Organic and Biological Chemistry

# Structure and Mechanism in Intramolecular Catalysis. The Hydrolysis of Substituted Aspirins

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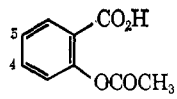
**Abstract:** The rate of hydrolysis of aspirin is notably insensitive to the effects of substituents in the 5 and particularly the 4 position. The 4-methoxy and 4-nitro compounds, for example, are hydrolyzed at the same rate. This is a consequence of the larger but opposite effects of substituents on the interacting carboxyl and ester groups. These effects can be separated using Jaffé's equation, and the $\rho$ values obtained are compared with values for intermolecular catalysis of ester hydrolysis by various mechanisms. They are consistent with a mechanism for intramolecular catalysis in which the ionized carboxyl group acts not as a nucleophile but as a general base.

As part of a detailed investigation of the mechanism of hydrolysis of aspirin,[1] we have studied the effect on the rate of hydrolysis of substituents in the 4 and 5 position. The structure and reactivity of aryl acetates




substituted in the *meta* or *para* positions are correlated by the Hammett equation.[2] A second substituent in the *ortho* position affects the reactivity of each one of a series of such esters, but as long as this group is not involved directly in the reaction process their relative reactivity, and thus the $\rho$ value for the reaction, is not affected.[2,3]

If, however, the group in the *ortho* position is involved in bond making or breaking in the transition state, a substituent in the 4 or 5 position will affect the reactivity of both reacting centers. We have attempted to separate the effects of substituents on the carboxylic acid and the ester group in aspirin hydrolysis in the hope that a comparison of the two $\rho$ values thus obtained with those for intermolecular reactions of known mechanism may allow definite conclusions about the mechanism of intramolecular catalysis in the hydrolysis of aspirin.

## Experimental Section

**Materials.** Inorganic salts were of analytical grade, and were used without further purification. Distilled water was further glass distilled twice before use. 5-Bromo- and 5-iodosalicylic acids, as well as the unsubstituted compound, were obtained commercially. The 4-chloro, 4-bromo, and 4-iodo compounds were prepared by the method of Ohta.[4] Published procedures were used also for the preparation of the 5-chloro,[5] 5-methoxy,[6] 4-nitro,[7] and 5-nitro[8] compounds. The 4-methoxy derivative was obtained in 90% yield by diazotizing 4-aminosalicylic acid with amyl nitrite in methanolic HCl, and had mp 158–159.5° (lit.[9] 157°). *Anal.* Calcd for $C_8H_8O_4$: C, 57.14; H, 4.76. Found: C, 57.29; H, 4.82.

**Acetylsalicylic Acids.** Substituted salicylic acids were acetylated by the method of Ciampa,[5] and recrystallized from ethanol, chloroform, or benzene. The analytical data and melting points are listed in Table I.

**Table I.** Analytical Data for Substituted Aspirins

| Aspirin | Mp,[a] °C | Lit. mp, °C | Calcd, % C | Calcd, % H | Found, % C | Found, % H |
|---|---|---|---|---|---|---|
| 4-Cl | 133–135 | 131.5[b] | 50.4 | 3.26 | 50.1 | 3.61 |
| 4-Br | 151–152 | ... | 41.7 | 2.70 | 41.7 | 2.92 |
| 4-I | 157–158 | 156[c] | 35.3 | 2.29 | 35.6 | 2.38 |
| 4-$NO_2$ | 153–154 | 155[d] | 48.0 | 3.11 | 48.1 | 3.10 |
| 4-MeO | 123–124 | 119–121[e] | 57.1 | 4.76 | 57.4 | 4.99 |
| 5-Cl | 147–149 | 148[f] | 50.4 | 3.26 | 50.5 | 3.24 |
| 5-Br | 155–157 | 156,[g] 168[f] | 41.7 | 2.70 | 41.5 | 2.95 |
| 5-I | 164–166 | 166[f] | 35.3 | 2.29 | 35.2 | 2.38 |
| 5-$NO_2$ | 153.5–154.5 | ... | 48.0 | 3.11 | 47.9 | 3.12 |
| 5-MeO[h] | 154–156 | ... | 57.14 | 4.78 | 57.29 | 4.82 |

[a] Uncorrected. Taken on a Kofler block. [b] R. Kuhn and H. R. Hansel, *Chem. Ber.*, **84**, 557 (1951). [c] P. Brenans and C. Post, *Compt. Rend.*, **178**, 1012 (1920). [d] M. Viscontini and J. Pudles, *Helv. Chim. Acta*, **33**, 591 (1950). [e] W. Schulemann and F. Schönhöfer, U. S. Patent 1,588,814; *Chem. Absts.* **20**, 2563 (1926). [f] Reference 5. [g] P. Brenans and C. Girod, *Compt. Rend.*, **186**, 1128 (1928). The compound was recrystallized to constant melting point from benzene, from ethanol, and from chloroform. [h] The analysis of the acetyl compound was identical with that of the parent salicylic acid, which has the same empirical formula. The melting points are also closely similar. The ultraviolet spectra were sufficiently different, however, to follow the hydrolysis of one to the other.

**Kinetic Measurements.** The rates of hydrolysis of the substituted aspirins were measured by following the initial rates of release of substituted salicylate anions, at the ultraviolet absorption maxima of the latter (Table II), at 39° and ionic strength 1.0 (KCl). The methods are described in detail in the following paper.

The neutral hydrolysis rate was measured for each ester at five or more different pH values between pH 5.4 and 6.6, in 0.05 *M* phosphate buffers. The observed rates were not independent of buffer concentration, so the buffer constant was obtained for each ester by

(1) A. R. Fersht and A. J. Kirby, *J. Am. Chem. Soc.*, **89**, 4857 (1967).
(2) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).
(3) H. H. Jaffé, *Science*, **118**, 246 (1953).
(4) H. Ohta, *Nippon Kagaku Zasshi*, **78**, 1608 (1957).
(5) G. Ciampa, *Ann. Chim.* (Rome), **54**, 975 (1964).
(6) D. N. Chaudhury, H. I. King, and A. Robertson, *J. Chem. Soc.*, 2220 (1948).
(7) H. Seidel and J. C. Bittner, *Monatsh. Chem.*, **23**, 431 (1902).
(8) H. C. Barary and M. Pianka, *J. Chem. Soc.*, 965 (1946).
(9) M. Gomberg and L. C. Johnson, *J. Am. Chem. Soc.*, **39**, 1687 (1917).

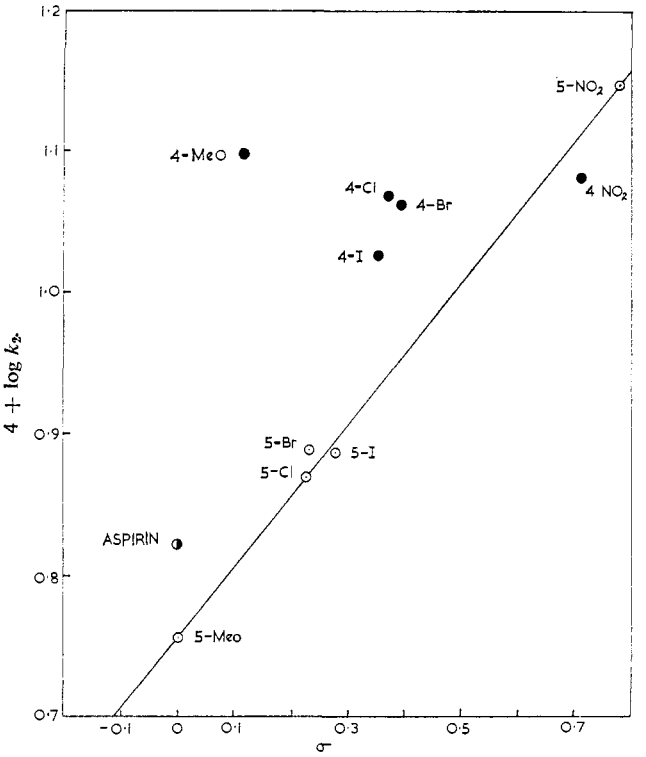



Figure 1. Hammett plot of the hydrolysis data of Table II. $\sigma_m$ and $\sigma_p$ values taken from ref 2, except for *p*-MeO. $\sigma_p$ for the methoxyl group is well known to vary considerably with the reaction concerned.[2] We have used a value of −0.01, obtained by fitting the point for the 5-methoxy compound to the Hammett plot of the phosphate buffer constants from Table II. This value is identical with that obtained by H. van Bekkum, P. E. Verkade, and B. M. Wepster [*Rec. Trav. Chim.*, **78**, 815 (1959)], using data for the ionization of substituted phenols in 8% dioxane–water at 38°. They calculate a value of −0.109 for the same reaction at 25° in water, while a positive value near 0.07 is necessary to account for the rate of hydrolysis of 5-methoxyphenyl salicylate at 59.2° [B. Capon and B. C. Ghosh, *J. Chem. Soc., Phys. Org. Sect.*, 472 (1966)], suggesting that $\sigma_p$ for the *p*-methoxy group may be temperature dependent.

measuring the hydrolysis rate at three further concentrations of phosphate buffer, up to 0.25 *M* (50% free base). The second-order constant for phosphate catalysis was obtained from the slope of the linear plot of $k_{obsd}$ *vs.* [$HPO_4^{2-}$].

## Results

Pseudo-unimolecular rate constants for the hydrolysis of substituted aspirins are listed in Table II. These values are the means from measurements at five different pH's between 5.4 and 6.6, corrected for phosphate buffer catalysis using the catalytic constants shown. They clearly fall in the pH-independent region, and represent the intramolecularly catalyzed reaction.

The most notable feature of the hydrolysis rates is their very low sensitivity to substituents. Thus the 5-nitro group increases the rate of hydrolysis by a factor of only 2, although *p*-nitrophenyl acetate is hydrolyzed, and reacts with acetate ion, 15 times faster than phenyl acetate.[10] The 4-substituted compounds are all hydrolyzed at very similar rates, the effect of the 4-methoxy group, for example, being identical, within experimental error, with that of the 4-nitro group (Table II).

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

**Table II.** The Hydrolysis of Substituted Aspirins at 39°, Ionic Strength 1.0

| Compd | Followed at mμ | $k_{hyd} \times 10^4$,[a] $min^{-1}$ | $k_2$ for $HPO_4^{2-}$ catalysis, $M^{-1}$ $min^{-1} \times 10^4$ [b] |
|---|---|---|---|
| Aspirin | 298.5 | 6.65 ± 0.01[c] | 6.93 ± 0.12[c] |
| 4-Cl | 297 | 11.73 ± 0.07 | 16.0 |
| 4-Br | 297 | 11.54 ± 0.09 | 16.1 |
| 4-I | 300 | 10.62 ± 0.05 | 14.4 |
| 4-$NO_2$ | 349 | 12.64 ± 0.09 | 24.2 |
| 4-MeO | 291.5 | 12.52 ± 0.10 | 10.8 |
| 5-Cl | 309 | 7.41 ± 0.06 | 11.5 |
| 5-Br | 308 | 7.75 ± 0.05 | 10.5 |
| 5-I | 313 | 7.70 ± 0.05 | 12.8 |
| 5-$NO_2$ | 317 | 14.03 ± 0.09 | 63.3 |
| 5-MeO | 318 | 5.71 ± 0.03 | 6.74 |

[a] Mean and standard error from measurements at 5 pH's between 5.4 and 6.6. [b] Buffer constants for substituted aspirins are accurate to ±4%. [c] Data from ref 1.

## Discussion

The Hammett plot of the hydrolysis data of Table II for 5-substituted aspirins (using $\sigma_p$) gives an acceptable straight line (Figure 1), and a $\rho$ value of 0.50. Such a low value of $\rho$ suggests that the effect of the substituent on the phenolic oxygen atom of the ester is partially offset by an opposite effect on the reactivity of the catalyzing carboxyl group.

The data for 4-substituted compounds, on the other hand, fall apparently randomly on this plot (using $\sigma_m$), except that the deviation of the points from the line for the 5-substituted compounds is least for electron-withdrawing 4 substituents (Figure 1). As expected, the simple two-parameter Hammett relation has broken down because substituents have separate, in this case probably opposite, effects on the reactivity of the electrophilic and nucleophilic centers involved in the transition state.

This type of problem has been treated previously by Jaffé;[3,11] who proposed for reactions between side chains of the same ring the equation

$$\log k/k_0 = \sigma_1\rho_1 + \sigma_2\rho_2 \qquad (1)$$

where $\sigma_1$ and $\sigma_2$ are the substituent constants ($\sigma_m$ and $\sigma_p$) of the group in the 4 or 5 position, relative to the reacting groups in the 1 and 2 positions, and $\rho_1$ and $\rho_2$ are the reaction constants for the effect of the substituent on the groups in the 1 and 2 positions, respectively. Not surprisingly, this four-parameter equation gives a better fit than the simple Hammett equation for many sets of data, including some where no *ortho* substituent is present. Jaffé considers that such spurious results arise where there is a strong correlation between the values of $\sigma_m$ and $\sigma_p$, and suggests that the usefulness of eq 1 may be limited to series where the correlation coefficient between $\sigma_m$ and $\sigma_p$ is less than 0.9.

With this restriction Jaffé[11] obtained two separate $\rho$ values for the effect of substituents on the $pK_a$'s of catechols and of 2-hydroxymethylbenzoic acids. The $pK_a$'s of substituted salicylic acids, however, were not correlated by eq 1 significantly better than by the simple Hammett equation.[11] This has been confirmed recently by a careful study[12] using 17 substituted salicylic

(11) H. H. Jaffé, *J. Am. Chem. Soc.*, 76, 4261 (1954).
(12) G. E. Dunn and F.-L. Kung, *Can. J. Chem.*, 44, 1261 (1966).

acids, with the low correlation coefficient of 0.723 between $\sigma_m$ and $\sigma^-$ for the substituents.

The application of eq 1 to the hydrolysis of substituted aspirins makes no assumptions about the mechanism of catalysis by the carboxyl groups except that the two groups are affected separately by a given substituent. The hydrolysis of substituted phenyl acetates can be correlated by Hammett's equation whether the rate-determining step is attack by water, hydroxide ion, or a catalyzing carboxylate anion. Also the reactivity of the carboxyl group should follow Brønsted's equation, whether it is acting as a general acid,[13] a general base, or a nucleophile. Also, the $pK_a$ of this group is known to follow a Hammett relation for substituted salicylic acids[12] in which deviations would seem to be more likely, because of intramolecular hydrogen bonding, than for the corresponding acetyl compounds.

Equation 1 can therefore be written in the specific form

$$\log k/k_0 = \rho_{\text{acid}}\sigma_1 + \rho_{\text{phenol}}\sigma_2 \qquad (2)$$

where the $\rho$'s measure the separate effects of the 4 and 5 substituents on the reactivity of the carboxyl[13] and phenol ester groups, $\sigma_1$ is $\sigma_p$ for a 4 substituent, $\sigma_m$ for a 5 substituent, and $\sigma_2$ is $\sigma_m$ for a 4 substituent and $\sigma_p$ for a group in the 5 position. Equation 2 can be written as the equation (3) of a straight line.

$$1/\sigma_1(\log k/k_0) = (\sigma_2/\sigma_1)\rho_{\text{phenol}} + \rho_{\text{acid}} \qquad (3)$$

The data of Table II for the hydrolysis of both 4- and 5-substituted aspirins are plotted according to eq 3 in Figure 2. They now give an excellent straight line (with correlation coefficient 0.994), and the slope and intercept, respectively, give values for

$$\rho_{\text{phenol}} = 0.96 \pm 0.04$$

$$\rho_{\text{acid}} = -0.52 \pm 0.03$$

The correlation coefficient between $\sigma_m$ and $\sigma_p$ for the substituents used is 0.758, and therefore satisfies Jaffé's criterion discussed above.

**Comparison with Intermolecular Catalysis.** Three possible mechanisms are discussed in the following paper[1] for intramolecular catalysis of the hydrolysis of aspirin by the carboxyl group. These are (a) intramolecular nucleophilic catalysis by the carboxylate anion; (b) intramolecular general acid catalysis of the attack of hydroxide ion by the undissociated carboxylic acid group; and (c) intramolecular general base catalysis of the attack of a water molecule by the carboxylate anion.

We can make a tentative choice between these three possibilities by comparing the $\rho$ values obtained above with those for similar intermolecular reactions of known mechanism. This procedure is based on the assumption that the reaction constant, $\rho$, will be the same, or closely similar, for the intramolecular reaction of a given nucleophile with the carbonyl group of a series of substituted phenyl acetates as it is for the corresponding intermolecular reaction, as long as the same mechanism is involved. If it is accepted that the increased rates of

(13) In the case of general acid catalysis by the carboxylic acid group of attack by hydroxide ion, the rate constants correlated by the Brønsted equation, and by eq 2, are the second-order constants for attack by $OH^-$, rather than the observed pseudo-unimolecular constants. We show in the Appendix that the observed rate constants are also correlated by an equation of the same form as (2), in which the parameter $\rho_{acid}$ is, in fact, a composite constant.

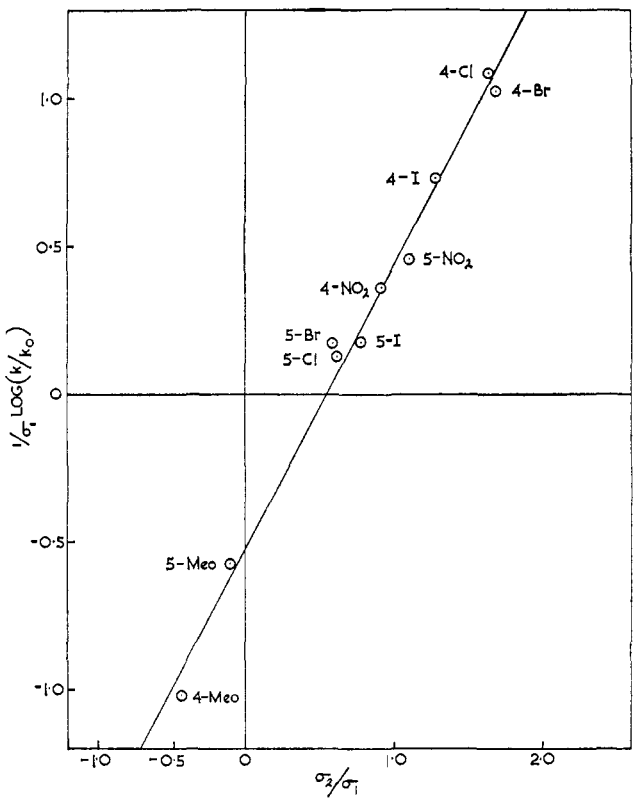



Figure 2. Modified Hammett plot of the hydrolysis data of Table II. $\sigma_m$ and $\sigma_p$ values from ref 2, except for *p*-MeO (see caption for Figure 1).

intramolecular reactions are due almost entirely to more favorable entropies of activation this proposition seems unexceptionable. There is, however, not sufficient experimental evidence to establish its generality. The most directly relevant information available comes from a comparison by Bruice and Benkovic[14] of the catalysis of the hydrolysis of substituted phenyl acetates by trimethylamine with the corresponding intramolecular reaction of the ω-dimethylaminobutyrate and -valerate esters. The enthalpies of activation were closely similar for the three reactions, and the higher rates for intramolecular catalysis were due to more favorable entropies of activation. The $\rho$ values were identical (+2.2) for the intramolecular reactions, involving five- and six-membered ring formation, and close to the value for the bimolecular reaction ($\rho$ = 2.5). This was taken as evidence that the same mechanism (rate-determining breakdown of the tetrahedral addition intermediate) is involved in each case.

A direct comparison of $\rho$ values for inter- and intramolecular catalysis can also be made using the data of Table II. For reasons discussed in the following paper[1] we believe that phosphate buffer catalysis of aspirin hydrolysis involves a simple reaction between the ester anion and the phosphate dianion, without catalysis by the carboxyl group. In agreement with this, the bimolecular rate constants for phosphate catalysis of the hydrolysis of both 4- and 5-substituted aspirins (Table II) follow the simple Hammett relation. The $\rho$ value obtained is 0.96, identical with $\rho_{\text{phenol}}$ obtained from the hydrolysis data plotted according to eq 3. We have independent evidence[1] that the two reactions involve the

(14) T. C. Bruice and S. J. Benkovic, *J. Am. Chem. Soc.*, **85**, 1 (1963).

same mechanism, so that this equality is further justification for the proposition stated above.

Gaetjens and Morawetz[15] found that the hydrolysis of substituted monophenyl succinates and glutarates, catalyzed by the terminal carboxyl group, is much more sensitive ($\rho = +2.5$) to substituents than the corresponding intermolecular reaction ($\rho = 1.1$[14] or 1.7 (see below)). This difference is taken[14,15] as evidence of a change in the rate-determining step from formation of the tetrahedral addition intermediate, in the bimolecular case, to its breakdown,[14] in the intermolecular reaction. In this second mechanism the bond to the phenol oxygen is broken in the slow step of the reaction, thus accounting for its much greater sensitivity to substitution in the aromatic ring.

The hydrolysis of substituted aspirins ($\rho_{phenol} = 0.96$) is much less sensitive to substitution than these two intramolecular reactions, and we consider that this rules out mechanisms in which the slow step is the breakdown of the tetrahedral addition intermediate. Therefore we limit the discussion to mechanisms involving the addition of a nucleophile to the carbonyl group of the ester in the rate-determining step.

**Nucleophilic Catalysis.** It is well known that the rates of bimolecular reactions of nucleophiles of similar structure with *p*-nitrophenyl acetate are correlated by the Brønsted equation, with a Brønsted coefficient $\beta$ near 0.8. This is true in particular for substituted phenols,[16] and corresponds to a $\rho$ value of 1.6–1.7, sharply different from the $\rho_{acid} = 0.52$ observed for substituted aspirin hydrolysis.

$\rho_{phenol}$ for nucleophilic catalysis of the hydrolysis of substituted phenyl acetates by acetate ion can be calculated from the data of Oakenfull, Riley, and Gold,[17] who have separated the contributions of nucleophilic and general base catalysis. The value obtained is 1.7, again much greater than the figure (0.96) for the aspirin reaction.

**General Acid Catalysis of the Attack of Hydroxide Ion.**[18] In this case the intermolecular reaction has never been identified, although molecules of hydroxylic solvents presumably act as general acids to some extent in the alkaline hydrolysis of esters. $\rho$ for the hydroxide-catalyzed hydrolysis of substituted phenyl acetates is approximately 0.55,[16] and would presumably be lowered still further if more effective general acids than water catalyzed the addition of hydroxide ion to the ester carbonyl group. Since $\rho_{phenol}$ for substituted aspirin hydrolysis (0.96) lies between the values for bimolecular attack by hydroxide and by acetate ion, it seems likely that a nucleophile intermediate in basicity between these two anions is involved in aspirin hydrolysis. An obvious possibility is the partially protonated hydroxide ion which must develop in the general base catalyzed attack of a molecule of water.

(15) E. Gaetjens and H. Morawetz *J. Am. Chem. Soc.*, **82**, 5328 (1960).

(16) (a) T. C. Bruice and R. Lapinski, *ibid.*, **80**, 2265 (1958); (b) T. C. Bruice, T. H. Fife, J. J. Bruno, and N. E. Brandon, *Biochemistry*, 1, 7 (1962).

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

(18) Since intermolecular general acid catalyzed addition of hydroxide ion has not been measured, no Brønsted $\alpha$ is available to compare with $\rho_{acid}$. It should be noted, however, that since the observed $\rho_{acid}$ is a composite constant for this mechanism,[13] the correct comparison is with $\rho'_{acid} = (\rho_{acid} + \rho_{ionization})$. Since $\rho$ for the ionization of substituted benzoic acids[2] is generally close to 1, $\alpha$ and $\rho'_{acid}$ are probably roughly equal, with a value of about $(-0.52 + 1) = 0.5$.

**General Base Catalysis.** Since $\rho$ for the ionization of substituted benzoic acids is generally close to 1,[2] $\rho_{acid}$ for the mechanism in which the carboxylate group acts as a general base is numerically close to the Brønsted coefficient, $\beta$, and can be compared directly with $\beta$ values observed for intermolecular reactions.

There are no data available for general base catalysis by substituted benzoate anions of the hydrolysis of a phenyl acetate. Only a small number of general base catalyzed ester hydrolyses have been measured, and the $\beta$ values observed are for reactions not exactly analogous to aspirin hydrolysis. Some reactions known to be catalyzed by oxyanions acting as general bases are the hydrolysis of ethyl dichloroacetate[19] ($\beta = 0.47$) and of phenyl dichloroacetate[1,20] ($\beta = 0.35$). A similar value (0.30) is observed for the intermolecular catalysis of aspirin hydrolysis by oxyanions, which we consider to be general base catalysis.[1] The observed $\rho_{acid}$ (0.52) is close enough to these figures, with the uncertainties involved, to be considered not inconsistent with the mechanism in which the carboxylate group acts as a general base.

$\rho_{phenol}$ can be compared directly with the value for the general base catalyzed hydrolysis of substituted phenyl acetates by acetate ion. For this reaction $\rho$ can be calculated from the data of Oakenfull, Riley, and Gold[17] as $1.1 \pm 0.2$. $\rho_{phenol}$ for the hydrolysis of substituted aspirins is 0.96.

Thus in the case of general base catalysis, and in this case only, both $\rho_{phenol}$ and $\rho_{acid}$ are consistent with values observed for the corresponding intermolecular reactions.

## Conclusions

Within the limits of the necessary assumptions the separation of the $\rho$ values for the two groups involved in aspirin hydrolysis, and the comparison of these with values observed for intermolecular reactions, does permit an unambiguous conclusion to be drawn: that the most probable mechanism for the hydrolysis of aspirin is that in which the ionized carboxyl group acts as a general base.

The mechanism is discussed in detail in the following paper,[1] in the light of new evidence concerning the hydrolysis of aspirin itself. Consideration of this evidence leads independently to the same conclusion about the hydrolysis mechanism, which is some evidence that the assumptions made in this paper are correct.

## Appendix

Equation 2 applies for the observed pseudo-unimolecular rate constants for mechanisms which involve only the aspirin anion, or the anion and one or more molecules of water. For the mechanism involving intramolecular general acid catalyzed attack by hydroxide ion, the equation correlates the second-order constants for the attack of hydroxide

$$\log k_2/k_2^0 = \rho'_{acid}\sigma_1 + \rho_{phenol}\sigma_2$$

$k_2$ is related to the observed pseudo-unimolecular rate constant $k$ by the expression

$$k_2 = kK_a/K_w$$

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

(20) K. Koehler, R. Skora, and E. H. Cordes, *ibid.*, **88**, 3577 (1966).

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 $\rho_{acid}$ 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

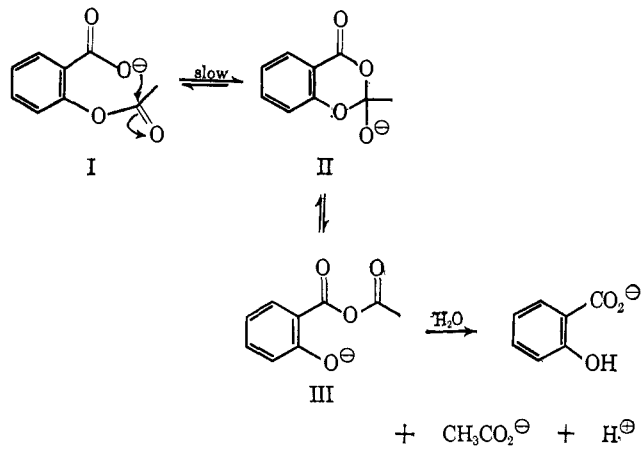
**A. R. Fersht and A. J. Kirby**

*Contribution from the University Chemical Laboratory, Cambridge, England.*
*Received May 3, 1967*

**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).