2-Phenyl-4,5-dihydrofuran (11) was formed by heating 4-hydroxybutyrophenone at reduced pressure. The material collected, bp 65° (0.07 mm), did not contain the alcohol function, but did contain a band in the ir corresponding to the vinyl ether of a dihydrofuran (1690 cm^{-1}); nmr, τ 2.3–3.0 (m, five protons), 4.8 (t, J = 3 Hz, one proton), 5.6 (t, J = 9.5 Hz, two protons), and 7.3 (t of d, J = 3, 9 Hz, two protons); mass spectrum, *m/e* (relative intensity) 146 (85), (17), 115 (34), 105 (100), and 77 (54).

4-Chlorobutyrophenone. The chloro ketones were all prepared in a manner similar to that described for this ketone.[4] The ketal of methyl benzoylpropionate (2.8 g, 0.0118 mol) in 25 ml of diethyl ether was added slowly to 0.5 g (0.013 mol) of lithium aluminum hydride in ether solution. This was stirred overnight at room temperature. The solution was hydrolyzed with water, the layers were separated, the ether layer was washed with dilute hydrochloric acid, and the ether removed under vacuum. The crude ketal alcohol was heated for 3 hr with concentrated hydrochloric acid at 60°. The mixture was cooled and extracted with ether. The ether layer was washed with water and sodium bicarbonate solution. After drying with magnesium sulfate and evaporating the ether, 1.45 g of pale yellow oil, 4-chlorobutyrophenone (67%), was obtained. The structure was confirmed by the nmr and infrared spectra: ir, 1685 cm^{-1}; nmr, τ 2.1, 2.5 (m, five protons), 6.37 (t, two protons), 6.89 (t, two protons), and 7.83 (p, two protons).

5-Chloro-2-pentanone was prepared from 5.0 g (0.05 mol) of 5-hydroxy-2-pentanone and 30 ml of concentrated hydrochloric acid. The keto chloride (4.3 g, 69%) was distilled, bp 71° (30 mm) (lit.[19] 76° (34 mm); nmr, τ 6.45 (t, two protons), 7.40 (t, two protons), 7.88 (s, three protons), and 8.02 (p, two protons).

5-Chlorovalerophenone was prepared from 3.0 g (0.012 mol) of the ketal of 5-hydroxyvalerophenone and 30 ml of concentrated hydrochloric acid. The keto chloride (1.19 g) was obtained in 50% yield, mp 48.5–49° (lit.[4] 49–50°); nmr, τ 1.92–2.8 (m, five protons), 6.49 (t, two protons), 7.08 (t, two protons), and 8.2 (m, four protons).

(19) "Handbook of Chemistry and Physics," College Edition, No. 46, The Chemical Rubber Co., Cleveland, Ohio, 1965–1966, p C 458.

2-Phenyl-1-oxonia-1-cyclopentene Hexachloroantimonate (15). The organohexachloroantimonate salts were all prepared in a similar manner.[13]

To 0.18 g (0.001 mol) of 4-chlorobutyrophenone in 2.5 ml of methylene chloride was added 0.3 g (0.001 mol) of antimony pentachloride. The white crystals which formed were filtered and washed with small amounts of cold methylene chloride. The salt (0.31 g) was obtained in 65% yield, mp 120–123° dec; ir bands at 1595, 1510, 1440, 1390, and 1270 cm^{-1}; no carbonyl absorption; nmr (CH_3CN), τ 1.9 (m), 4.42 (t, J = 8 Hz), 5.88 (t, J = 8 Hz), and 7.40 (p, J = 8 Hz).

Anal. Calcd for $C_{10}H_{11}Cl_6OSb$: C, 24.93; H, 2.30; Cl, 44.16. Found: C, 25.38; H, 2.27; Cl, 43.09.

2-Phenyl-1-oxonia-1-cyclohexene hexachloroantimonate was prepared from 0.20 g (0.001 mol) of 5-chlorovalerophenone and 0.3 g (0.001 mol) of antimony pentachloride. Cooling of this solution overnight gave crystals which could not be easily isolated, and decomposed when heated above 110°. The isolated crystals decomposed rapidly on exposure to the atmosphere.

2-Methyl-1-oxonia-1-cyclopentene hexachloroantimonate was prepared from 0.24 g (0.002 mol) of 5-chloro-2-pentanone and 0.60 g (0.002 mol) of antimony pentachloride. Prolonged cooling of this solution at 0° gave white crystals which decomposed rapidly when exposed to the atmosphere and decomposed about 90° when heated in a capillary. The nmr spectrum of the methylene chloride solution showed the characteristic low-field triplet of the cations at τ 4.23.

Methanolysis of the Hexachloroantimonate Salt of 1. To 0.1 g of 2-phenyl-1-oxonia-1-cyclopentene hexachloroantimonate was added 0.2 ml of methanol containing 1 equiv of methoxide. The nmr spectrum contained peaks at τ 2.4–2.9 (m, five protons), 5.96 (complex triplet, two protons), and 7.6–8.4 (m, four protons) consistent with 2-methoxy-2-phenyltetrahydrofuran. The infrared spectrum showed the absence of a carbonyl; mass spectrum, *m/e* (relative intensity) 146 (69), 117 (16), 115 (27), 105 (100), and 77 (39).

Performing the same reaction but with the absence of methoxide and observing the nmr showed initial formation of the adduct as above, followed by rearrangement of this to a compound consistent with 4-methoxybutyrophenone; nmr, split aromatic proton absorption, τ 2.0 (*ortho*) and 2.5 (*meta* and *para*); ir, 1700 cm^{-1} (ArC=O).

Intramolecular Catalysis in the Reactions of Nucleophilic Reagents with Aspirin[1]

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Contribution No. 576 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02154. *Received January 18, 1968*

Abstract: The rates of reactions of aspirin and some related phenyl esters with a series of nucleophilic reagents have been measured in order to determine the nature of catalysis by the *o*-carboxyl group in kinetically unambiguous reactions. The reactions of aspirin with the weakly basic amines nicotinamide, semicarbazide, and methoxyamine occur predominantly with the acidic, uncharged species of aspirin and exhibit rate accelerations of up to 150-fold which are ascribed to intramolecular general acid catalysis. The reactions of aspirin anion with water, semicarbazide, and methoxyamine (but not nicotinamide) exhibit rate accelerations of a similar or slightly smaller magnitude which are ascribed to general base catalysis by the *o*-carboxylate anion. Estimates have been made of the polar, steric, and electrostatic effects of *p*-COO^-, *o*-CO_2CH_3, and *o*-COO^- groups on nucleophilic reactions of substituted phenyl acetates; the value of σ for *p*-COO^-, based on the reaction with the uncharged piperidine molecule, is 0.46. These results, the failure to observe a comparable rate acceleration with more strongly basic nucleophiles, kinetic arguments, and the failure to trap an anhydride intermediate in the presence of dilute hydroxylamine rule out several alternative mechanisms for intramolecular catalysis.

It has been generally believed that the hydrolysis of aspirin monoanion,[3] a classical example of intramolecular catalysis, proceeds by a rate-determining intramolecular attack of carboxylate ion to give the

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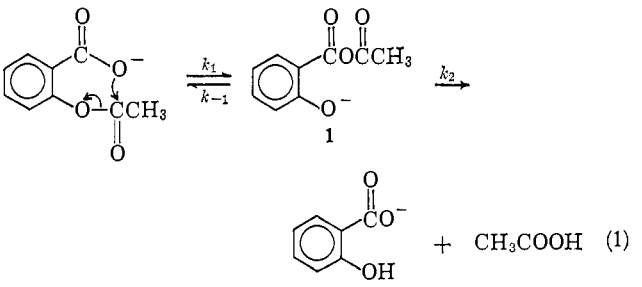
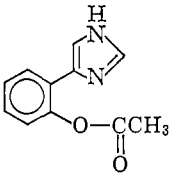
(2) This work was carried out by T. S. P. with support from a Public Health Service Fellowship from the National Institute of Arthritis and Metabolic Diseases (F2-AM29, 076-01 and 02).

(3) L. J. Edwards, *Trans. Faraday Soc.*, 46, 723 (1950); 48, 696 (1952).

mixed anhydride of acetic and salicylic acids, which undergoes hydrolysis in a subsequent fast step (eq 1); variations of this mechanism involving tetrahedral addi-



tion intermediates have also been proposed.[4-8] The following evidence supports this mechanism. (a) The hydrolysis of aspirin in ^{18}O-labeled water has been reported to result in the incorporation of labeled oxygen into the salicylate product.[7] (b) Aspirin in pyridine solution undergoes reactions characteristic of anhydrides, whereas the *para*-substituted analog is inactive; furthermore, benzoylsalicylate reacts with toluidine in pyridine to give an 8% yield of salicyltoluide, suggesting the intermediate formation of benzoyl salicyloyl anhydride.[5] (c) The acetyl group of O-acetylsalicylamide undergoes a rapid migration to the anion of the amide to give the N-acetyl imide, analogous to the anhydride **1**.[9,10] The following evidence is difficult to explain by the anhydride mechanism with rate-determining anhydride formation. (a) Ethanol causes an increase in the rate of aspirin solvolysis and gives ethyl acetate as a product, suggesting that ethanol is in the transition state and acts as an effective nucleophile toward aspirin; dioxane has little effect on the rate of solvolysis.[6,11,12] (b) The entropy of activation for aspirin hydrolysis of -24.7 eu[6] is difficult to reconcile with a monomolecular mechanism, which would be expected[13] to have a value of $\Delta S^{\pm}$ near 0. (c) There is an appreciable solvent deuterium isotope effect, $k_{H_2O}/k_{D_2O} = 1.8$, whereas nucleophilic reactions which do not involve proton transfer generally do not show a significant isotope effect.[14,15] (d) The analogous hydrolysis of salicyl phosphate dianion does not proceed through an anhydride intermediate, as shown by the failure to trap an anhydride in the presence of hydroxylamine; the neighboring group assistance in this reaction probably involves proton donation to the leaving phenolic oxygen atom.[16] (e) The imidazole analog of aspirin monoanion, **2**, undergoes hydrolysis only four times faster than aspirin[17] in spite of the fact that imidazole is more than 10^4 times as reactive a nucleophile as acetate ion.[18,19] (f) The hypothesis that anhydride formation is rate determining in the mechanism of eq 1 requires that the intermediate anhydride react more rapidly with water than it reacts intramolecularly with the phenolic oxygen atom of aspirin to regenerate starting material, *i.e.*, $k_2 > k_{-1}$. This requirement seems improbable in view of the high nucleophilic reactivity of phenols and the intramolecular nature of this back reaction; this point, as well as the improbability of a mechanism involving rate-determining hydrolysis of the anhydride, will be developed further in the Discussion.



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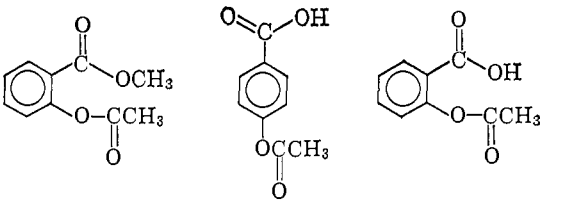
These considerations and the difficulty of identifying the reacting ionic species in a reaction with water led us to an examination of the reactions of aspirin with a series of nucleophiles in which the reacting ionic species was known unequivocally and in which the presence or absence of hydrogen atoms on the reacting atom of the nucleophile might help to elucidate the mechanism of catalysis. It was shown in preliminary experiments that the reaction of aspirin with pyridine occurs predominantly through a reaction of the acidic rather than the anionic form of aspirin.[20] The experiments reported here represent an extension of this approach to a series of nucleophiles of varying structure and to the reactions of the same nucleophiles with the structurally related compounds *o*-carboxyphenyl acetate methyl ester (*o*-CPAM, **3**) and *p*-carboxyphenyl acetate (*p*-CPA, **4**) as well as with aspirin itself (*o*-carboxyphenyl acetate, *o*-CPA, **5**).



3 **4** **5**

In an independent series of experiments, Fersht and Kirby[21] have shown there is no incorporation of ^{18}O into salicylate during aspirin hydrolysis, thus removing the strongest evidence in favor of the anhydride mechanism for the solvolysis of aspirin anion in water, and have shown that the effects of substituents on the rates of hydrolysis of substituted aspirins and analogies to the bimolecular reactions of weakly basic oxygen anions

(4) J. D. Chanley, E. M. Gindler, and H. Sobotka, *J. Am. Chem. Soc.*, 74, 4347 (1952).
(5) D. Davidson and L. Auerbach, *ibid.*, 75, 5984 (1953).
(6) E. R. Garrett, *ibid.*, 79, 3401 (1957).
(7) M. L. Bender, F. Chloupek, and M. C. Neveu, *ibid.*, 80, 5384 (1958).
(8) M. L. Bender, *Chem. Rev.*, 60, 53 (1960).
(9) J. McConnan and A. W. Titherley, *J. Chem. Soc.*, 1318 (1906).
(10) M. T. Behme and E. H. Cordes, *J. Org. Chem.*, 29, 1255 (1964).
(11) E. R. Garrett, *ibid.*, 26, 3660 (1961).
(12) Solvolysis of the mixed anhydride of acetic and *o*-methoxybenzoic acids in 60% ethanol at an apparent pH of 6 gave a yield of approximately 50% ethyl acetate, identified by chromatography after conversion to the hydroxamic acid, and no detectable *o*-methoxybenzohydroxamic acid (C. Greenspan and W. P. Jencks, unpublished experiments, 1962); this is in contrast to the report that no ethyl acetate was detected upon the solvolysis of the mixed anhydride of acetic acid and aspirin under similar conditions.[11]
(13) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, 1, 1 (1963).
(14) M. L. Bender, E. J. Pollock, and M. C. Neveu, *J. Am. Chem. Soc.*, 84, 595 (1962).
(15) B. M. Anderson, E. H. Cordes, and W. P. Jencks, *J. Biol. Chem.*, 236, 455 (1961), but see D. G. Oakenfull, T. Riley, and V. Gold, *Chem. Commun.*, 385 (1966).
(16) M. L. Bender and J. M. Lawlor, *J. Am. Chem. Soc.*, 85, 3010 (1963).
(17) G. L. Schmir and T. C. Bruice, *ibid.*, 80, 1173 (1958).
(18) M. L. Bender and B. W. Turnquest, *ibid.*, 79, 1656 (1957).
(19) See Oakenfull, Riley, and Gold, ref 15.
(20) A. J. Kirby and W. P. Jencks, unpublished experiments.
(21) A. R. Fersht and A. J. Kirby, *J. Am. Chem. Soc.*, 89, 4853, 4857 (1967).

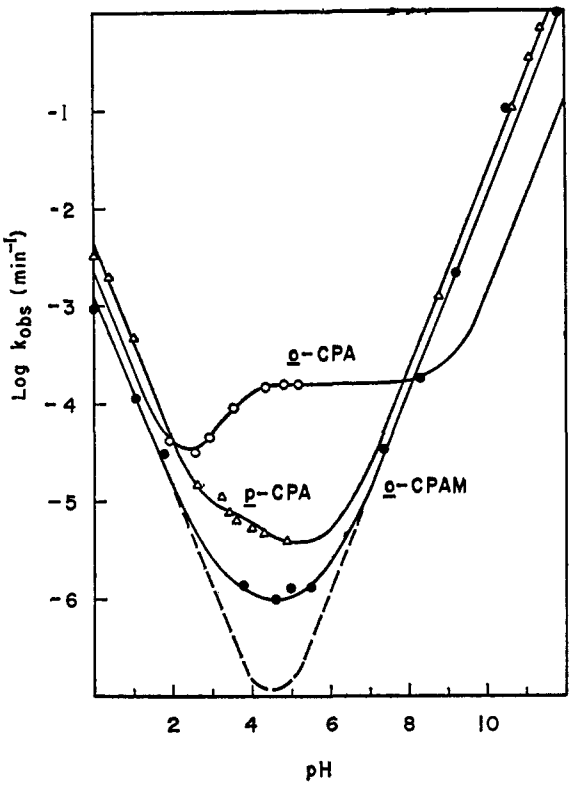


Figure 1. The pH–rate profile for the hydrolysis of aspirin (*o*-CPA), ○; *p*-carboxyphenyl acetate (*p*-CPA), △; and methyl aspirin (*o*-CPAM), ●. The solid lines are calculated on the basis of the rate constants given in Table I. The difference between the solid line and broken line for the hydrolysis of *o*-CPAM is due to $k_{H_2O}[H_2O]$. The rate constants were determined in dilute hydrochloric acid or potassium hydroxide or in cyanoacetate, formate, acetate, and tris(hydroxymethyl)aminoethane buffers. A (very small) extrapolation to zero buffer concentration was made if necessary.

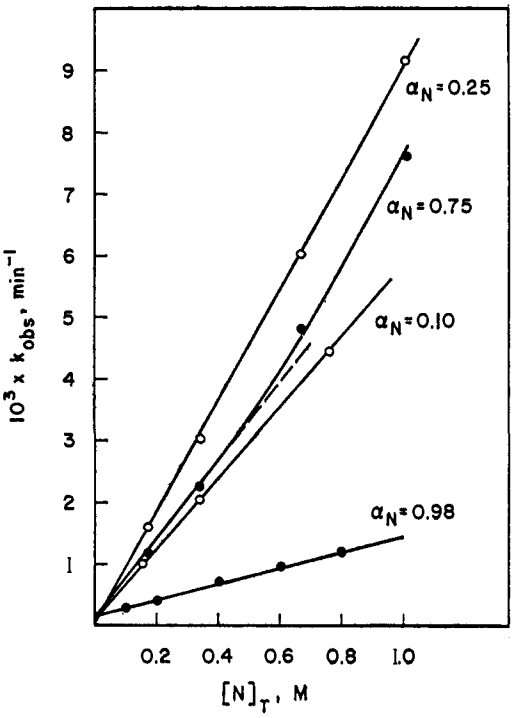


Figure 2. The observed rate constants for the reaction of aspirin (*o*-CPA) with semicarbazide as a function of total semicarbazide concentration and as a function of the fraction of semicarbazide in the base form (α_N). The observed rate constants are not corrected for aspirin ionization.

with both phenyl acetate and aspirin itself support a mechanism involving general base catalysis by the adjacent carboxylate group of the attack of water on the ester group of aspirin, the same conclusion as is reached from the experiments reported here. These workers have further shown that the hydrolysis of 3,5-dinitroaspirin monoanion proceeds through an intermediate anhydride, with incorporation of oxygen from water into the salicylate product, and that the acidic species of this compound undergoes hydrolysis 28 times faster than the monoanion, presumably with assistance from the neighboring carboxylic acid group.[22]

Results

The solid lines of the pH–rate profiles for the hydrolysis of *o*-CPA (aspirin), $pK_a' = 3.38$, *p*-CPA, $pK_a' = 3.92$, and *o*-CPAM (Figure 1) are calculated from the rate constants given in Table I. The rate constants are in satisfactory agreement with previously reported values for *o*-CPA and *p*-CPA, which were obtained under somewhat different experimental conditions.[3,6,17]

The second-order reactions of nucleophile, N, and substrate, S, can be described by the rate expression

$$v = k_1[S^-][N]_T\alpha_N + k_2[S^0][N]_T\alpha_N + \ldots \quad (2)$$

in which $[S^-]$ and $[S^0]$ are the concentrations of substrate anion and neutral substrate, $[N]_T$ is the concentration of nucleophile and its conjugate acid, and α_N is the fraction of nucleophile in the base form. In the presence of a large excess of the nucleophile the observed pseudo-first-order rate constant is

$$k_{obsd} = k_{hyd} + k_1\alpha_S[N]_T\alpha_N + k_2(1 - \alpha_S)[N]_T\alpha_N + \ldots \quad (3)$$

where k_{hyd} is the pseudo-first-order rate constant for hydrolysis at a given pH in the absence of nucleophile and α_S is the fraction of substrate as the anion.

Table I. Second-Order Rate Constants for the Hydrolysis of Aspirin (*o*-CPA), Methyl Aspirin (*o*-CPAM), and *p*-Carboxyphenyl Acetate (*p*-CPA) at 25°, Ionic Strength, 1.0 *M*

Substrates	M^{-1} min^{-1}		
	$k_{a_{H^+}}$	k_{H_2O}	$k_{a_{OH^-}}$
o-CPA^0	2.8×10^{-3} [a]	3.4×10^{-7} [a]	(6.9×10^6)[e]
o-CPA$^-$	(7.0×10^{-2})[a,e]	2.8×10^{-6} [d]	19.7[c]
o-CPAM	1.2×10^{-3} [b]	1.8×10^{-8} [d]	130[c]
p-CPA^0	4.6×10^{-3} [b]	1.7×10^{-7} [d]	(3.2×10^4)[e]
p-CPA$^-$	(8.0×10^{-2})[e]	5.3×10^{-8} [d]	194[f]

[a] Data of Edwards,[3] ionic strength 0.1–0.6, corrected to 25°. The pseudo-first-order rate constant for the water reaction was divided by 55.5 *M*. [b] From the slope of a plot of k_{obsd} against a_{H^+}. [c] From the slope of a plot of k_{obsd} against a_{OH^-}, where $a_{OH^-} = 10^{-14}/a_{H^+}$. [d] $k_{H_2O} = (k_{obsd} - k_{H^+}a_{H^+} - k_{OH^-}a_{OH^-})/[H_2O]$ for *o*-CPAM. A plot of $(k_{obsd} - k_{H^+}a_{H^+} - k_{OH^-}a_{OH^-})/[H_2O]$ against the fraction of substrate as anion, α_S, gives k_{H_2O} for the neutral substrate at $\alpha_S = 0$ and k_{H_2O} for the anionic substrate at $\alpha_S = 1$. [e] Calculated from the kinetically equivalent rate constant; *e.g.*, $k_{H^+}a_{H^+}[o\text{-CPA}^-] = k_{H_2O}[H_2O][o\text{-CPA}^0]$. [f] The apparent second-order rate constant of 130 M^{-1} min^{-1} from experiments with 0.0033 to 0.01 *M* hydroxide ion was corrected to hydroxide ion activity with the activity coefficient 0.67 (J. F. Kirsch and W. P. Jencks, *J. Am. Chem. Soc.*, **86**, 837, (1964)).

(22) A. R. Fersht and A. J. Kirby, *J. Am. Chem. Soc.*, **89**, 5960, 5961 (1967).

Table II. Experimental Conditions and Apparent Second-Order Rate Constants for Reactions of Nucleophiles with Aspirin (*o*-CPA) at 25°, Ionic Strength 1.0 *M*

Nucleophile[a] and kinetic conditions	$[N]_T$,[b] *M*	α_N[c]	α_S[d]	No. of runs	$10^3 \times k$,[e] M^{-1} min^{-1}
Nicotinamide	0.10–1.0	0.10	0.12	6	2.0[f]
$[S]_T = 3.3–17 \times 10^{-3}$ *M*	0.10–1.0	0.50	0.50	6	4.3
λ 320 mμ	0.10–1.0	0.90	0.89	6	1.6[f]
Initial rate	0.20–1.0	1.0	1.0	10	0.63
	1.0	0.05–0.95	0.05–0.94	6	...
Semicarbazide	0.15–0.76	0.10	0.22	3	5.8
$[S]_T = 3.3 \times 10^{-3}$ *M*	0.17–1.0	0.25	0.47	4	9.0
λ 299 mμ	0.17–1.0	0.75	0.91	4	6.3[f]
Initial rate	0.10–0.80	0.98	0.995	5	1.4
	0.33	0.10–0.90	0.24–0.97	5	...
Azide	0.10–0.40	0.10	0.56	4	15
$[S]_T = 3.3–10 \times 10^{-3}$ *M*	0.10–0.40	0.20	0.73	4	23
λ 320 mμ	0.17–0.83	0.90	0.99	5	5.4
Initial rate	0.33	0.20–0.98	0.77–1.0	5	..
Methoxyamine	0.10–1.0	0.030	0.39	5	6.5[f]
$[S]_T = 3.3 \times 10^{-3}$ *M*	0.17–1.0	0.065	0.57	5	9.4[f]
λ 299 mμ	0.17–1.0	0.50	0.96	5	12[f]
Initial rate	0.33–1.0	0.95	1.0	5	11[f]
Hydroxylamine[h]	0.17–0.67	0.0010	0.31	5	12
$[S]_T = 3.3 \times 10^{-3}$ *M*	0.05–0.17	0.0038	0.60	4	26
λ 299 mμ	0.07–0.67	0.0063	0.76	5	35
Initial rate	0.05–0.17	0.24	0.99	3	320
	0.17	0.004–0.24	0.60–0.99	5	...
	0.33	0.003–0.025	0.56–0.93	3	...
Methylamine	0.90	2.3×10^{-7}	0.91	1	*g*
$[S]_T = 1.7 \times 10^{-4}$ *M*	0.10–0.63	0.10	1.0	5	4,000
λ 299 mμ	0.014–0.23	0.33	1.0	6	14,000
Pseudo first order	0.027–0.10	0.55	1.0	5	21,000
	0.10	0.17–0.67	1.0	4	...
Piperidine[h]	0.17–0.66	1.5×10^{-7}	0.62	3	*g*
$[S]_T = 3.3 \times 10^{-3}$ *M*	0.17–0.66	0.48×10^{-3}	1.0	6	11.7
λ 299 mμ					
Initial rate					
Hydroperoxide[h]	0.21–0.50	6.3×10^{-9}	0.52	3	0.68
$[S]_T = 0.17–3.3 \times 10^{-3}$ *M*	0.21–0.50	5.0×10^{-8}	0.90	3	1.3
λ 299 mμ	0.21–0.50	3.2×10^{-6}	1.0	3	18
Initial rate and pseudo first order	0.10–0.50	4.3×10^{-4}	1.0	4	2,500

[a] Listed under each nucleophile are the substrate concentration $[S]_T$, the wavelength used to determine product formation, and the kinetic method used to determine rate constants. [b] $[N]_T$ = concentration of nucleophile in all its forms. [c] α_N = fraction of nucleophile as conjugate base, based on stoichiometry except for hydroxylamine, piperidine, and hydrogen peroxide which are based on the pK_a' of the nucleophile and the pH of the solution. [d] α_S = fraction of substrate as conjugate base, based on $pK_a' = 3.38$ and the pH of the solution. [e] k is the apparent second-order rate constant based on the slope of a plot of k_{obsd} against $[N]_T$ unless noted otherwise. [f] k is the intercept of a plot of $(k_{obsd} - k_{hyd})/[N]_T$ against $[N]_T$. [g] Under these conditions, there is no detectable reaction with the nucleophile. [h] These reactions were buffered with formate, acetate, phosphate, or tris(hydroxymethyl)aminoethane. No catalysis of the reaction of *o*-CPA with hydroxylamine was found with acetate buffers, 10, 30, and 50% anion from 0.03 to 0.80 *M*. In every other case the buffer concentration was ≤ 0.01 *M*

Apparent second-order rate constants (eq 4) were obtained from the slopes of plots of k_{obsd} against [N]. If these plots exhibited curvature because of general base

$$(k_{obsd} - k_{hyd})/[N]_T = k_1\alpha_S\alpha_N + k_2(1 - \alpha_S)\alpha_N \quad (4)$$

catalysis by a second mole of nucleophile,[23] as shown for the reaction with semicarbazide in Figure 2, $\alpha_N = 0.75$, or because of an activity coefficient effect or complex formation of the reactants,[24,25] the apparent second-order constants were extrapolated to zero amine concentration. The latter effect is particularly significant in the reaction of *o*-CPA with nicotinamide, which exhibits a positive deviation, no deviation, and a negative deviation in such plots at $\alpha_N = 0.9$, 0.5, and 0.1, respectively; this effect probably includes a change in the state of ionization of the substrate caused by nicotinamide. The apparent second-order rate constants and the experimental conditions under which they were determined for the various substrates and nucleophiles are summarized in Tables II, III, and IV.

To evaluate the rate constants k_1 and k_2 the corrected apparent second-order rate constants $(k_{obsd} - k_{hyd})/[N]_T\alpha_N$ were plotted against the fraction of substrate as the anion, α_S, as illustrated in Figure 3. The intercept at $\alpha_S = 1$ is k_1 and the intercept at $\alpha_S = 0$ is k_2. For semicarbazide and other weakly basic nucleophiles the value of k_2, for reaction with the acidic form of *o*-CPA, is much larger than k_1, for reaction with the anion of *o*-CPA. However, the intercept for the k_1 term is unquestionably real (see inset) and under the conditions of the experiment at $\alpha_N = 0.98$ the k_1 term accounts for

(23) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, 88, 104 (1966), and references therein.
(24) A. J. Kirby and W. P. Jencks, *ibid.*, 87, 3209 (1965).
(25) W. P. Jencks and M. Gilchrist, *ibid.*, 90, 2622 (1968).

Table III. Experimental Conditions and Apparent Second-Order Rate Constants for Reactions of Nucleophiles with Methyl Aspirin (*o*-CPAM) at 25°, Ionic Strength 1.0 *M*

Nucleophile[a] and kinetic conditions	$[N]_T$,[b] *M*	α_N[c]	No. of runs	$10^3 \times k$,[e] M^{-1} min^{-1}
Semicarbazide	0.16–0.78	0.30	5	0.084[f]
[S] = 1.7–3.3 × 10^{-3} *M*	0.11–0.72	0.50	15	0.24[f]
λ 302 mμ	0.43–0.72	0.70	3	0.23[f]
Initial rate	0.14–0.67	0.90	5	0.35[f]
	0.069–0.57	0.95	6	0.42
	0.067–0.56	0.97	6	0.46
	0.11–0.56	0.99	5	0.47
	0.5	0.20–0.99	5	...
Hydroxylamine	0.033–0.70	0.50	5	1,500
[S] = 1.7 × 10^{-4} *M*	0.033–0.50	0.95	5	2,800
λ 302 mμ				
Pseudo first order				
Methylamine	0.016–0.32	0.10	6	44,000
[S] = 1.7 × 10^{-4} *M*	0.014–0.11	0.33	4	14,000
λ 311 mμ				
Pseudo first order				
Piperidine[h]	0.17–0.67	0.59 × 10^{-3}	3	31
[S] = 3.3 × 10^{-3} *M*	0.33	0.09–1.8 × 10^{-3}	3	...
λ 302 mμ				
Initial rate				
Hydroperoxide[h]	0.010–0.063	4.7 × 10^{-4}	3	1,600
[S] = 1.3 × 10^{-4} *M*				
λ 302 mμ				
Pseudo first order				

[a–h] The footnotes have the same meaning as in Table II.

Table IV. Experimental Conditions and Apparent Second-Order Rate Constants for Reactions of Nucleophiles with *p*-Carboxyphenyl Acetate (*p*-CPA) at 25°, Ionic Strength 1.0 *M*

Nucleophile[a] and kinetic conditions	$[N]_T$,[b] *M*	α_N[c]	α_S[d]	No. of runs	k,[e] M^{-1} min^{-1}
Hydroxylamine	0.033–0.50	0.95	1.0	5	4.0[f]
[S] = 3.3–6.6 × 10^{-5} *M*					
λ 256 mμ					
Pseudo first order					
Methylamine	0.032–0.32	0.10	1.0	5	15
[S] = 3.3 × 10^{-5} *M*	0.014–0.11	0.33	1.0	4	47
λ 280 mμ					
Pseudo first order					
Piperidine	0.031–0.094	0.1	1.0	3	3.5[f]
[S] = 3.3 × 10^{-5} *M*	0.014–0.055	0.2	1.0	3	8.0[f]
λ 280 mμ					
Pseudo first order					

[a–f] The footnotes have the same meaning as in Table II.

77% of the observed reaction. The second-order rate constants for the various substrates and nucleophiles are summarized in Table V.

Third-order terms for general acid or base catalysis, when significant, contribute to k_{obsd} as shown in eq 5. The contribution of a third-order term in the reaction

$$k_{obsd} = k_3[N]_T^2(1 - \alpha_S)\alpha_N(1 - \alpha_N) + k_4[N]_T^2\alpha_S\alpha_N(1 - \alpha_N) \text{ (or } k_4'[N]_T^2(1 - \alpha_S)\alpha_N^2) + k_5[N]_T^2\alpha_S\alpha_N^2 + \ldots \quad (5)$$

of semicarbazide with *o*-CPA at $\alpha_N = 0.75$ (Figure 2) is expected if only the third-order k_4 term, which makes a maximum contribution to k_{obsd} at $\alpha_N = 0.66$, is significant. Apparent third-order rate constants were obtained from the slopes of plots of $(k_{obsd} - k_{hyd})/[N]_T$ against $[N]_T$, divided by $(1 - \alpha_N)\alpha_N$ or α_N^2, and then

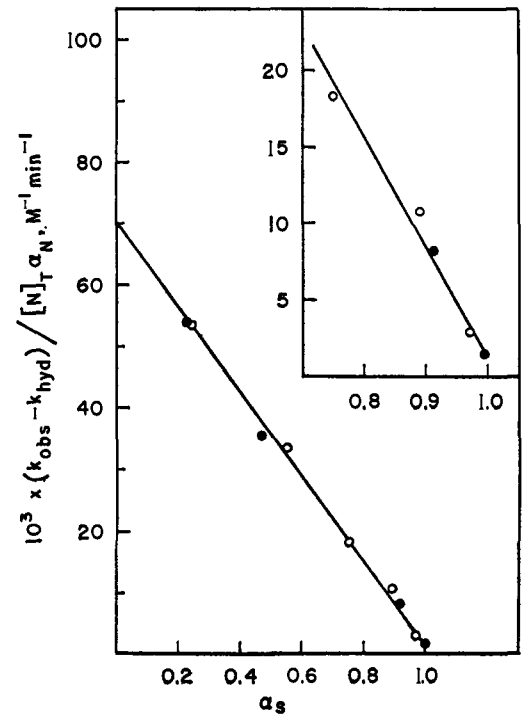


Figure 3. The second-order rate constant for the reaction of aspirin (*o*-CPA) and semicarbazide free base as a function of the fraction of *o*-CPA as *o*-CPA$^-$. The filled circles represent data from experiments at constant α_N and α_S and the open circles an experiment at constant $[N]_T$, 0.33 *M*.

Table V. Second-Order Rate Constants for the Reactions of Nucleophiles with *p*-Carboxyphenyl Acetate (*p*-CPA), Aspirin (*o*-CPA), Methyl Aspirin (*o*-CPAM), and Phenyl Acetate (PA) at 25°, Ionic Strength 1.0 *M*

Nucleophile[b]	pK_a' [c]	k,[a] M^{-1} min^{-1}				
		p-CPA$^-$	*o*-CPA$^-$	*o*-CPA^0	*o*-CPAM	PA[d]
Water[a]	−1.7	5.3×10^{-8}	2.8×10^{-6}	3.4×10^{-7} [e]	1.8×10^{-8}	2×10^{-8}
Nicotinamide	3.56	...	5.3×10^{-5}	1.9×10^{-2}	...	1.2×10^{-5}
Semicarbazide	3.84	...	1.2×10^{-3}	7.0×10^{-2}	4.5×10^{-4}	4.3×10^{-5}
Azide ion	4.45	...	*Ca.* 2×10^{-3}	3.6×10^{-1}	...	1.4×10^{-2}
Methoxyamine	4.73	...	1.0×10^{-2}	3.3×10^{-1}	...	1.5×10^{-3} [f]
Hydroxylamine	6.06	4.2	1.3	1.7 × 10	3.0	7.0×10^{-1} [f]
Methylamine	11.0[d]	1.5×10^{2}	4.2 × 10	...	1.4×10^{2}	1.7 × 10
Piperidine	11.4[d]	3.7 × 10	1.2 × 10	...	5.2 × 10	4.3 [f]
Hydroperoxide ion	11.6[d]	...	5.6×10^{3}	2.0×10^{5}	3.5×10^{4}	3.2×10^{4}
Hydroxide ion[a]	15.8	1.3×10^{2}	1.3 × 10	...	9.5 × 10	7.6 × 10

[a] All rate constants are based on concentration. [b] The names indicate the reacting form of the nucleophiles. [c] The apparent pK_a' of the nucleophile at 25° and ionic strength 1.0 *M* as determined by pH = pK + log [$\alpha_N/(1 - \alpha_N)$] except where noted. [d] Rate constants and pK_a of ref 25 unless otherwise noted. [e] Rate constant of Edwards[3] corrected to 25°. [f] Rate constants of W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **82**, 675 (1960).

plotted against α_S to give k_3 and k_4 or k_4' and k_5 as the intercepts at $\alpha_S = 0$ and 1.0. The value of k_4 for the reaction of *o*-CPA with methoxyamine is 7.1×10^{-2} M^{-2} min^{-1}; the kinetically equivalent k_4' term was discounted by analogy with the predominant general acid catalysis for the reactions of phenyl acetate with methoxyamine and semicarbazide.[25-27] The reaction

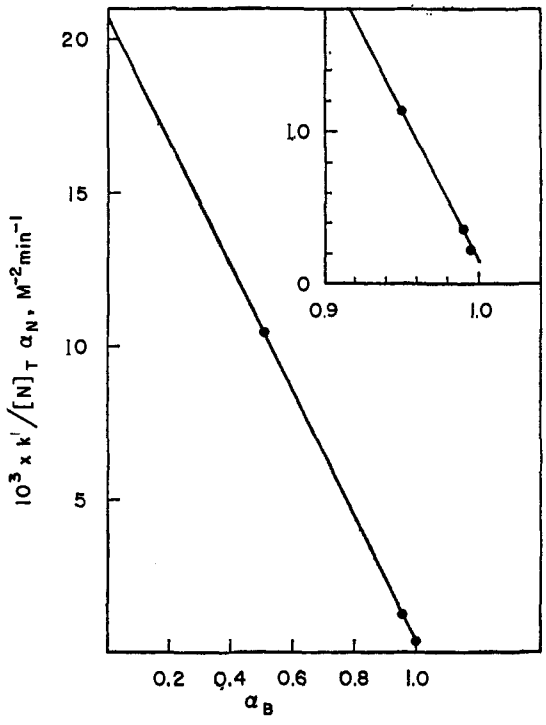


Figure 4. The catalytic rate constant for the acetic acid–acetate catalyzed reaction of phenyl acetate and semicarbazide as a function of the fraction of acetate buffer as the anion. The rate constants were determined with 0.2 *M* semicarbazide and 0.1–0.8 *M* acetate buffers.

of semicarbazide with *o*-CPAM exhibits significant general acid catalysis ($k_3 = 2.5 \times 10^{-3}$ M^{-2} min^{-1}), but no detectable general base catalysis at $\alpha_N > 0.95$. For the reaction of hydroxylamine with *o*-CPAM the values of k_3 and k_4' for general acid and base catalysis are 0.2 ± 0.2 and 5.9 M^{-2} min^{-1}, respectively.

(26) L. do Amaral, K. Koehler, D. Bartenbach, T. Pletcher, and E. H. Cordes, *J. Am. Chem. Soc.*, 89, 3537 (1967).
(27) W. P. Jencks and J. Carriuolo, *ibid.*, 82, 675 (1960).

The calculated rate constants were used to construct theoretical pH–rate profiles, which showed satisfactory agreement with the observed pH–rate profiles. For the reactions of aspirin with weakly basic nucleophiles, such as semicarbazide, the predominance of the reaction with the acidic form of aspirin and the ionization constant of the nucleophile result in bell-shaped profiles.

If the reactions of weakly basic nucleophiles with aspirin are catalyzed intramolecularly by its *o*-carboxyl group it might be expected that intermolecular catalysis of the corresponding reactions with phenyl acetate by acetate buffers would be detectable. The reaction of phenyl acetate with semicarbazide (0.2 *M*, 83–100% free base) was found to be catalyzed by acetate buffer (0–0.8 *M*, 50–99.5% anion), but for the reaction of the same substrate with methylamine (0.01 *M*, 40% free base) catalysis by acetate (0–0.83 *M*, 100% anion) was not detected. The observed rate constant for the catalyzed semicarbazide reaction was determined by measuring the initial rate of phenol release from 0.01 *M* phenyl acetate at 275 mμ as a function of buffer concentration, [B], and the fraction of buffer as the acetate anion, $\alpha_B = 0.5$, 0.95, 0.99, and 0.995. The observed rate constant (eq 6) was separated into its buffer-dependent

$$k_{obsd} = k_1[OH^-] + k_2[N]_T\alpha_N + k_3[B]_T\alpha_B + k_4[N]_T[B]_T\alpha_N\alpha_B + k_5[N]_T[B]_T\alpha_N(1 - \alpha_B) \quad (6)$$

and -independent terms by plotting k_{obsd} against $[B]_T$ at constant pH. The slope of the resulting straight line is an apparent second-order rate constant which was corrected for acetate-catalyzed hydrolysis, based on a value[25] of k_3 of 2.1×10^{-5} M^{-1} min^{-1}. The remaining buffer-catalyzed semicarbazide reaction (eq 7) was

$$\frac{k'}{[N]_T\alpha_N} = k_4\alpha_B + k_5(1 - \alpha_B) \quad (7)$$

separated into the catalytic rate constant for acetate anion, k_4, and that for acetic acid, k_5, by plotting $k'/[N]_T(\alpha_N)$ against α_B (Figure 4). Values of $k_4 = 1.5 \times 10^{-4}$ and $k_5 = 2.1 \times 10^{-2}$ M^{-2} min^{-1} are given by the intercepts at $\alpha_B = 1.0$ and $\alpha_B = 0$, respectively.

If an anhydride is formed during the hydrolysis of aspirin, it should be possible to trap it by reaction with a nucleophilic reagent which does not itself react rapidly with aspirin under the conditions of the experiment.[19] Such an experiment was carried out in the presence of $3–5 \times 10^{-3}$ *M* hydroxylamine at pH 3.74 (Table VI).

Table VI. Hydroxamic Acid Formed under Conditions for Trapping Acetic Salicylic Anhydride with Hydroxylamine

Reactants,[a] M		$10^3 \times k_{obsd}$, min^{-1}		% k_{obsd} due to	% hydroxamic acid products[d]	
Aspirin	NH_2OH	Calcd[b]	Obsd	$k[N]$[c]	Obsd[e]	Cor[f]
1×10^{-3}	0	0.108	0.104	0	0	0
1×10^{-3}	3×10^{-3}	0.196	0.196	47	38	48
1×10^{-3}	5×10^{-3}	0.230	0.242	57	49	56

[a] In 0.01 M acetate buffer, pH 3.74. [b] Calculated rate constants based on eq 3 and the rate constants given in Table V. [c] $100 \times (k_{obsd} - k_{hyd})/k_{obsd}$. [d] The yield of hydroxamic acid product was determined as the ferric chloride complex (W. P. Jencks, *J. Am. Chem. Soc.*, **80**, 4581, 4585 (1958)). Prior incubation of aliquots with concentrated hydroxylamine (to convert any remaining O-acylhydroxylamine to hydroxamic acid) gave less than a 3% increase in yield; the reported values are based on these assays. The results were corrected for the color formed from the ferric salicylate complex and the same results were obtained with experiments in which the assay was carried out at a final hydrochloric acid concentration of 1.1 M, which effectively suppresses the formation of this complex. [e] Determined after ten or more half-lives. Quantitative yields of hydroxamic acid were obtained from acetic anhydride and the mixed anhydride of acetic and *o*-methoxybenzoic acids upon addition to the same concentrations of hydroxylamine which were present in the reaction mixtures. The same results were obtained with freshly prepared hydroxylamine solutions and solutions which had been allowed to stand for 21 days. [f] Corrected for 21 and 13% loss for 3×10^{-3} M and 5×10^{-3} M NH_2OH, respectively, as determined by control experiments with acetic anhydride in the dilute hydroxylamine solutions, which were assayed after standing for 21 days. This loss is presumably caused by decomposition of O-acylhydroxylamine. Comparisons of the yields of hydroxamic acid after addition to the dilute hydroxylamine solution and after subsequent incubation with concentrated hydroxylamine indicated that acetic and *o*-methoxybenzoic acetic anhydrides gave 54 and 65% O-acylhydroxylamines, respectively, in the initial incubation.

Under the conditions of the experiments, approximately half of the observed reaction proceeded by nucleophilic attack of hydroxylamine on aspirin and any formation of hydroxamic acid in excess of the approximately 50% expected from the nucleophilic reaction would constitute evidence for the trapping of an intermediate during the hydrolysis. No such increase in yield of hydroxamic acid was observed, although acetic anhydride and the mixed anhydride of acetic and *o*-methoxybenzoic acids were shown to give quantitative yields of hydroxamic acids under the conditions of the trapping experiment. This experiment provides evidence that the anhydride pathway does not account for a large fraction of the hydrolysis of aspirin anion.

Discussion

The Reactive Ionic Species of Aspirin. The kinetic ambiguity with respect to the nature of the reacting species is clearly resolved for the reactions of aspirin with weakly basic amines and azide ion, in which the basic species of the nucleophile with a free electron pair is certainly the reactive form. As shown for the reaction with semicarbazide in Figure 3, the neutral, acidic form of aspirin is much more reactive than the anion. Larger differences, of more than two orders of magnitude, are observed for nicotinamide and azide ion, which have no proton on the attacking nitrogen atom. Even a reaction of hydroperoxide anion ($pK = 11.6$) with the acidic form of aspirin can be detected, as a pH-independent reaction in weakly acidic solution, with a rate constant 36-fold larger than that for the reaction with aspirin anion.

Although these observations show that the acidic form of aspirin is more reactive toward nucleophiles than the anionic form, it is certain that an enhanced reactivity of this form toward nucleophilic attack by hydroxide ion does not account for the pH-independent hydrolysis of aspirin anion, which follows a kinetically indistinguishable rate law. Such an interpretation would require that hydroxide ion react 3.5×10^5 times faster with aspirin acid than with aspirin anion, whereas the observed rate accelerations caused by the *o*-carboxyl group are on the order of 10^2 for weak nucleophiles and even less for strongly basic nucleophiles, such as hydroperoxide anion. No reaction of the acidic form of aspirin with the basic amines methylamine and piperidine could be detected.

Rate Accelerations Caused by the *o*-Carboxyl Group of Aspirin. The *o*-carboxyl group of aspirin can influence reactions of its neighboring ester group with nucleophilic reagents by (a) polar effects, (b) steric effects, (c) electrostatic effects, and (d) catalytic effects. These effects may be evaluated from comparisons of the second-order rate constants, k, for the reactions of nucleophiles with *p*-CPA^-, *o*-CPAM, *o*-CPA^0, and *o*-CPA^- with the rate constant, k_0, for the corresponding reaction with phenyl acetate, as shown in the logarithmic plots of Figures 5 and 6.

The *polar effects* are best considered on the basis of the Hammett equation, $\log k/k_0 = \sigma\rho$. Values of ρ for reactions of oxygen anions with substituted phenyl acetates are near 1.0, whereas those for nitrogen nucleophiles are close to 2.0; the hydroxide ion reaction in water is best correlated by $\rho = 0.8$ and the piperidine reaction by $\rho = 2.1$.[26,28]

The faster reaction of hydroxide ion with *p*-CPA^- compared to phenyl acetate corresponds to a value of σ for the *p*-COO^- group of 0.29. This is larger than the usual value of 0.12–0.13 for this substituent[29,30] but is similar to a value of 0.23, calculated from the ionization constants of substituted phenols.[31,32] However, for the neutral nucleophile, piperidine, the value of $\log k/k_0 = 0.93$ corresponds to a σ value of 0.46. Methylamine and hydroxylamine exhibit similar rate accelerations with *p*-CPA^- compared to phenyl acetate (Figure 5). The value of $\sigma = 0.12$–0.13 is based on reactions in which the product of transition state has one more negative charge than the starting materials, and this result suggests that the value of σ is considerably more positive for a *p*-COO^- group in a reaction in which there is no change in over-all charge.

The *steric effect* of an *o*-carboxylate or ester group causes a rate decrease of two- to threefold, based on the following comparisons. (a) Hydroxide ion, hydroperoxide ion, and water react at almost identical rates with *o*-CPAM and phenyl acetate, whereas a rate increase of $\log k/k_0 = 0.37$ is expected from the polar effect of the *o*-CO_2CH_3 group, assuming a similar polar

(28) T. C. Bruice and S. J. Benkovic, *J. Am. Chem. Soc.*, 86, 418 (1964).
(29) H. H. Jaffé, *Chem. Rev.*, 53, 191 (1953).
(30) P. R. Wells, *ibid.*, 63, 171 (1963).
(31) J. J. Ryan and A. A. Humffray, *J. Chem. Soc., B*, 842 (1966).
(32) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley and Sons, Inc., New York, N. Y., 1962.

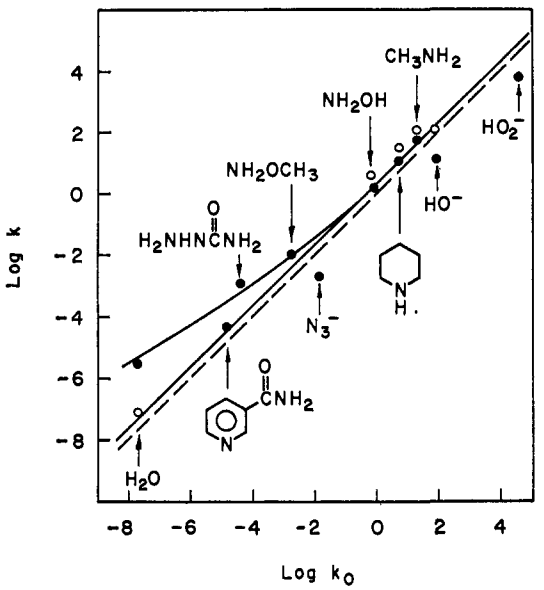


Figure 5. A comparison of the second-order rate constants, k, for the reaction of nucleophiles with aspirin anion (o-CPA$^-$), ●, and p-carboxyphenyl acetate anion (p-CPA$^-$), ○, with the second-order rate constants, k_0, of the corresponding reactions with phenyl acetate (PA). All straight lines are drawn with slope 1.0. The dashed line represents $k = k_0$.

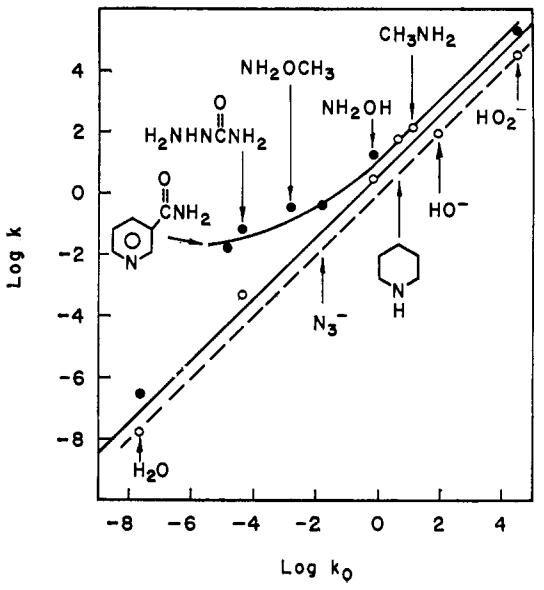


Figure 6. A comparison of the second-order rate constants, k, for the reaction of nucleophiles with undissociated aspirin (o-CPA^0), ●, and methyl aspirin (o-CPAM), ○, with the second-order rate constants, k_0, of the corresponding reactions with phenyl acetate (PA). All straight lines are drawn with slope 1.0. The dashed line represents $k = k_0$.

effect of this group and the p-CO_2CH_3 group, for which $\sigma = 0.46$.[30] (b) Similar considerations for the piperidine reaction give a predicted value of log $k/k_0 = 1.34$ (based on $\rho = 2.1$ and $\sigma^- = 0.64$[29]; this reaction is best correlated with σ^- values[26]). The difference of 0.24 between this value and the observed log $k/k_0 = 1.1$ presumably reflects the steric effect; similar differences are observed with methylamine and semicarbazide. Hydroxylamine, which acts as both a nitrogen and oxygen nucleophile,[33] occupies a position intermediate between those of oxygen anions and amines (Figure 6). (c) The rate constants for the reactions of hydroxylamine, piperidine, and methylamine with o-CPA$^-$ are about threefold smaller than those for the corresponding reactions with p-CPA$^-$. The straight solid reference line of Figure 5 is drawn through the points for these reactions of o-CPA$^-$; there is no evidence for a special catalytic effect of the o-carboxylate group in these reactions. The absence of such a catalytic effect is not surprising, because there is no detectable intermolecular catalysis of the reaction of phenyl acetate with methylamine by acetate ion, presumably because of the small basicity of the carboxylate group.

The *electrostatic effect* of the carboxylate group is evident in the retardation of the reactions of o-CPA$^-$ with hydroxide, hydroperoxide, and azide anions, for which log $k/k_0 = -0.9$. The difference between this and the value of log $k/k_0 = 0.23$ for p-CPA$^-$ is -1.1. After correction for a steric effect of twofold, this corresponds to a rate decrease of approximately sevenfold which may be attributed to the electrostatic effect. A similar factor is apparent from the negative deviation of the points for these anions below the solid line for the reactions of uncharged nucleophiles with o-CPA$^-$ in Figure 5.

The *catalytic effects* of the o-carboxylic acid and carboxylate groups of aspirin and its anion are evident in the upward curvature of the plots for the reactions of these compounds with weakly basic nucleophiles in Figures 5 and 6. It should be noted that although the upward deviations of the points for these reactions appear small, the figures are plotted with a condensed logarithmic scale, and the rate accelerations are in some cases more than two orders of magnitude. For o-CPA^0 the rate accelerations compared to o-CPAM of about sixfold for hydroperoxide ion and hydroxylamine and of 19-fold for the water reaction probably represent a catalytic effect of the o-COOH group. The polar effect of this group ($\sigma^- = 0.73$[29]) is only slightly larger than that of the ester and the steric effect is probably similar, because the methyl group of the ester is expected to be in a position rotated away from the acetyl group. There can be no question but that the much larger rate accelerations in the reactions of o-CPA^0 with nicotinamide and the primary amines semicarbazide and methoxyamine (Figure 6) must represent a specific catalytic effect of the o-COOH group. No significant rate accelerations are observed for the reactions of o-CPA$^-$ with strongly basic nucleophiles, the rate constants for which can be reasonably accounted for by electronic, steric, and electrostatic effects. For the reactions of aspirin anion with weakly basic nucleophiles, no rate acceleration is observed for the tertiary amine, nicotinamide, but significant rate accelerations are observed for the reactions with methoxyamine, semicarbazide, and water, which have a dissociable proton on the attacking nitrogen or oxygen atom (Figure 5).

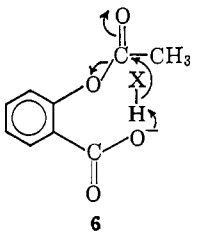
These observations suggest that the carboxyl and carboxylate groups accelerate the reactions of aspirin with weak nucleophiles by general acid and general base catalysis, respectively. An anhydride mechanism, if it caused an acceleration of the rate of reaction with a nucleophile at all, would not be expected to show the discrimination among different nucleophiles which is

(33) W. P. Jencks, *J. Am. Chem. Soc.*, 80, 4581, 4585 (1958).

observed for the aspirin reactions; the anhydride mechanism is discussed in more detail below.

There is ample precedent for intermolecular general base catalysis of the aminolysis and hydrolysis of esters[26,27,34,35] and the reactions of phenyl acetate with water,[19] semicarbazide (this study), and methoxyamine[26] have been shown to be subject to general base catalysis by acetate ion. The ratio of the rate constants for the intramolecular reaction of aspirin anion with semicarbazide to the corresponding intermolecular acetate-catalyzed reaction with phenyl acetate is 8 *M*, which might be regarded as the "effective concentration" of the carboxylate group of aspirin for catalysis of the reaction with semicarbazide. A better comparison may be made by (a) considering only the *difference* between the observed rate constant for aspirin and that predicted by the straight line of Figure 5 for a compound with the electronic and steric properties of aspirin in the absence of intramolecular catalysis and (b) making allowance for the fact that the carboxylate group of aspirin is a weaker base than acetate by a correction based on a β value of 0.45, which has been observed for catalysis of the reaction of methoxyamine with phenyl acetate by carboxylate ions.[26] The corrected "effective concentration" of the carboxylate group of aspirin for the reaction with semicarbazide is 23 *M*. A similar value of 7 *M*, uncorrected, is obtained for the hydrolysis of aspirin anion, which is increased to 28 *M* after correction, based on a β value of 0.47 for general base catalysis of ester hydrolysis.[35] The corrected "effective concentration" for the methoxyaminolysis of aspirin, compared to the intermolecular reaction,[26] is the smaller value of 1 *M*.

Evidence has been summarized elsewhere[25,36] that the rate-determining step for the aminolysis of phenyl acetates involves attack of the amine on the ester; the departure of the leaving group may or may not be concerted with this attack. Since amine anions are too unstable thermodynamically to be free intermediates in aminolysis, the mechanism of the intramolecularly general base catalyzed aminolysis of aspirin may be formulated as **6**, the same as that for the intermolecular



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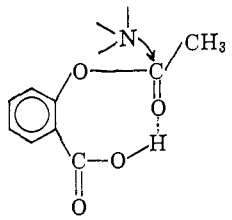
reaction, without taking a position with respect to the possible formation of a metastable tetrahedral addition intermediate. It is reasonable to formulate the mechanism of the general base catalyzed water reaction in the same way (**6**, X = OH). The rate constant for this reaction falls on the same line as the rate constants for the intramolecularly general base catalyzed reactions of weakly basic amines (Figure 5). This assignment of mechanism for the water reaction is the same as for the intermolecular general base catalyzed hydrolysis of phenyl acetate by acetate anion.[19] However, the analogy does not provide proof of mechanism because a suitably located carboxylate group can displace a phenolate ion intramolecularly to give an anhydride intermediate, as in the rapid hydrolysis of monophenyl phthalate, for example.[37]

The kinetic ambiguity in the rapid hydrolysis of salicylate ester anions has also been resolved in favor of a general base catalyzed mechanism by the demonstration that the rates of reaction of these esters with such nucleophiles as imidazole and sulfite are not abnormally fast.[38,39]

The catalysis by the carboxylic *acid* group of aspirin is also in accord with the known intermolecular general acid catalysis of reactions of phenyl esters with weakly basic amines.[27] For the reaction of phenyl acetate with semicarbazide, acetic acid is a more effective catalyst than acetate anion by a factor of $2.1 \times 10^{-2}/1.5 \times 10^{-4} = 140$, just as the $-CO_2H$ group of aspirin is a more effective catalyst than the $-CO_2^-$ group in the corresponding intramolecular reaction by a factor $7.0 \times 10^{-2}/1.2 \times 10^{-3} = 59$. For intramolecular general acid catalysis the "effective concentration" of the carboxylic acid group of aspirin corresponds to 3.3 *M* acetic acid, based on the rate constant for acetic acid catalysis of the reaction of phenyl acetate with semicarbazide and the increase in rate for *o*-CPA^0 compared to *o*-CPAM. Similar increases are observed for the reactions with nicotinamide and methoxyamine. No correction for the p*K* of the carboxylic acid group of aspirin is made in this case, because the value of α for catalysis of the reaction of methoxyamine with phenyl acetate by carboxylic acids is zero.[26] The smaller catalysis in the water reaction of free aspirin is in accord with the experimental fact that intermolecular general acid catalysis of ester hydrolysis by carboxylic acids, if it occurs at all, is much less significant than general base catalysis by carboxylate ions.[35] In general, intramolecular acid catalysis is most significant for the weakest nucleophiles (Figure 6), so that it would be expected that nucleophilic attack of acetate ion would be subject to such catalysis. This is in contrast to a recent conclusion based on the failure to detect an acid-catalyzed attack of acetate,[21] but this failure means only that the nucleophilic reaction does not proceed at a measurable rate compared to the much faster general base reaction, not that it is slow compared to the (still undetected) nucleophilic reaction of acetate with phenyl acetate.

In view of the fact that the rate-determining step of the aminolysis of phenyl esters involves attack of the amine, the most probable transition state for the intramolecularly general acid catalyzed reaction is **7**, in which the catalyst polarizes the carbonyl group in the same manner as for general acid catalysis of addition reactions to the carbonyl group. However, mechanism **8**, in which the acidic group donates a proton to the phenolic oxygen atom, is not ruled out.[40]

(34) J. F. Bunnett and G. I. Davis, *J. Am. Chem. Soc.*, **82**, 665 (1960); T. C. Bruice and M. F. Mayahi, *ibid.*, **82**, 3067 (1960).
(35) W. P. Jencks and J. Carriuolo, *ibid.*, **83**, 1743 (1961).
(36) G. M. Blackburn and W. P. Jencks, *J. Am. Chem. Soc.*, **90**, 2638 (1968).
(37) J. W. Thanassi and T. C. Bruice, *ibid.*, **88**, 747 (1966).
(38) M. L. Bender, F. J. Kézdy, and B. Zerner, *ibid.*, **85**, 3017 (1963).
(39) B. Capon and B. Ch. Ghosh, *J. Chem. Soc., B*, 472 (1966).
(40) The reactions of a series of substituted aspirins with water and weakly basic oxyanions have been shown to be faster than the reactions of the corresponding methyl esters, which indicates that these reactions are subject to intramolecular general acid catalysis by the carboxyl group (A. R. Fersht and A. J. Kirby, personal communication).



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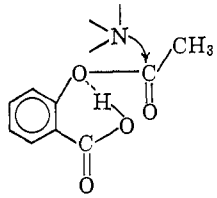

8

The Question of an Anhydride Intermediate. The formation of an anhydride intermediate, by intramolecular nucleophilic attack of the carboxylate group on the ester (eq 1), is rejected as a significant contributing mechanism to the rapid rate of hydrolysis of aspirin for the following reasons.

If such an anhydride is formed, either its formation or its hydrolysis must be rate determining. The statement that its *formation* is rate determining means that $k_2 \gg k_{-1}$ (eq 1); *i.e.*, the anhydride must react with water faster than it reacts intramolecularly with the phenolic hydroxyl group to regenerate starting material. But phenol is a highly reactive nucleophile toward activated acyl groups near neutrality, even in intermolecular reactions, and would be expected to react even more rapidly in an intramolecular reaction. At pH 7.3 (a pH at which aspirin hydrolysis proceeds almost completely by the monoanion reaction) 0.001 *M* acetic anhydride was found to react with 0.01 *M* phenol in 0.01 *M* phosphate buffer to give a 44% yield of phenyl acetate, measured by the hydroxamic acid method. This means that the reactivity of 0.01 *M* phenol is equivalent to that of 55 *M* water. Therefore, in order that formation of the anhydride be rate determining in aspirin hydrolysis ($k_2 \gg k_{-1}$, eq 1), the effective concentration of the adjacent phenolic hydroxyl group would have to be less than 0.001 *M*. This is an unreasonably low reactivity in view of the large effective concentrations of 10 *M* or more which have been found for adjacent functional groups in many intramolecular reactions. Furthermore, according to this mechanism the rate of anhydride formation is equal to the rate of aspirin hydrolysis, so that any increase in the rate of aspirin disappearance above this value, such as is seen in the semicarbazide reaction, cannot be accounted for by the same mechanism.

If *hydrolysis* is rate determining ($k_{-1} \gg k_2$, eq 1), anhydride formation is a rapid, reversible reaction, and the transition state for the over-all, hydrolytic reaction must have the same charge as that for the hydrolysis of an anhydride at the same pH. The hydrolysis of acetic and acetylsalicylic anhydrides at neutral and moderately acidic pH proceeds exclusively through a pH-independent water reaction with a transition state carrying no net charge.[41,42] Thus, rate-determining hydrolysis of an intermediate anhydride does not provide an explanation for the hydrolysis of aspirin anion, which proceeds through a transition state with a charge of -1; such a reaction could only provide an explanation for the hydrolysis of the acidic form of aspirin through an uncharged transition state.[43] Intramolecular general base catalysis of water attack on the anhydride by phenolate ion would not be expected to cause a sufficient rate acceleration to account for hydrolysis exclusively through an anionic transition state over the pH range 4 to 8. The rate acceleration caused by an *o*-phenoxide group is only some 60-fold in the hydrolysis of phenyl salicylate[39] and is even less for the hydrolysis of *p*-nitrophenyl salicylate.[38] The rates of the water and hydroxide ion hydrolyses of acetylsalicylic acid anhydride are equal at pH 7.9. A rate acceleration of 10^4 would be required to account for the predominant hydrolysis of aspirin *via* an anhydride through an anionic transition state, rather than a water reaction, at pH 4.

If anhydride formation is fast and its breakdown is rate determining, nucleophilic reagents other than water should be able to react with it and, consequently, should exhibit an enhanced rate of reaction. The data shown in Figures 5 and 6, however, show that the rate accelerations observed with nucleophiles are highly specific and with many nucleophiles no rate acceleration at all is observed. Furthermore, the transition state for the reaction of a neutral nucleophile with an anhydride has no net charge, so that an anhydride mechanism cannot account for a reaction with aspirin anion, as in the case of the hydrolysis reaction.

If anhydride formation is fast and its breakdown is rate determining, it should be possible to increase its rate of breakdown by reaction with increasing concentrations of a nucleophile, until the breakdown step becomes faster than the attack step and the formation of anhydride becomes rate determining. This should result in a leveling off of the rate at the rate of anhydride formation as the concentration of nucleophile is increased. A search was made for such a leveling off in the reaction with hydroxylamine, but no leveling occurs and the rate was found to be strictly proportional to hydroxylamine concentration up to a rate constant of 0.047 min^{-1}, 300 times faster than the rate of hydrolysis. In order to form anhydride at a rate faster than this, the effective concentration of the carboxylate group adjacent to the ester in aspirin would have to be 2000 *M*, based on the rate constant for the intermolecular reaction of acetate ion with phenyl acetate.[19,25] In fact, the concentration would have to be larger than this, because the observed reaction of phenyl acetate with acetate represents general base catalysis rather than nucleophilic attack[19] and the reactivity of the weakly basic carboxylate group of aspirin is less than that of acetate ion.

Finally, if an anhydride is formed as an intermediate, it should be possible to trap it by reaction with a nucleophilic reagent.[19] Hydrolysis of aspirin in the presence of hydroxylamine under conditions in which other anhydrides react quantitatively with hydroxylamine gives no more hydroxamic acid than is expected from the known rate of bimolecular reaction of hydroxylamine with aspirin.

Experimental Section[44]

Materials. Distilled water was used throughout these experiments. Dioxane was distilled, bp 101–102°, from benzophenone ketyl.[45]

(41) J. F. Kirsch and W. P. Jencks, *J. Am. Chem. Soc.*, 86, 837 (1964).
(42) E. R. Garrett, *ibid.*, 82, 711 (1960).
(43) The reason that the rate of such a reaction must be proportional to the concentration of aspirin acid is that the equilibrium concentration of anhydride is proportional to the concentration of aspirin acid, rather than aspirin anion; if the over-all rate is proportional to the concentration of the intermediate and its pH-independent rate of breakdown, it will therefore be proportional to the concentration of aspirin acid.

The following nucleophiles were recrystallized (solvents and melting point as indicated): nicotinamide, acetone, 129–130°; hydroxylamine hydrochloride, ethanol–water, 153–155°; semicarbazide hydrochloride, ethanol–water, 175–176°; piperidine hydrochloride, ethanol, 244–245°; and methylamine hydrochloride, ethanol, 231–233°. Methoxyamine hydrochloride was sublimed at 65° (2 mm), mp 151–152°. Hydrogen peroxide, 30% (Fisher reagent), was used as received after titrating with potassium permanganate. Sodium azide (Fisher, purified) was used as received. Reagent grade chemicals were used as buffers.

The following esters were recrystallized: acetylsalicylic acid (aspirin) from acetone, mp 136.5–139°, and *p*-carboxyphenyl acetate from methanol–water, mp 49°. Phenyl acetate was purifield by treatment with aqueous sodium carbonate and then acetic anhydride, followed by vacuum distillation through a packed column, bp 75° (10 mm).[25] Methyl acetylsalicylate (*o*-CPAM) was prepared from methyl salicylate and acetic anhydride, mp 48–49° (lit.[46] 49°). For comparison with reaction products, salicylic acid was recrystallized from water, mp 158–160°, and *p*-carboxyphenol was recrystallized from water, mp 214-215°. Methyl salicylate was redistilled, bp 107° (19 mm). Phenol was also redistilled, bp 177–178°.

Acetic *o*-methoxybenzoic anhydride was prepared from *o*-methoxybenzoic acid and acetyl chloride by the general method of Wedekind.[47] *o*-Methoxybenzoic acid (7.6 g, 0.05 mol) and freshly distilled (from BaO) pyridine (8.1 ml) in anhydrous ether (50 ml) were cooled in an ice bath. Acetyl chloride (3.6 ml, 0.05 mol) was then slowly added, resulting in the almost immediate formation of a precipitate. After 10 min the reaction mixture was filtered into a separatory funnel, and the ether filtrate was washed with three 25-ml portions each of cold 10% hydrochloric acid, 10% sodium bicarbonate, and water. The ether solution was shaken with calcium sulfate and then transferred in portions to a two-necked (14/20), 25-ml distilling flask. The ether was removed with a stream of nitrogen, and after the entire ether solution was added and all the ether removed, the product was distilled through a short-path distilling head. The second fraction, bp 133–134° (0.35 mm), a colorless viscous liquid, was used in the trapping experiments. *Anal.* Calcd for $C_9H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.75; H, 5.25. Acetohydroxamic acid[48] (mp 89–93°) and commercial benzohydroxamic acid (mp 128–129°) were recrystallized.

Kinetic Measurements. The reaction rates were determined from the rate of formation of phenolic products, measured spectrophotometrically in thermostated cell compartments maintained at 25 ± 0.1° with a Zeiss M4QII spectrophotometer. Reaction conditions were adjusted to observe initial rates of slow reactions or pseudo-first-order rates of fast reactions. For initial rates it was necessary to observe product formation at a wavelength at which substrate absorption is negligible. The reaction mixtures were usually prepared directly in 3-ml quartz cuvettes. If the nucleophile could not act as buffer in the desired concentration or pH range, external buffers which are poor nucleophiles were used and corrections were made for buffer catalysis of the reaction if necessary (see Tables II–IV).

The reaction mixtures were equilibrated at 25 ± 0.1° and the reaction was initiated with 5–20 μl of a freshly prepared 1 *M* or 0.05 *M* solution of ester in dioxane. The formation of salicylic acid–salicylate was followed at 299 mμ where absorption due to aspirin is negligible and pH has no effect on the extinction coefficient. For reactions involving sodium azide or nicotinamide the phenolic product was observed at 302 mμ where these nucleophiles do not absorb. Methyl salicylate formation was followed at 302 mμ where methyl acetylsalicylate does not absorb and the extinction coefficient does not vary with pH at pH <9.5. Under more basic conditions, where there may be a secondary hydrolysis of methyl salicylate, the reaction was followed at the isosbestic point of methyl salicylate and salicylate. *p*-Carboxyphenol monoanion–dianion was followed at 280 mμ. *p*-Carboxyphenol was observed at 256 mμ for pseudo-first-order rates, but for initial rates it was necessary to determine phenol concentration in aliquots of the reaction mixture by an azo coupling procedure.[25] Phenol formation was followed at 275 mμ. The pH of reaction mixtures was determined after the kinetic run and before if buffering capacity was in doubt or the pH critical. The acid dissociation constants at ionic strength 1.0 *M* of aspirin, $pK_a' = 3.38$, and *p*-carboxyphenyl acetate, $pK_a' = 3.92$, were measured spectrophotometrically[32] and the acid dissociation constants of the various nucleophiles were either measured potentiometrically[32] or literature values for the same experimental conditions were used. All pH measurements were made with a Radiometer pH meter 4 using a calomel electrode and a glass electrode, Type G220C (Type G220B at pH >10).

Extinction coefficients of the reaction mixtures at completion were determined by (1) allowing the reaction to go to completion (>10 × $t_{1/2}$) and using spacers where necessary to reduce the path length to 0.05–0.2 cm; (2) hydrolyzing an aliquot of substrate solution with 0.1 *M* sodium hydroxide and adjusting to reaction conditions; or (3) adding 5–10 μl of phenol solution to the reaction mixture.

For the initial rate experiments, <5% reaction, a plot of absorbance *vs.* time yields a straight line, the slope of which is related to k_{obsd} by

$$k_{obsd} = \frac{(A_2 - A_1)}{(t_2 - t_1)}\frac{1}{[S]_0\epsilon_p} = \frac{(A_2 - A_1)}{(t_2 - t_1)}\frac{1}{A_\infty} \qquad (8)$$

where A = absorbance, t = time, $[S]_0$ = initial substrate concentration, and ϵ_p = extinction coefficient of product.

Pseudo-first-order rate constants were obtained from the slope of plots of 2.303 log $(A_\infty - A_t)$ against time, which were linear for three half-times.

Trapping Experiment. The rate and the products of the decomposition of aspirin were determined in the presence of dilute hydroxylamine in an attempt to trap any anhydride which might be formed during the hydrolysis. The reaction mixtures described in Table VI were used to determine k_{obsd} and to determine the amount of hydroxamic acid formed, after ten half-lives, as the ferric chloride complex. Acetic anhydride and the mixed anhydride of acetic acid and *o*-methoxybenzoic acid were converted to the hydroxamic acids under identical conditions. The results were compared with the results obtained from the reaction of acetic anhydride, acetic *o*-methoxybenzoic anhydride, and aspirin with 1 *M* hydroxylamine and authentic acetohydroxamic acid, benzohydroxamic acid, and salicylic acid (which also forms a ferric chloride complex).

Acknowledgment. We are grateful to A. J. Kirby and A. R. Fersht for keeping us informed of the progress of their work on the reactions of aspirin and related compounds before publication.

(44) Melting points and boiling points are uncorrected. The melting points and boiling points with no specific literature reference are in agreement with those given in "The Merck Index" 7th ed, Merck and Co., Inc., Rahway, N. J., 1960, Microanalyses were performed by Dr. Carol K. Fitz, Needham Heights, Mass. 02194.

(45) K. B. Wiberg, "Laboratory Technique in Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960.

(46) M. A. Stahmann, I. Wolf, and K. P. Link, *J. Am. Chem. Soc.*, 65, 2285 (1943).

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(48) E. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, 84, 4319 (1962).