acid-catalyzed esterifications of many aliphatic acids. The percentage increase in ΔH_a for acid esterification of trimethylacetic acid over acetic acid is 14% and for diethylacetic acid is 24%. The comparable activation values for acid hydrolysis (k_1) of the salicylic esters of these acids are similar percentages of 15% and 30%. Acid-catalyzed esterifications of solely β-disubstituted acids show no significant difference in ΔH_a over acetic acid. The ΔH_a's for the acid hydrolysis of acetyl- and β-cyclopentylpropionylsalicylic acid are also similar. The heats of activation are in the order appropriate to the effect of α-carbon substituents on the positivity of the carbonyl carbon,[16] acetyl- ∼ β-cyclopentylpropionyl- < trimethylacetyl- < diethylacetylsalicylic acid.

Neutral Hydrolysis.—Edwards[1] has shown the absence of general acid–base catalysis[17] in the hydrolysis of aspirin at *p*H 4.7 in aqueous media by varying the concentration of acetic acid–acetate buffers at half-neutralization from 0.05 to 0.3 *M* in acetate ion and observing no significant rate increase. At this *p*H the hydrolysis of aspirin has been ascribed almost completely to the "spontaneous" water hydrolysis of the aspirin anion. If this is a true "water" reaction, general acid–base catalysis is to be expected.[4,17] Its absence casts considerable doubt on the mechanism implied in Edwards' kinetic equations.[1]

Amis[4,18,19] has considered the variation of specific rate with dielectric constant. If the aspirin anion reacts with the dipolar molecule, water, the specific rate $k_5 C_{H_2O}/C_{H_2O}$ or the rate divided by the water concentration, plotted against the reciprocal of the dielectric constant[12] for the ethanol–water solutions, should be of negative slope. When the values from Table VI are so treated, the plot is of positive slope and numerically equal to 14. The only sensible value of r of molecular dimensions obtainable from Amis' expressions is on the premise of reaction of a dipolar molecule (water) and a positively charged ion where the rate is still a function of water content. The value of the dipole moment μ was assumed to be 1.8 debye units[4] and resulted in a reasonable value of r, 2.6×10^{-8} cm.

Since the region of *p*H-independent rate is the region of the anionic form of aspirin, it is difficult to believe this happy result to be naught but fortuitous else the anion must react with two protons in a neutral solution before hydrolysis.

A more consistent mechanism for *p*H-independent hydrolysis where rate is not significantly affected by increasing dioxane concentration (Table VI) is one which does not involve water in the rate-determining step and may be due to an intramolecular rearrangement similar to the proposals sub-

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[14] E. S. Amis, "Kinetics of Chemical Change in Solution," The Macmillan Co., New York, N. Y., 1949, Chapt. VI, p. 242.

[15] K. L. Loening, A. B. Garrett and M. S. Newman, THIS JOURNAL, **74**, 3929 (1952).

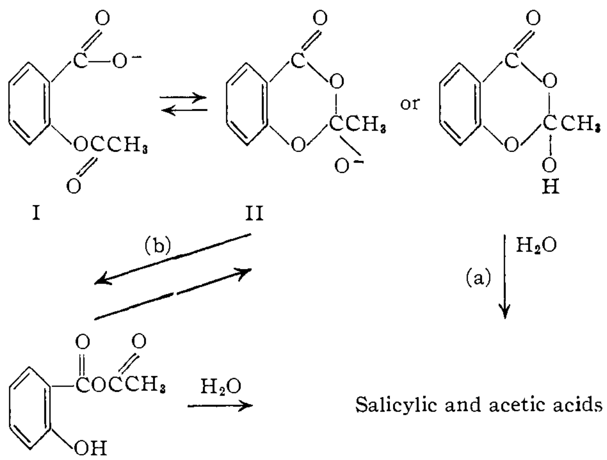
[16] S. Glasstone, K. J. Laidler and H. Eyring, ref. 9, p. 451.

[17] R. P. Bell, "Acid–Base Catalysis," Oxford University Press, London, 1941.

[18] E. S. Amis, *J. Chem. Ed.*, **29**, 337 (1952).

[19] E. S. Amis, *Anal. Chem.*, **27**, 1672 (1955).

mitted by Chanley, *et al.*,[5,20,21] and Davidson and Auerbach.[6]



The presumed rate-determining step in these proposals is I to II and the subsequent route is either (a) or (b) to the final products. The presence of the anionic form of aspirin (I) is consistent with their argument that cyclization to II is favored by the carboxylate ion being more nucleophilic than carboxyl. The two possible mechanisms proposed for salicyl phosphate hydrolysis[5] are analogous to (a) and (b), the extremely quick hydrolysis of the cyclic intermediate II either in the anionic[5] or neutral form[6] or the intermediate formation of salicoyl phosphate (or salicoyl acetate (III)) which is subsequently hydrolyzed. The latter can be argued against since acetyl phosphate and benzoyl phosphate have half-life periods similar to salicyl phosphate.[5,22]

The higher ΔH_a for $k_5C_{H_2O}$ (Table V) of trimethylacetyl- and diethylacetyl- relative to β-cyclopentylpropionyl- and acetylsalicylic acids may be explained by pronounced steric interference in the formation of the activated cyclic intermediate II. In this closed form (II), the number and length of the alkyls on the β-carbon appears to hinder free rotation about the β-carbon as per Fisher–Taylor–Hirshfelder models and thus steric restrictions on activation are feasible.

The hydrolysis rate attributed by Edwards[1] to hydrogen ion attack on the anion (k_4 in Table V) may be alternatively considered as "spontaneous" hydrolysis of the undissociated acid (Edwards,[1] $k_2C_{H_2O} = k_4K_a$). It would appear that substitution on the fifth atom from the carbonyl oxygen, or Newman's six number,[15,23] raises the activation energy for this hydrolysis of the β-cyclopentylpropionyl- and diethylacetylsalicylic acids by sterically hindering the formation of an activated complex or transition state. However, this is also accompanied by a much smaller decrease in entropy, $\Delta S^{\ddagger}$. Chanley, *et al.*,[5] explain a similarly low $\Delta S^{\ddagger}$ in the hydrolysis of salicyl phosphate by the mutually hindering rotation of phosphate and carboxyl in the open form and thus little loss in degrees of freedom in the cyclic intermediate. Trimethylacetylsalicylic acid has no more restricted rotation of both carbonyls in the open form than does the diethylacetylsalicylic acid. The latter should have more internal energy to lose on activation and thus a more negative $\Delta S^{\ddagger}$.

This implies that the rate-determining step for k_4 or k_4K_a may not be in a step similar to the cyclization[6] (I to II) but in some other simultaneous or subsequent step where the rate-determining step is to a transition state with less restriction of rotation of β-substituted alkyls.[24]

pH-Independent Hydrolysis in Aqueous Ethanol.—The anomalous increase in rate with increasing ethanol content of the solvent in the *p*H-independent hydrolysis of aspirin is of interest (Table VI). Increase in alcohol content decreases acid-catalyzed hydrolysis as is expected, but the converse occurs in the neutral *p*H range over which rate is independent of *p*H. That this is not a dielectric phenomenon is apparent from the small changes in rate in varying dioxane–water mixtures. The alcohol must be specifically involved in the solvolytic mechanism. This is difficult to explain since for solvolysis in alcohol–water mixtures a paraphrase is apt: what alcohol can do, water can do better. Yet a decrease to 40% water in dioxane–water did not show any highly significant kinetic result.

Table VII lists the average of the pseudo first-order rate constant (k_{obs} for the *p*H-independent region of hydrolysis as given in Table VI and the more rigorously calculated molarities in ethanol and water when the mode of preparation of the solutions is considered).[25]

TABLE VII

AVERAGE *p*H-INDEPENDENT RATE CONSTANTS (k_{obs}[a] IN SEC.$^{-1}$) FOR THE HYDROLYSIS OF ASPIRIN ANION IN ETHANOL–WATER MIXTURES

Approx. % ethanol	10^6k_{obs}[a]	*M* in water [H_2O]	*M* in ethanol [C_2H_5OH]
0	3.65	55.5	0
20	5.02	45.7	3.33
40	9.24	35.9	6.66
60	14.3	24.1	10.29

[a] Previously referred to as $k_5C_{H_2O}$.

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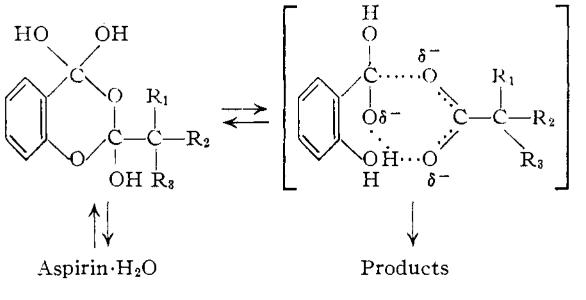
[20] J. D. Chanley and E. M. Gindler, THIS JOURNAL, **75**, 4035 (1953).

[21] J. D. Chanley and E. Feageson, *ibid.*, **77**, 4002 (1955).

[22] R. D. Birkenmeyer of The Upjohn Co. has succeeded in synthesizing salicoyl acetate (III), although in poor yield. This material decomposed in 24 hr. to an insoluble material and an oil.

[23] M. S. Newman, THIS JOURNAL, **72**, 4783 (1950).

[24] A possible transition state (in brackets) may be postulated that fulfills these requirements, *i.e.*



[25] "Handbook of Chemistry and Physics," 36th Ed., Chemical Rubber Publishing Company, Cleveland, Ohio, 1954, pp. 1932–1942.

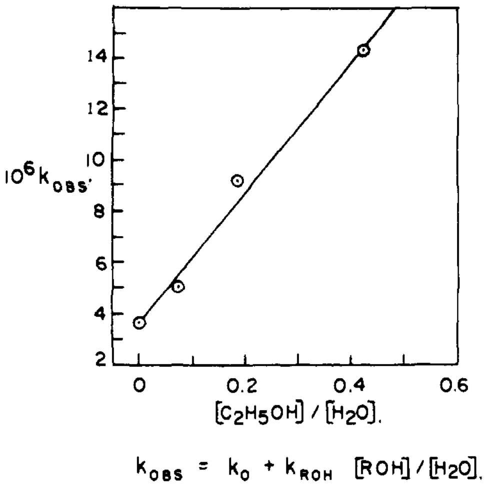
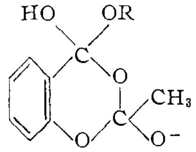


Fig. 6.—Plot of the observed rate constant for *p*H-independent hydrolysis of aspirin anion at 25° against the molar ratio of ethanol to water. The postulated dependence of this plot is the equation $k_{obs} = k_0 + k_{ROH}[ROH]/[H_2O]$.

If it is assumed that water and alcohol compete for aspirin anion ion II to form a reacting cyclic intermediate such as



IV

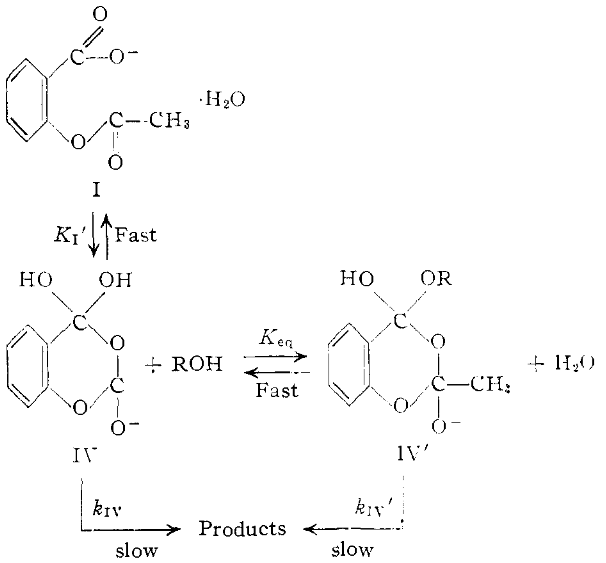
where R is H– or C_2H_5–, then

$$k_{obs} = k_a[H_2O] + k_b[ROH] \quad (9)$$

However, the data of Table VII do not follow equation 9. At best, a linear representation is valid only for $[C_2H_5OH] > 3.33$ and

$$k_{obs} = 1.43 \times 10^{-6}[C_2H_5OH];\ k_a = 0 \quad (10)$$

A possible explanation that best fits the data is that the cyclic intermediate in the hydrolysis of an aspirin anion II is formed stoichiometrically as the hydrate IV and $[IV] = K_{I'}[I']$ in a non-rate-determining step. Subsequently, the alcoholate equilibrates with the hydrate and the further steps to products are rate determining



On the basis of this mechanism, the rate expression can be formulated.

$$\begin{aligned} k_{obs}[I'] &= k_{IV}[IV] + k_{IV}'[IV'] \\ &= k_{IV}[IV] + k_{IV}'K_{eq}[IV][ROH]/[H_2O] \\ &= k_{IV}K_{I}'[I'] + k_{IV}'K_{eq}K_{I}'[I'][ROH]/[H_2O] \quad (11) \end{aligned}$$

Thus

$$k_{obs} = k_0 + k_{ROH}[ROH]/[H_2O] \quad (12)$$

Equation 11 best fits the data which are plotted accordingly in Fig. 6. The resultant quantitative equation is

$$k_{obs} = 3.65 \times 10^{-6} + 25.5 \times 10^{-6}[C_2H_5OH]/[H_2O] \quad (13)$$

Acknowledgment.—The author is greatly indebted to Miss Kathryn G. Stimson for excellent technical assistance and to Mr. Maxton Murray for the supply of the esters.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MAINE]

The Effect of Various Solvents on the Carbonyl Absorption Spectrum of Glycidic Esters

BY HORTON H. MORRIS[1] AND RAYMOND H. YOUNG, JR.

RECEIVED JANUARY 7, 1957

The infrared spectra of a number of glycidic esters show two well-defined absorption bands of approximately equal intensity in the 1800–1700 cm.$^{-1}$ carbonyl stretching region instead of the one to be expected. Of greater interest is the fact that, although the spectra of solutions of the esters in non-hydrogen bonding solvents show the two absorption bands in the carbonyl region, the two bands disappear and are replaced by a single band when the esters are dissolved in a solvent capable of forming hydrogen bonds with the ester. Possible explanations of these effects are advanced.

We have determined the infrared spectra of a number of previously reported[2] glycidic esters and have found that, without exception, the esters give two well-defined absorption bands of almost equal intensity in the 1800–1700 cm.$^{-1}$ carbonyl stretching region instead of the one expected band. The average position of the centers of the two bands for the esters studied are 1729 and 1753 cm.$^{-1}$.

Of even greater interest is the fact that the two bands disappear and are replaced by a single, rather broad band centering at about 1737 cm.$^{-1}$ when the

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[1] Southern Clays, Inc., Gordon, Ga.

[2] H. H. Morris and R. H. Young, Jr., THIS JOURNAL, **77**, 6678 (1955) and previous papers.