where K_a is the dissociation constant of the substituted aspirin. Therefore

$$\log k_2 = \log k + \log K_a - \log K_w$$

$$\log k_2/k_2^0 = \log k/k_0 + \log K_a/K_a^0$$

$$= \log k/k_0 + \rho_{ionization}\sigma_1$$

where $\rho_{ionization}$ is the reaction constant for the ionization of substituted aspirins. Thus

$$\log k/k_0 = (\rho'_{acid} - \rho_{ionization})\sigma_1 + \rho_{phenol}\sigma_2 \quad (4)$$

$$= \rho_{acid}\sigma_1 + \rho_{phenol}\sigma_2 \quad (5)$$

and the observed rate constants are related by an equation of the same form as eq 2. However, the *sign* of the observed ρ_{acid} is not a good criterion of mechanism, and cannot be used to reject the bimolecular mechanism, as explained qualitatively by Capon and Ghosh (see reference in Figure 1 caption).

The Hydrolysis of Aspirin. Intramolecular General Base Catalysis of Ester Hydrolysis

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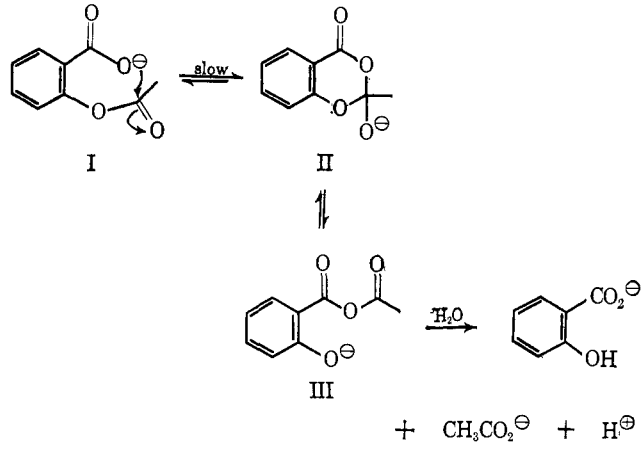
Abstract: Oxygen-18 from the enriched solvent is not incorporated into the salicylic acid produced on hydrolysis of aspirin anion at 39°. This removes the only piece of experimental evidence which specifically supports the accepted mechanism, intramolecular nucleophilic catalysis of hydrolysis. Catalysis of the hydrolysis by oxyanions is observed, including weak catalysis by acetate ion. This reaction of acetate with aspirin is compared with the corresponding reaction with phenyl acetate, which is known to involve general base catalysis, and with aspirin hydrolysis. It is concluded that all three reactions involve the same mechanism, and, consequently, that the mechanism of hydrolysis of aspirin is intramolecular general base catalysis by the carboxylate group. Specifically, the reaction is thought to involve classical general base catalysis, rather than the kinetically equivalent mechanism of general acid–specific base catalysis, and it is suggested that this is generally true for general base catalysis of ester hydrolysis.

Since Edwards[1] first showed that the rate of hydrolysis of aspirin is independent of pH between pH 4 and 8, the reaction has been the subject of a number of studies, particularly by Garrett.[2] Edwards considered that hydrolysis in the pH-independent region involves attack by a molecule of water on the aspirin anion (I), but several authors have pointed out that this mechanism is not consistent with Edwards' own demonstration[1] that the hydrolysis is not catalyzed by acetate ion, a considerably more powerful nucleophile than water. They considered that the facts point rather to intramolecular nucleophilic catalysis by the ionized carboxyl group.[2b,3,4] This mechanism has been set out in its most acceptable form by Bender[5] (Scheme I).

Scheme I



The scheme is supported by a study by the same author[6] which showed that a small amount of labeled oxygen from solvent $H_2{}^{18}O$ appears in the salicylic acid produced. The amount of incorporation agreed with the percentage of attack at the salicoyl carbonyl group expected in the hydrolysis of the anhydride III.

Only Garrett has seriously questioned this mechanism.[2] He found that the addition of ethanol to the solvent increases the rate of solvolysis,[2a] and that ethyl acetate is then a product. He ruled out the possibility that the rate increase is a generalized solvent effect by showing that the addition of dioxane has very little effect on the rate of hydrolysis of aspirin. Garrett tried to explain his results by proposing a mechanism involving nucleophilic attack by ethanol on the tetrahedral carbon atom of the intermediate II, but this explanation has not been generally accepted.[5] Nevertheless, the demonstration that the addition of ethanol increases the rate of solvolysis does suggest strongly that the question of the involvement of a molecule of solvent in the transition state ought to be reopened. Ethanol and ethoxide ion are stronger nucleophiles than water and hydroxide ion in reactions at the carbonyl group (see, for example,

(1) L. J. Edwards, *Trans. Faraday Soc.*, 46, 723 (1950).
(2) E. R. Garrett, *J. Am. Chem. Soc.*, 79, 3401 (1957); (b) *ibid.*, 79, 5206 (1957); (c) *J. Org. Chem.*, 26, 3660 (1961); (d) *J. Am. Chem. Soc.*, 80, 4049 (1958); (e) *ibid.*, 82, 711 (1960).
(3) J. D. Chanley, E. M. Gindler, and H. Sobotka, *ibid.*, 74, 4347 (1952).
(4) D. Davidson and L. Auerbach, *ibid.*, 75, 5984 (1953).
(5) M. L. Bender, *Chem. Rev.*, 60, 53 (1960).
(6) M. L. Bender, F. Chlouprek, and M. C. Neveu, *J. Am. Chem. Soc.*, 80, 5384 (1958).

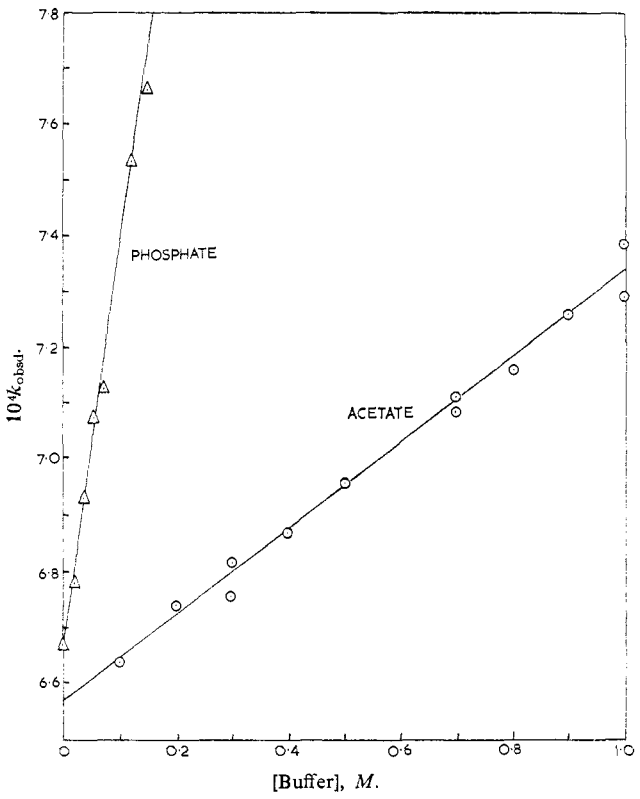


Figure 1. Catalysis of aspirin hydrolysis by phosphate and acetate buffers (at 39°, ionic strength 1.0) at pH 6.3–6.6 and 5.5–5.7, respectively. The difference between the intercepts is accounted for by the small amount of protonation of aspirin at the lower pH, and by a small contribution from the hydroxide-catalyzed reaction.

Jencks and Gilchrist[7]), and a rate-determining step involving attack by either species would explain Garrett's results. This, and a number of other unsatisfactory features of the accepted mechanism, which are discussed below, led us to reexamine the evidence. In an attempt to circumvent the problems raised by the kinetic equivalence of the several possible mechanisms, we looked first at the reactivity toward hydrolysis of a series of substituted aspirins. The results of this work have been presented and briefly discussed in the preceding paper.[8] They suggest unambiguously that the most likely mechanism for the hydrolysis of aspirin is one in which the carboxylate group acts not as a nucleophile, but as a general base. In this paper we present new evidence concerning the hydrolysis of aspirin itself, and discuss the mechanism of the reaction in more detail.

Experimental Section

Materials. Inorganic salts were of analytical grade, and were used without further purification. Sodium formate was recrystallized from its saturated aqueous solution above 30°, then dried *in vacuo* at 130°.[9] Analytical grade sodium acetate was also used without further purification. Water was further glass distilled twice before use. Acetylsalicylic acid was obtained commercially, and had mp 135° (lit.[10] 135 ± 0.2°) only after many recrystallizations from ethanol, chloroform and benzene. Phenyl dichloroacetate was prepared by the method of Koehler, Skora, and Cordes,[11] and had mp 47–48°. ^{18}O-enriched water was obtained from the Yeda Research and Development Co.

Kinetic Methods and Results. The rate of hydrolysis of aspirin was measured by following the initial rate of release of salicylate anion at the isosbestic point, 298.5 mμ,[1] in the thermostated cell compartment of a Zeiss PMQ II spectrophotometer. The temperature was maintained at 39.0 ± 0.03°, and the ionic strength at 1.0 with added KCl. Reactions were followed over a change in optical density of 0.25–0.3 (the first 3–5% of reaction), and infinity values obtained after at least ten half-lives by diluting aliquots tenfold with 1 *M* KCl solution. Rate constants obtained in this way were identical with those calculated by Guggenheim's method[12] from runs followed for up to six half-lives and had similar standard errors. The pH of the reaction mixture was measured at the end of each run, at 39°, using a Vibron electrometer fitted with a C-33B pH-measuring attachment and a Pye-Ingold combined glass reference electrode.

The rate of hydrolysis was measured in several buffers and salt solutions and corrected for buffer catalysis where necessary. Buffer constants were measured by varying the buffer concentration: for acetate at 50 and 90% free base; for succinate at 80% free base (dianion); and for phosphate at 50% free base. The constants for formate and trifluoroacetate were measured using the sodium salts in phosphate and acetate buffers, respectively. Those for carbonate and hydroxide were obtained from a single set of experiments, in which the pH was between 9.1 and 10.0, by plotting $(k_{obsd} - k_{hyd})/[CO_3^{2-}]$ against $[OH^-]/[CO_3^{2-}]$. The slope of this plot gives k_2 for hydroxide ion attack, and the intercept k_2 for carbonate.

The second-order rate constants obtained are shown in Table I, and rate constants for hydrolysis, from the same experiments, in Table II. Edwards[1] failed to detect catalysis by acetate ion because the ionic strength was not kept constant in his experiments. We find that the small acceleration due to the addition of a given concentration of acetate is almost exactly equal to the opposite effect of the increase in ionic strength. Thus the observed rates in 0.1, 0.3, and 0.7 *M* acetate, with no KCl added, were 7.75, 7.78, and 7.65×10^{-4} min^{-1} at 39° (Figure 1).

Trifluoroacetate, too weakly basic to catalyze the reaction, had a small negative effect on the rate of hydrolysis at ionic strength 1.0, in acetate buffer at pH 5.6.

The apparent pK_a of aspirin at ionic strength 1.0 and 39° was measured spectrophotometrically, using a series of formate buffers, by the procedure of Albert and Sergeant.[13] Seven separate values obtained in this way had a mean of 3.36 ± 0.015.

Reactions of phenyl dichloroacetate were followed at 25.0 ± 0.05° and ionic strength 1.0, in the thermostated block of the spectrophotometer, as described by Koehler, Skora, and Cordes.[11] The first-order rate constant for the uncatalyzed reaction with water was measured directly at pH 1 and 3 as 0.174 min^{-1}. Second-order rate constants for the reaction of the ester with several oxygen nucleophiles are listed in Table III. Where direct comparison is possible there are differences between these data and those of Koehler, Skora, and Cordes,[11] our rate constants being from two to five times greater. We are unable to account for these differences: the data of Table III were obtained from excellent pseudo-first-order plots; they are accurately reproducible, and they are related by the Brønsted equation to the pK_a's of the conjugate acids of the bases concerned (see Figure 2 below).

Hydrolysis in $H_2{}^{18}O$. Two separate hydrolyses were carried out in 20.1% ^{18}O-enriched water, using the same conditions as Bender's original experiments.[6] Two identical sealed tubes were made up, each containing 48 mg of aspirin, 82 mg of sodium acetate, and 0.1 ml of 1 *N* HCl, in 1.0 ml of 22.15 atom % enriched $H_2{}^{18}O$. One tube was heated to 100° for 23 hr; the other was incubated for 8 days at 39° (ten half-lives), then opened, and the contents divided into two equal parts. The salicylic acid was obtained from one part by the addition of a few drops of concentrated HCl. The second part was sealed in a tube and heated at 100° for 23 hr. This part of the experiment was designed to measure any incorporation of $H_2{}^{18}O$ at 100° into the salicylic acid produced. The salicylic

(7) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **84**, 2910 (1962).
(8) A. R. Fersht and A. J. Kirby, *J. Am. Chem. Soc.*, **89**, 4853 (1967).
(9) E. F. Westrum, S.-S. Chung, and N. E. Levitin, *J. Phys. Chem.*, **64**, 1553 (1960).
(10) T. J. Carswell, *J. Am. Pharm. Assoc.*, **16**, 306 (1927).
(11) K. Koehler, R. Skora, and E. H. Cordes, *J. Am. Chem. Soc.*, **88**, 3577 (1966).
(12) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).
(13) A. Albert and E. J. Sergeant, "Ionization Constants of Acids and Bases," Methuen and Co., Ltd., London, 1962.

Table I. Second-Order Rate Constants for Buffer Catalysis of Aspirin Hydrolysis, at 39°, Ionic Strength 1.0

Buffer[a]	pH	Concn range, M	No. of runs	$k_2 \times 10^5$, M^{-1} min^{-1}
Formate	6.27[b]	0.1–0.9	6	5.4 ± 0.9
Acetate	4.6–4.7[c]	0.1–1.0	3	7.4 ± 0.5
Acetate	5.5–5.7[d]	0.1–1.0	12	7.64 ± 0.26
Acetate in D_2O	*d,e*	0.1–1.0	6	3.41 ± 0.35
Succinate	5.6–5.8[f]	0.08–0.4	6	16.6 ± 1.9
Phosphate	6.3–6.6[e]	0.01–0.25	11	69.3 ± 1.2
Carbonate	9.1–10.0		8	291 ± 16
Hydroxide	9.1–10.0[g]			(33.9 ± 1) × 10^6
Acetate at 47.25°	5.5–5.7[d]	0.1–1.0	9	15.8 ± 1.4
Acetate at 55.1°	5.5–5.7[d]	0.1–1.0	10	31.3 ± 3.8
$\Delta H_{39}^{\ddagger}$ for acetate catalysis = 17.4 ± 0.2 kcal/mole				
$\Delta S_{39}^{\ddagger}$ for acetate catalysis = −30.7 ± 0.7 eu				

[a] Na salts were used throughout. [b] In 0.05 M phosphate buffer (see footnote *c*). [c] 50% free base. [d] 90% free base. [e] pH 5.5–5.7 in water. [f] 80% free base. [g] Calculated from measurements in carbonate buffer, using activity of hydroxide ion.

Table II. Hydrolysis Data for Aspirin at 39°, Ionic Strength 1.0

Conditions[a]	pH	$k_0 \times 10^4$, min^{-1} [b]
Acetate buffer	5.5–5.7	6.57 ± 0.02
Acetate at 47.25°	5.5–5.7	14.48 ± 0.09
Acetate at 55.1°	5.5–5.7	29.18 ± 0.24
Acetate, in D_2O	*c*	3.00 ± 0.03
Phosphate buffer	6.3–6.6	6.67 ± 0.02
Corrected for ionization of aspirin and catalysis by hydroxide ion		6.64 ± 0.01
$\Delta H_{39}^{\ddagger}$ = 18.36 ± 0.01 kcal/mole		
$\Delta S_{39}^{\ddagger}$ = −22.5 ± 0.02 eu		

[a] For details of buffers see Table I. [b] Extrapolated to zero buffer concentration. [c] pH 5.5–5.7 in H_2O.

Table III. Second-Order Rate Constants for Buffer Catalysis of the Hydrolysis of Phenyl Dichloroacetate at 25°, Ionic Strength 1.0

Buffer	pH	Concn range,[a] M	k_2, M^{-1} min^{-1} [b]
(H_2O)	1,3.0	...	3.13 × 10^{-3}
Formate	3.56	0.2–0.6	0.320
Acetate	4.76	0.2–0.8	0.428
Succinate	5.78	0.08–0.4	1.32
Phosphate	6.5–6.7	0.05–0.25	5.30
Hydroxide	6.4–7.5[c]	...	1.21 × 10^6

[a] Of free base form. [b] Accurate to the third figure given, except for the hydroxide value, which is ±0.02 × 10^6. [c] In phosphate buffers.

acid was isolated from each of the two 100° tubes as before. A fourth sample, for use as a control, was obtained from the same batch of aspirin by hydrolysis in natural abundance H_2O.

The mass spectrum of each sample was recorded on an A.E.I. MS-9 instrument. Salicylic acid gives a strong molecular ion peak, and the percentage enrichment is readily obtained from the ratio of the heights of the M + 2 and M peaks relative to those of natural abundance samples.[14] The reproducibility of the results was demonstrated, and the accuracy of the measurements increased, by repeated scanning of the molecular ion region of the spectrum.

Since all four samples measured had little or no enrichment, a fifth sample of salicylic acid was deliberately enriched by heating 50 mg of the natural abundance sample in 0.5 ml of 19% enriched $H_2^{18}O$, 0.4 N in HCl, to 118° for 23 hr. The observed enrichment was 30.8%, the same, within experimental error, as the figure calculated for complete exchange. The results of these measurements are listed in Table IV.

(14) C. G. Swain, G. I. Tsuchihashi, and L. J. Taylor, *Anal. Chem.*, 35, 1415 (1963).

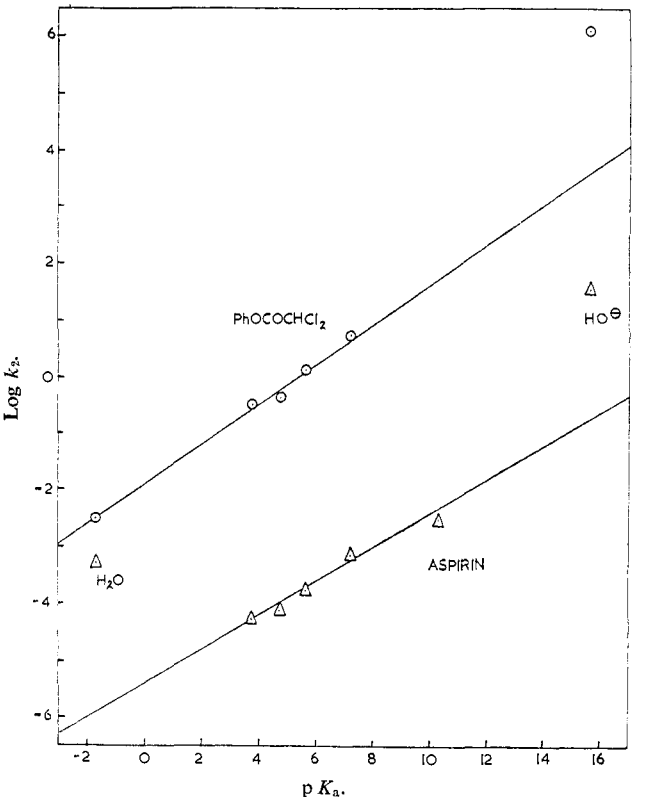


Figure 2. Brønsted plot for the general base catalyzed hydrolysis of aspirin anion at 39°, ionic strength 1.0, Δ, and of phenyl dichloroacetate, O, at 25°, ionic strength 1.0. Data from Tables I and III for H_2O, formate, acetate, succinate, phosphate, and hydroxide.

Table IV. Incorporation of ^{18}O into Salicylic Acid on Hydrolysis of Aspirin in $H_2^{18}O$[a]

Conditions[b]	Incorporation, atom %[c]
Hydrolysis at 39°	0.05 ± 0.04
Hydrolysis at 100°	1.93 ± 0.04
Into salicylic acid at 100°	1.12 ± 0.04

[a] Solvent contained 20.1 atoms % $H_2^{18}O$. [b] See text. [c] Mean and standard error from ten spectra.

Hydrolysis in Alcohol–Water Mixtures. The rate of hydrolysis of aspirin was followed as before, at 39°, in solvents containing 50 vol. % of the alcohol, at ionic strength 0.1 (0.05 M phosphate buffer, 50% free base). Results are shown in Table V.

Table V

Alcohol	Concn, M	$k_{obsd} \times 10^4$, min^{-1}
(H_2O)	(55.5)	7.75
MeOH	12.8	78.4
EtOH	9.2	27.0
i-PrOH	7	17.7
t-BuOH	5.5	6.47

Discussion

The pH–rate profile for aspirin hydrolysis, measured by Edwards,[1] tells us that the transition state for hy-

drolysis in the pH-independent region involves the aspirin anion, either alone, in a unimolecular reaction, or together with one or more molecules of solvent. Three mechanisms are consistent with this kinetic result: a unimolecular process in which the carboxylate group acts as a nucleophile, and two bimolecular mechanisms involving general base catalysis of attack by water and general acid catalysis of the attack of hydroxide ion. These three possible mechanisms are considered separately below. For reasons discussed in the preceding paper on substituent effects, it is unlikely that the slow step of the reaction is the breakdown of a tetrahedral addition intermediate, and we limit discussion to those mechanisms which involve the rate-determining addition of the nucleophile to the ester carbonyl group.

Intramolecular Nucleophilic Catalysis. The accepted mechanism for aspirin hydrolysis, set out in Scheme I, above, involves rate-determining nucleophilic attack by the carboxylate anion on the ester carbonyl group, in a unimolecular reaction. The entropy of activation for aspirin hydrolysis, however, is −22.5 eu (Table II), a conspicuous exception to the generalization that unimolecular solvolysis reactions have entropies of activation near zero.[15] The observed figure falls in the "bimolecular region," *cf.* −25.6[16] and −26[17] eu for the attack of hydroxide ion on *p*-carboxyphenyl and phenyl acetates, respectively, and suggests that a second molecule may be involved in the transition state.

The same possibility is suggested by the fact that ethanolysis is faster than hydrolysis,[2a] as discussed above. We have confirmed this observation, and find that other alcohols also increase the rate of solvolysis. In 50% alcohol–water mixtures the bimolecular rate constants for the various carbinols, relative to water (1.0), are 42, 18, 10, and 3.5, for methanol, ethanol, 2-propanol, and *t*-butyl alcohol, respectively. This series is that expected for nucleophilic reactions of the alcohols; it is not easily explained in terms of solvent effects on a unimolecular reaction.

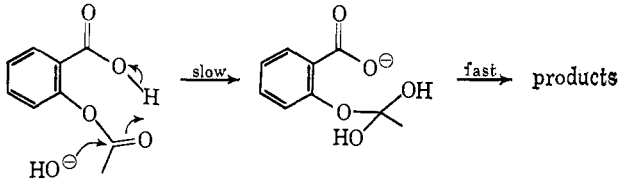
The only piece of experimental evidence which specifically supports the nucleophilic mechanisms is the incorporation of ^{18}O into the salicylic acid produced on hydrolysis at 100° in enriched water.[6] The 6% incorporation found agreed with a prediction[5] of the percentage of attack by water expected at the salicoyl carbonyl group of salicylic acetic anhydride, a prediction based on the relative amounts of the two hydroxamic acids produced when a solution of benzoic acetic anhydride in benzene is shaken with an aqueous solution of hydroxylamine hydrochloride.[18]

More recent knowledge of the hydrolytic behavior of this anhydride suggests that the predicted figure is too low. Acetic benzoic anhydride is an intermediate in the acetate-catalyzed hydrolysis of 2,4-dinitrophenyl benzoate.[19] By using ^{18}O-labeled acetate it was shown that in the hydrolysis of the anhydride 25% of attack occurred at the benzoyl carbonyl group. The introduction of the *o*-phenol or phenolate group might well increase this proportion: the phenolate group of *p*-nitrophenyl 5-nitrosalicylate, for example, catalyzes the rate of attack of water at the salicoyl carbonyl group by many 100-fold.[20] So salicylic acetic anhydride might be expected to be hydrolyzed with a high, perhaps even predominant, proportion of attack at the salicoyl carbonyl group.

In fact we find no significant incorporation of ^{18}O into the salicylic acid produced on hydrolysis of aspirin at 39° in 20 atom % enriched $H_2{}^{18}O$ (Table III). At 100° some 2% of incorporation occurs, but even this is mostly due to slow acid-catalyzed exchange into salicylic acid after hydrolysis is complete.

There is, therefore, no longer any evidence which specifically supports the nucleophilic mechanism. It is not consistent with the effect of substituents on the reaction,[8] and there are several indications that the rate-determining step is not a unimolecular process. We turn therefore to the two kinetically equivalent bimolecular mechanisms, involving attack of hydroxide ion on acetylsalicylic acid and of a molecule of water on the aspirin anion, respectively.

General Acid Catalyzed Attack of Hydroxide Ion. Bender has shown that the hydrolysis of salicyl phosphate involves protonation of the departing phenolate anion by the carboxyl group of the monoanion.[21] The relevant bimolecular mechanism for aspirin hydrolysis is



Our evidence suggests that this mechanism does not make a significant contribution in the hydrolysis reaction.

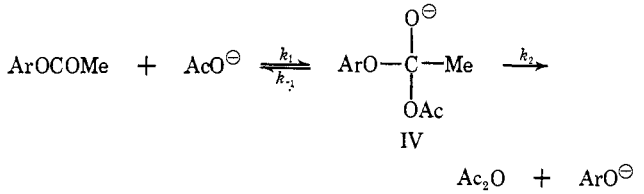
The bimolecular rate constant for hydroxide attack necessary to account for the observed rate by this mechanism is of the order of 10^7 M^{-1} min^{-1} (using the equation given in the Appendix to the preceding paper[8]). The enthalpy of activation for the bimolecular reaction is given the expression $\Delta H_2^{\ddagger} = \Delta H_1^{\ddagger} - \Delta H^{\circ}_{asp} + \Delta H^{\circ}_{H_2O}$, where $\Delta H_1^{\ddagger}$ is the enthalpy of activation observed assuming a unimolecular reaction (18.36 kcal/mole from Table II) and ΔH°_{asp} and $\Delta H^{\circ}_{H_2O}$ are the enthalpies of ionization for aspirin and water, being +4.6 and −13.6 kcal/mole, respectively. This gives a value for $\Delta H_2^{\ddagger}$ close to zero (160 cal/mole). Kinetically, therefore, this would be a rather unusual reaction.

Firmer evidence against intramolecular general acid catalysis of hydroxide ion attack is found in the data of Table I, for the reactions of aspirin with other anions. If the undissociated carboxyl group is able to catalyze the attack of hydroxide ion, then catalysis should be observed also with other general bases. Acetate ion, for example, though less reactive than hydroxide (by 3×10^6 times) toward phenyl dichloroacetate, is present in much higher concentrations (by up to 10^9 times) under the conditions of our experiments. But attack by acetate ion on aspirin is not catalyzed by the carboxyl group acting as a general acid because: (a) the

(15) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, 1, 1 (1963).
(16) G. L. Schmir and T. C. Bruice, *J. Am. Chem. Soc.*, **80**, 1163 (1958).
(17) E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1801 (1938).
(18) T. Wieland and D. Stimming *Ann.*, **579**, 97 (1963).
(19) M. L. Bender and M. C. Neveu, *J. Am. Chem. Soc.*, **80**, 5388 (1958).
(20) M. L. Bender, F. J. Kezdy, and B. Zerner, *ibid.*, **85**, 3017 (1963).
(21) M. L. Bender and J. M. Lawlor, *ibid.*, **85**, 3010 (1963)

rate constant for attack by acetate is in the region expected for the uncatalyzed reaction: k_2 is 7.64×10^{-5} M^{-1} min^{-1} at 39°, and (calculated from the Arrhenius plot of the data of Table I) 2.4×10^{-5} M^{-1} min^{-1} at 25°; k_2 for catalysis by acetate ion of the hydrolysis of phenyl acetate is 2.3×10^{-5} M^{-1} min^{-1} at 25°.[22] (b) The rate constant for the attack of acetate ion on aspirin is the same at pH 4.6 as it is at pH 5.6, although the concentration of the protonated form of aspirin is ten times larger at the lower pH.

Intramolecular General Base Catalysis. Oakenfull, Riley, and Gold[22] have identified intermolecular general base catalysis by acetate ion of the hydrolysis of certain substituted phenyl acetates. Acetate catalyzes the hydrolysis of these esters in two ways. The acetates of strongly acidic phenols, such as 2,4- and 2,6-dinitrophenol, are hydrolyzed by way of acetic anhydride, in a reaction involving nucleophilic catalysis by acetate ion.



IV

Acetic anhydride is trapped if these reactions are carried out in the presence of aniline.[22]

The hydrolysis of phenyl and *p*-methylphenyl acetates, on the other hand, is catalyzed by acetate ion in a reaction in which acetic anhydride is not an intermediate. The mechanism of these reactions is taken to be general base catalysis. Presumably acetate is so much better a leaving group than the anions of weakly acidic phenols that the tetrahedral intermediates IV break down in one direction only, to regenerate the starting materials ($k_{-1} \gg k_2$).[22]

Intermolecular catalysis of aspirin hydrolysis by acetate would be expected to fall in this second category, with the catalyst acting as a general base, since the salicylate dianion is probably about as good a leaving group as phenoxide ion.[23]

The evidence that acetate does act as a general base in its reaction with aspirin is discussed below, but because catalysis has not been observed previously, and because it is relatively small, the 1 *M* acetate causing an increase of 12% in the hydrolysis rate at 39° and ionic strength 1.0, we first discuss our reasons for believing that this rate enhancement does represent true catalysis, rather than a specific salt effect.

The second-order rate constant for acetate catalysis of aspirin hydrolysis is in the region expected[23] for a reaction not catalyzed by the carboxyl group. Catalysis is small for aspirin relative to the rate of hydrolysis in the absence of added catalyst, because there is strong intramolecular catalysis of hydrolysis, by the carboxyl group. Thus $k_{OAc}:k_0$ is much lower, at 1:8.6, than for the general base catalyzed hydrolysis of phenyl acetate,

(22) D. G. Oakenfull, T. Riley, and V. Gold, *Chem. Commun.*, 385 (1966).

(23) The pK_a for the second dissociation of salicylic acid is of course much higher than that of phenol, about 13.5,[13] but this is a consequence of the stabilization of the monoanion by intramolecular hydrogen bonding, which is not possible for the acetylated compound, and the second-order rate constant for acetate catalysis of aspirin hydrolysis is in fact almost the same as that for the reaction with phenyl acetate, as discussed above.

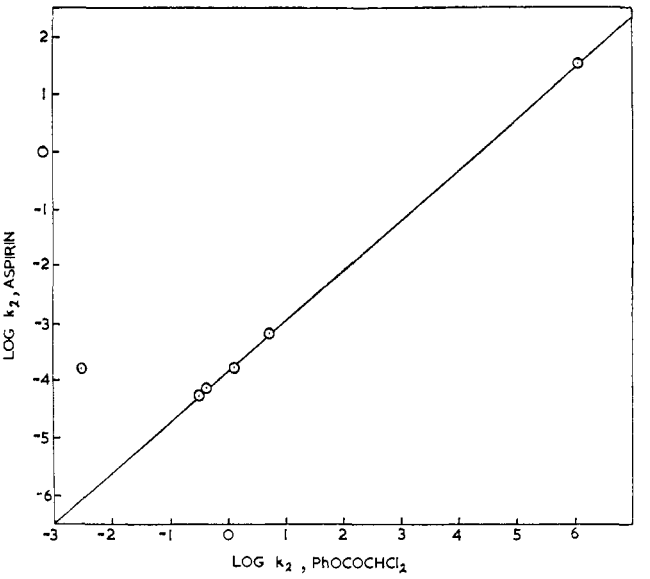


Figure 3. Double-logarithmic plot of the second-order rate constants for general base catalyzed hydrolysis of aspirin anion and phenyl dichloroacetate. Data from Tables I and III for (left to right) H_2O, formate, acetate, succinate, phosphate, and hydroxide.

for which $k_{OAc}:k_0 = 5.8$,[22] and acetate catalysis accounts for only this small fraction of the total hydrolysis rate even in 1 *M* acetate. For this reason we have not attempted to use Gold's aniline-trapping technique[22] to demonstrate the absence of acetic anhydride as an intermediate.[24]

The thermodynamic parameters measured for the acetate-catalyzed reaction (Table VI, below) are consistent with general base catalysis. The second-order rate constant for acetate is related to that for the other oxyanions tested, except hydroxide ion (see below), by the Brønsted equation (Figure 2). Also, a double-logarithmic plot of these rate constants, including that for hydroxide ion, against those for the reaction with phenyl dichloroacetate gives a good straight line (Figure 3). This latter ester was chosen because the hydrolysis of esters activated in the acyl portion, and in particular that of ethyl dichloroacetate, is known to be subject to general base catalysis;[25] because the leaving group (phenolate) is comparable to that in aspirin hydrolysis;[23] and because some data were already available.[11] These comparisons are consistent with true catalysis by acetate ion and suggest that the observed second-order rate constant is a valid measure of this catalysis.

All our evidence is consistent with a general base catalyzed mechanism for intermolecular catalysis by acetate ion of the hydrolysis of aspirin. The reaction is similar in detail to the corresponding reaction with phenyl acetate, which is known to involve general base catalysis.[22] The rate is almost the same, as discussed above; the entropy of activation is almost identical, −30.7 eu compared with −31.2 eu for the phenyl acetate reaction[19] (so also therefore must be the enthalpy of activation); and the solvent isotope effect (Table VI) is the same within experimental error ($k_H/k_D = 2.4$ for the reaction with *p*-methylphenyl ace-

(24) The problem is further complicated by a relatively rapid reaction of aniline with aspirin acid, to give acetanilide (unpublished work with W. P. Jencks).

(25) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **83**, 1743 (1961).

tate[22]). The Hammett reaction constant, ρ_{phenol}, is also the same within experimental error for the reactions of the substituted compounds.[8] Also, the reactivity of a series of oxyanions toward aspirin accurately parallels their reactivity toward phenyl dichloroacetate (Figure 2) in what are almost certainly general base catalyzed reactions.[26]

Table VI. Comparison of Data for Intermolecular and Intramolecular Catalysis of Aspirin Hydrolysis[a]

	Hydrolysis	Acetate catalysis
k_H/k_D	2.2 ± 0.03	2.2 ± 0.2
$\Delta H^{\ddagger}$	18.36 ± 0.07	17.4 ± 0.2
$\Delta S^{\ddagger}$	−22.5 ± 0.02	−30.7 ± 0.7

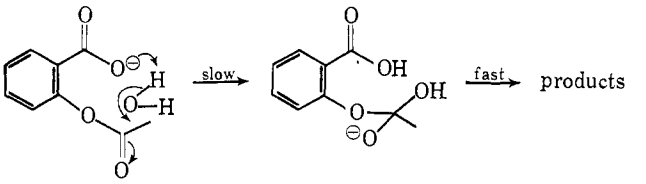
[a] Based on data of Tables I and II.

There seems little doubt, therefore, that the intermolecular reaction of acetate with the aspirin anion represents general base catalysis. There is even less doubt that intramolecular catalysis of hydrolysis by the carboxylate group of aspirin involves the same mechanism as the intermolecular reaction with acetate ion. The data in Table VI show that the solvent isotope effect is identical for the two reactions: the enthalpies of activation are closely similar, and the entropies of activation differ in the expected way. Thus $\Delta S^{\ddagger}$ is 8.2 eu less favorable for the intermolecular reaction, a difference of the magnitude (6–10 eu) calculated[27] from the Sackur–Tetrode equation for the loss of independent translational modes when two molecules come together to form a complex. The experimentally observed values of $-\Delta S°$ for the formation of bimolecular complexes do in fact commonly fall in this range.[28]

The absence of catalysis of the intermolecular reactions with oxyanions is in accord with general base catalysis, since the attack of a nucleophile which has no acidic protons cannot be assisted by a base. The only significant lack of agreement is between the Brønsted coefficient, $\beta = 0.30$, for this intermolecular catalysis, with ρ_{acid} obtained from the data for substituted aspirins ($\rho_{acid} \simeq \beta = 0.5$).[8] In the absence of sufficient data for comparison it is not possible to say whether it is generally true that intramolecular general base catalyzed reactions are more sensitive to the basicity of the catalyst than are the corresponding intermolecular processes.

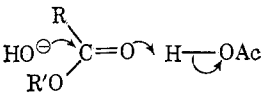
We showed in the preceding paper[8] that the effect of substituents on the leaving group in aspirin hydrolysis is consistent with general base catalysis ($\rho_{phenol} = 0.96$). Intermolecular catalysis by phosphate of the hydrolysis of substituted aspirins follows the simple Hammett equation with an identical $\rho = 0.96$.[8] Presumably phosphate, like acetate, acts as a general base, as suggested also by the Brønsted plot of Figure 2, although it is likely to be close in pK_a to the borderline between nucleophilic and general base catalysis (this is $pK_a = 7$–8 for attack on esters with activated acyl groups),[25] or, alternatively, in reactions of aryl acetates, occurs when the nucleophile is some three pK units less basic than the leaving group.[22]

We conclude that the mechanism of hydrolysis of aspirin is classical general base catalysis of attack by water by the carboxylate anion.



This is a bimolecular reaction, accounting for the observed entropy of activation. The intermolecular reactions with oxyanions, which appear to involve the same mechanism, must therefore be termolecular, in which case the second-order rate constants of Table I are directly comparable with the pseudo-first-order constant for hydrolysis (Figures 2 and 3). In this way it is possible to estimate the efficiency of the intramolecular catalysis in terms of concentrations. Using a value for the pK_a of aspirin of 3.69,[29] interpolation on the Brønsted plot of Figure 2 shows that an equivalent rate for intermolecular catalysis would require a 13 M solution of a carboxylate anion of this basicity.

In this work we have presented arguments to distinguish between different mechanisms which are kinetically equivalent to general base catalysis. We rejected the mechanism involving general acid–specific base catalysis because intermolecular general acid catalysis by the carboxyl group of aspirin should be observed for attack by acetate as well as by hydroxide ion. This type of argument can be extended to the general case of intermolecular catalysis. If the mechanism of general base catalysis by acetate ion of the hydrolysis of an ester were in fact general acid–specific base catalysis



then one would expect that attack by water would also be subject to general acid catalysis, since although water is much less reactive than hydroxide ion (by 10^8–10^9 times toward phenyl dichloroacetate, p-nitrophenyl chloroacetate, and 2,4-dinitrophenyl acetate)[11] it is always present in much higher concentrations (by more than 10^9 times in acetate buffers, for example).

Thus the assumption that general base catalysis of ester hydrolysis represents general acid–specific base catalysis leads to the conclusion that the reaction should in fact be general acid catalyzed. The same assumption for the particular case of aspirin hydrolysis leads to the conclusion that the free acid should be hydrolyzed more rapidly than the anion.[30]

These arguments, and the manifest similarities of detail between the acetate-catalyzed hydrolysis of

(26) Hydroxide ion shows a marked, but equivalent, positive deviation, in each case (Figures 2 and 3). As suggested by Jencks[25] these are probably nucleophilic reactions, rather than general base catalysis of attack by water.

(27) T. C. Bruice and S. J. Benkovic, *J. Am. Chem. Soc.*, **86**, 418 (1964), from the results of I. Z. Steinberg and H. A. Scheraga, *J. Biol. Chem.*, **238**, 172 (1963).

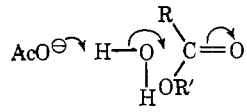
(28) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Complex Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, p 52.

(29) This is the thermodynamic value near 25°,[2a] as are the other pK_a's used for the plots of Figure 2.

(30) We have shown recently (A. R. Fersht and A. J. Kirby, *J. Am. Chem. Soc.*, in press) that the free acid is indeed hydrolyzed more rapidly than the anion in the case of 3,5-dinitroaspirin, by intramolecular general acid catalysis of the attack of water. The attack of other nucleophiles is also catalyzed, but general acid–specific base catalysis is not the predominant mechanism for hydrolysis of the anion.[31]

(31) A. R. Fersht and A. J. Kirby, *ibid.*, in press.

aspirin and the intramolecular reaction, are strong evidence that catalysis of ester hydrolysis by general bases actually represents classical general base catalysis of the attack of water rather than a kinetically equivalent alternative mechanism.



Finally we comment, at the request of a referee, on why aspirin hydrolysis should differ from a number of other examples of carboxyl group catalysis which do generally proceed, in the case of phenolic leaving groups, through anhydride intermediates.

It seems probable that the aspirin reaction lies close to the borderline between nucleophilic and general base catalysis; a few per cent of hydrolysis at 100° may in fact occur by the nucleophilic mechanism, and we have shown recently that the hydrolysis of the anion of 3,5-dinitroaspirin does involve the nucleophilic mechanism.[31] Thus a relatively small difference in activation enthalpy or entropy would account for the difference in mechanism.

We consider that the decisive factor is the fact that the leaving group in the case of aspirin remains attached to the anhydride produced by the nucleophilic mechanism (see Scheme I). This affects the equilibrium concentration of the anhydride III in two ways. The entropy of activation for the breakdown of the tetrahedral intermediate is less favorable because the leaving group does not gain independent translational modes, and the entropy of activation for the reverse reaction is particularly favorable, for a similar reason. In other words, rapid intramolecular acylation of the leaving group is possible, and this has a decisive effect on the partitioning of the tetrahedral intermediate.

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Solvolysis Mechanisms. SNl-Like Behavior of Methyl Chloromethyl Ether. Sensitivity to Solvent Ionizing Power and α-Deuterium Isotope Effect[1,2]

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Abstract: Solvolysis of methyl chloromethyl ether in a series of solvents and solvent mixtures gives a Winstein m value (sensitivity to solvent ionizing power) of 1.02 ± 0.03, within experimental error of that (1.00) defined for t-butyl chloride and significantly different from values for typical primary and secondary compounds (m = 0.2–0.5). Moreover, methyl chloromethyl ether gives a ratio of rates in aqueous ethanol (of the same ionizing power as glacial acetic acid) *vs.* glacial acetic acid of *ca.* 9, comparable with the ratios given by primary compounds (4–100) and secondary compounds (5–90). The α-deuterium isotope effect for methyl chloromethyl-d_2 ether is k_H/k_D = 1.24 ± 0.08 per deuterium atom (in 2-propanol), in the range typical of reactions involving "unimolecular" dissociation, *i.e.*, conversion of sp^3 carbon hydridization to sp^2. The solvent isotope effect in 95.2% acetone–H_2O (v/v) *vs.* 95.2% acetone–D_2O is k_{H_2O}/k_{D_2O} = 0.93 ± 0.05. The evidence indicates that methyl chloromethyl ether solvolyzes by a mechanism closely resembling that of t-butyl chloride, *i.e.*, SNl-like, even though the former is sterically much like a primary halide.

Alkyl chloromethyl ethers are known to decompose with extraordinary rapidity in solvolytic *and* in SN2 reactions.[4] This behavior is found for some other compounds, *e.g.*, allyl chloride,[5] but most compounds which undergo SN reactions tend to react slowly under SN2 conditions if they react rapidly in solvolysis, and *vice versa*. Some idea of the solvent sensitivity of the rates of solvolytic reactions of chloromethyl ethers was available[4] (similar to triphenylmethyl chloride[4j]); we felt a detailed study of the features of solvolytic

(1) Previous paper: G. J. Frisone and E. R. Thornton, *J. Am. Chem. Soc.*, in press.

(2) For further details, *cf.* T. C. Jones, Ph.D. Dissertation in Chemistry, University of Pennsylvania, 1966; submitted to University Microfilms, Ann Arbor, Mich.

(3) National Institutes of Health Predoctoral Fellow, 1964–1966; National Science Foundation Graduate Summer Research Fellow, 1964.

(4) (a) E. Wedekind, *Chem. Ber.*, **36**, 1383 (1903); (b) J. B. Conant, W. R. Kirner, and E. E. Hussey, *J. Am. Chem. Soc.*, 47, 488 (1925); (c) J. W. Farren, H. R. Fife, F. E. Clark, and C. E. Garland, *ibid.*, 47, 2419 (1925); (d) W. Cocker, A. Lapworth, and A. Watson, *J. Chem. Soc.*, 446 (1930); (e) F. Straus and H. Heinze, *Ann.*, **493**, 191 (1932); (f) H. Böhme, *Chem. Ber.*, 74B, 248 (1941); (g) R. Leimu, *Suomen Kemistilehti*, **B16**, 9 (1943); (h) R. Leimu and P. Salomaa, *Acta Chem. Scand.*, 1, 353 (1947); (i) P. Salomaa, *Ann. Univ. Turku.* A14, 1 (1953); (j) P. Ballinger, P. B. D. de la Mare, G. Kohnstam, and B. M. Presst, *J. Chem. Soc.*, 3641 (1955); (k) P. Salomaa, *Acta Chem. Scand.*, 11, 468 (1957); (l) P. Salomaa, *Suomen Kemistilehti*, B33, 11 (1960); (m) J. Hine, R. J. Rosscup, and D. C. Duffey, *J. Am. Chem. Soc.*, **82**, 6115, 6120 (1960).

(5) P. B. D. de la Mare and J. Vernon, *J. Chem. Soc.*, 2504 (1954).