

# Fluoride Ion Catalyzed Hydrolysis of Carboxylic Anhydrides<sup>1</sup>

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Fluoride ion will catalyze the hydrolysis of acetic and succinic anhydride in water and in aqueous dioxane. The ratios of the rates of the catalyzed to uncatalyzed reactions are larger in aqueous dioxane than in water. For the aqueous hydrolysis of acetic anhydride the rate of the catalyzed disappearance of anhydride is greater than the rate of appearance of acetic acid, showing that acetyl fluoride can build up in concentration, and can be aspirated out of the solution. Fluoride ion acts predominantly as a nucleophilic catalyst. Sodium hydrogen fluoride and hydrofluoric acid also catalyze the hydrolysis. The hydrolysis of succinic anhydride is catalyzed by fluoride ion, but in this system acyl fluoride does not build up in concentration.

Hydrolyses of carboxylic anhydrides and esters are catalyzed both by nucleophiles and by general bases.<sup>2</sup> A nucleophile can convert the substrate into a more reactive acyl compound; examples in anhydride hydrolysis are the formate and nitrite ion catalyzed hydrolyses of acetic anhydride, where acetyl formate and nitrite are intermediates.<sup>3,4</sup> General base catalysis could remove a proton from an attacking water molecule, or from a tetrahedral intermediate formed by addition of a water molecule to the substrate.<sup>5,6</sup>

It is often difficult to differentiate between these different reaction paths because basicity and nucleophilicity toward a carbonyl center are related. Tests based on the magnitude of the solvent deuterium isotope effect have been used, but are not completely reliable.<sup>7,8</sup>

Bell has noted that small basic anions of high charge density are often very effective as general base catalysts,<sup>9</sup> and fluoride ion must act as a base rather than a nucleophile in catalyzing the hydrolysis of acetyl fluoride.<sup>10</sup>

Fluoride ion can also act as a nucleophile. It is not particularly reactive toward alkyl groups,<sup>11</sup> but it is highly reactive toward acyl centers<sup>12</sup> and to aryl sulfites.<sup>13</sup> (In some of these reactions nucleophilic and general base catalysis were not separated.)

## Experimental Section

**Kinetics.**—Reaction was followed either titrimetrically, by following the formation of acetic acid, or by following the disappearance of acetic anhydride spectrophotometrically. These general methods have been described elsewhere.<sup>14</sup>

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(2) For a general review, see T. C. Bruice and S. Benkovic, "Bio-Organic Mechanisms," W. T. Benjamin Inc., New York, N. Y., 1966, Chapter I.

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(4) E. B. Lees and B. Saville, *ibid.*, 2262 (1958).

(5) A. R. Butler and V. Gold, *ibid.*, 2305 (1961); 2212 (1962).

(6) C. A. Bunton and V. J. Shiner, *J. Am. Chem. Soc.*, **83**, 3207 (1961); S. L. Johnson, *ibid.*, **84**, 1729 (1962); C. A. Bunton, N. A. Fuller, S. G. Perry, and V. J. Shiner, *J. Chem. Soc.*, 2918 (1963).

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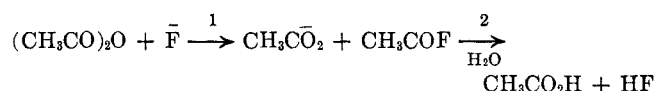
(10) C. A. Bunton and J. H. Fendler, *J. Org. Chem.*, **31**, 2307 (1966).

(11) R. F. Hudson, *Chimia (Aarau)*, **16**, 173 (1962).

(12) M. Green and R. F. Hudson, *J. Chem. Soc.*, 1055 (1962); W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **83**, 1743 (1961); J. O. Edwards and R. G. Pearson, *ibid.*, **84**, 16 (1962).

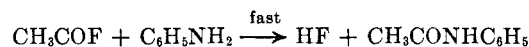
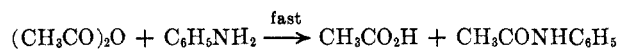
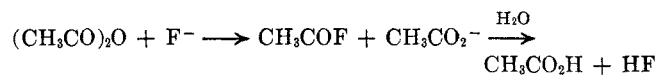
(13) C. A. Bunton and G. Schwerin, *J. Org. Chem.*, **31**, 842 (1966).

The appearance of acetic acid can be followed most conveniently by use of a pH-Stat, with disodium hydrogen phosphate as titrant. Under these conditions with this titrant there is no enhanced hydrolysis of any acetyl fluoride which may be formed as an intermediate,<sup>10</sup> so that for a possible two-stage reaction



it is the conversion of acylating agents (acetic anhydride plus acetyl fluoride) to acid which is being followed. Experiments on acetyl fluoride itself showed that it was not lost by evaporation during hydrolysis followed in a pH-Stat.

We made preliminary measurements on the rate of formation of acetic acid by adding portions of the reaction solution to an excess of aniline, which reacts rapidly with the acetylating agents as shown below, and then titrating the residual acid with dilute sodium hydroxide under nitrogen, using phenolphthalein as indicator.<sup>14</sup> This method is not particularly satisfactory for



following the fluoride ion catalyzed hydrolysis of acetic anhydride. There is a risk that the volatile acetyl fluoride would be lost during sampling, and the reaction rate is such that only the latter part of the reaction could be followed. However, this "aniline" method appears to be satisfactory for the slower fluoride ion catalyzed hydrolysis of succinic anhydride, and for hydrolyses in aqueous dioxane.

For hydrolysis followed by the "aniline" method 0.05 *M* anhydride was used, and the pH-Stat runs were carried out at pH 5.5 with 0.05 *M* acetic anhydride.

The extinction coefficient of acetic anhydride, measured in ethanol rather than water, because of the reactivity of the anhydride, is 61 at 2450 Å. At this wavelength the extinction coefficient of acetic acid is very low, and when acetyl fluoride, sufficient to give a 0.01 *M* solution, was injected into water, we observed no increase in absorbance at 0° within 5 sec, during which time there would have been little hydrolysis.<sup>10</sup> The conversion of acetic anhydride into either acetyl fluoride or acetic acid is followed spectrophotometrically, and by this method we should follow stage one of a hypothetical two-stage reaction. We used either a Cary 14 or a Gilford 220 spectrophotometer with thermostated cell compartments and added the anhydride to a cell which contained the reagents at the reaction temperature.<sup>14</sup>

All hydrolyses in aqueous dioxane were followed titrimetrically by addition of portions of the reaction mixture to aniline, and subsequent acid-base titration.

The hydrolysis of succinic anhydride was followed either spectrophotometrically, or by the "aniline" method. The integrated first-order rate constants were determined graphically.

**Aspiration Experiments.**—An amount of acetic anhydride, sufficient to give a 0.1 *M* solution, was dropped into an aqueous

(14) C. A. Bunton and S. G. Perry, *J. Chem. Soc.*, 3070 (1960); C. A. Bunton and J. H. Fendler, *J. Org. Chem.*, **30**, 1365 (1965).

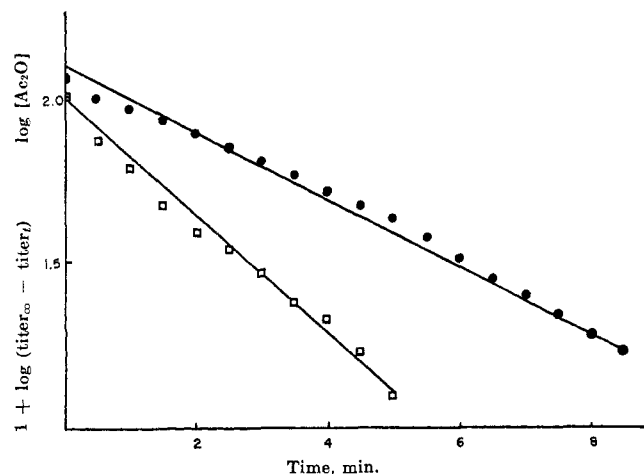


Figure 1.—Plots of  $\log (\text{titer}_\infty - \text{titer}_t)$  (solid points) and  $\log [\text{Ac}_2\text{O}]$  (open points) against time, for reaction of acetic anhydride in 0.3 *M* sodium fluoride at 0°. The straight line drawn approximately through the solid points corresponds to  $k_t = 39.0 \times 10^{-4} \text{ sec}^{-1}$ .

solution of sodium or potassium fluoride at 0° which had been saturated with nitrogen gas, and which was in a bubbler with a sintered-glass frit, so that the bubbles swept through all the solution. The bubbler was shaken, and a stream of nitrogen was passed through the solution. After complete reaction the acetic acid in the solution was titrated with dilute alkali, and from this titration value and the amount of acetic anhydride initially added we could calculate how much volatile material had been swept out. Control tests with a solution of acetic acid showed that <1% of it would have been lost in such an experiment.

The results of these experiments are in Table I. The values quoted for the amounts of reacting material swept out are not necessarily the amounts of acetyl fluoride which had been formed, and which but for the aspiration by the gas stream would have been hydrolyzed, because we do not know whether acetyl fluoride would be swept out of solution before it had time to be hydrolyzed. The uncertainties are greatest with the higher concentrations of fluoride ion, where the formation of acetyl fluoride would be fastest.

TABLE I

ASPIRATION EXPERIMENTS ON THE HYDROLYSIS OF ACETIC ANHYDRIDE<sup>a</sup>

Reagents	Anhydride, initial concn, <i>M</i>	Acid, <sup>b</sup> final concn, <i>M</i>	CH <sub>3</sub> COF lost, mole %
...	0.140	0.276	...
0.1 <i>M</i> KF	0.145	0.214	26
0.1 <i>M</i> KF	0.126	0.190	25
0.2 <i>M</i> NaF	0.135	0.202	25
0.3 <i>M</i> NaF	0.126	0.196	22
0.4 <i>M</i> NaF	0.118	0.178	25
0.5 <i>M</i> KF	0.132	0.200	24
0.5 <i>M</i> KF	0.121	0.198	18

<sup>a</sup> At 0°. <sup>b</sup> From titration after complete reaction.

In a separate experiment using 0.5 *M* potassium fluoride and 0.2 *M* acetic anhydride, the volatile material was identified qualitatively as acetyl fluoride, using a CEC cycloidal mass spectrometer. The mass spectrum had a parent peak at *M* = 62, and peaks at 63 (*P* + 1), 47 (*P* - 15), 43 (*P* - 19), and 15 (*P* - 47).

### Results

**Kinetics. Acetic Anhydride.**—In Table II we give the values of  $k_s$  determined spectrophotometrically for hydrolysis in water at 0°. Approximate values of  $k_t$ , the rate constant determined titrimetrically using a pH stat, are also given in Table II, but we note that

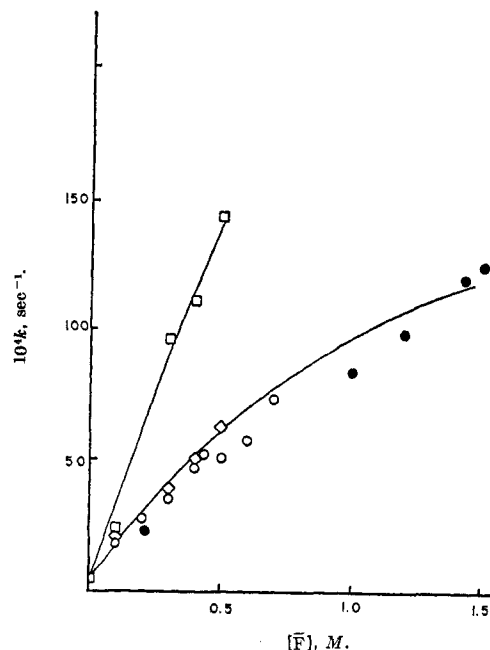


Figure 2.—Fluoride ion catalyzed hydrolysis of acetic anhydride at 0°: □, reaction in aqueous sodium fluoride followed spectrophotometrically, values of  $k_s$ ; ◇, reaction in aqueous sodium fluoride at pH 5.5 using a pH-Stat, values of  $k_t$ ; ○, reaction in aqueous sodium fluoride followed by the “aniline” method; ●, reaction in aqueous potassium fluoride followed by the “aniline” method.

TABLE II

FLUORIDE ION CATALYZED HYDROLYSIS OF ACETIC ANHYDRIDE<sup>a</sup>

[F], <i>M</i>	$10^4 k_t$ , <sup>b</sup> sec <sup>-1</sup>	$10^4 k_s$ , <sup>c</sup> sec <sup>-1</sup>	$10^4 k_t$ , <sup>d</sup> sec <sup>-1</sup>
...	...	4.6	...
0.10	21	23.6	...
0.20	31	44.8	45
0.30	39	74.5	69
0.40	51	99.1	96
0.50	63	136	125

<sup>a</sup> At 0°. <sup>b</sup> Approximate value of integrated first-order rate constant of hydrolysis determined with a pH-Stat at pH 5.5. <sup>c</sup> Determined spectrophotometrically. <sup>d</sup> Calculated first-order rate constant for disappearance of acetic anhydride at pH 5.5, determined from the rate of formation of acid and the known rate constant for hydrolysis of acetyl fluoride.

$k_t$  is not a true first-order rate constant, because intermediate builds up during reaction. In Figure 1 we show a plot of  $\log (\text{titer}_\infty - \text{titer}_t)$  for the hydrolysis followed by use of a pH-Stat (solid points). There is a significant curvature in the plot. In Figure 2 we plot  $k_s$  and the approximate values of  $k_t$  against fluoride ion concentration, and we include the values of  $k_t$  determined by the “aniline” method.

Figure 2 shows that the rate of disappearance of acetic anhydride is faster than that of appearance of acetic acid. The bending in the plot of  $k_t$  against fluoride ion concentration may be an electrolyte effect but it is probably an artefact arising from errors in  $k_t$  especially at high concentration of fluoride ion when only the “aniline” method was used to follow reaction.

In Tables III, IV, and V we give the apparent first-order rate constants ( $k_t$ ) for the hydrolysis in aqueous dioxane and in aqueous hydrofluoric acid and potassium hydrogen fluoride. They are subject to the same uncertainties as those of the values of  $k_t$  in water.

TABLE III

APPARENT FIRST-ORDER RATE CONSTANTS FOR THE FLUORIDE ION CATALYZED HYDROLYSIS OF ACETIC ANHYDRIDE IN AQUEOUS DIOXANE<sup>a</sup>

[KF], M	10 <sup>4</sup> k <sub>t</sub> , <sup>b</sup> sec <sup>-1</sup>
...	0.58 <sup>c</sup>
0.12	9.04
0.25	13.0
0.37	19.6
0.50	32.0
...	0.12 <sup>c,d</sup>
0.10	3.65 <sup>d</sup>

<sup>a</sup> At 0.0° in dioxane-water (40:60, v/v). <sup>b</sup> Determined titrimetrically. <sup>c</sup> Reference 6. <sup>d</sup> At 0° in dioxane-water (60:40, v/v).

TABLE IV

HYDROLYSIS OF ACETIC ANHYDRIDE IN AQUEOUS HYDROGEN FLUORIDE<sup>a</sup>

[HF], M	10 <sup>4</sup> k <sub>t</sub> , sec <sup>-1</sup>
...	4.60
0.08	7.32
0.17	7.80
0.32	8.03
0.49	7.97
0.82	8.70
1.28	8.62
1.98	9.08

<sup>a</sup> At 0°, apparent first-order rate constants, determined titrimetrically.

TABLE V

HYDROLYSIS OF ACETIC ANHYDRIDE IN AQUEOUS SODIUM HYDROGEN FLUORIDE<sup>a</sup>

[NaHF <sub>2</sub> ], M	10 <sup>4</sup> k <sub>t</sub> , sec <sup>-1</sup>
...	4.60
0.026	9.9
0.092	18

<sup>a</sup> At 0°, apparent first order rate constants, determined titrimetrically.

**Succinic Anhydride.**—In aqueous 0.5 M sodium fluoride the first-order rate constants are the same followed titrimetrically and spectrophotometrically, and therefore the values of *k<sub>t</sub>* have quantitative significance. Values of *k<sub>t</sub>* and *k<sub>s</sub>* are in Table VI.

TABLE VI

FLUORIDE ION CATALYZED HYDROLYSIS OF SUCCINIC ANHYDRIDE<sup>a</sup>

		In Water				
[NaF], M	...	0.50				0.66
10 <sup>5</sup> k, sec <sup>-1</sup>	34.7 <sup>b</sup>	94.0	91.0 <sup>c</sup>		119	
[HF], M	0.29	1.04				
10 <sup>5</sup> k <sub>t</sub> , sec <sup>-1</sup>	30.3	27.4				
In Dioxane-Water (40:60, v/v)						
[KF], M	...	0.11	0.12	0.25	0.48	
10 <sup>5</sup> k <sub>t</sub> , sec <sup>-1</sup>	6.75	51.0 <sup>d</sup>	257 <sup>d</sup>	25.0	42.0	67.0
In Dioxane-Water (60:40, v/v)						
[KF], M	...	0.10				
10 <sup>5</sup> k <sub>t</sub> , sec <sup>-1</sup>	1.22	11.2 <sup>d</sup>	6.78	66.0 <sup>d</sup>		

<sup>a</sup> At 0.0°. <sup>b</sup> Reference 6. <sup>c</sup> Followed spectrophotometrically; all other rate constants were determined titrimetrically. <sup>d</sup> At 25.0°.

**Catalysis by Acetate Ion.**—For comparison of solvent effects we examined the acetate ion catalyzed hydrolysis of acetic anhydride in dioxane-water (40:60, v/v; Table VII).

TABLE VII

HYDROLYSIS OF ACETIC ANHYDRIDE IN AQUEOUS DIOXANE WITH ADDED SODIUM ACETATE<sup>a</sup>

[CH <sub>3</sub> CO <sub>2</sub> <sup>-</sup> ], M	10 <sup>4</sup> k <sub>t</sub> , sec <sup>-1</sup>
...	0.58 <sup>b</sup>
0.40	2.36
0.50	2.91
	2.73 <sup>c</sup>
1.00	5.59

<sup>a</sup> At 0° in dioxane-water (40:60, v/v). <sup>b</sup> Reference 6. <sup>c</sup> CH<sub>3</sub>CO<sub>2</sub>K.

**Formation of Intermediate.**—The aspiration experiments (Table I) show that a volatile intermediate is formed equivalent to approximately one-fifth of the anhydride initially present, and can be swept out of solution during the fluoride ion catalyzed hydrolysis of acetic anhydride, and mass spectrometry confirms that the intermediate is acetyl fluoride.

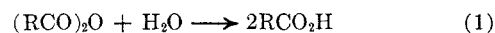
## Discussion

**Hydrolysis of Acetic Anhydride in Water.**—Fluoride ion could change the rate of hydrolysis of an anhydride in three ways: (1) it can act as an electrolyte; (2) it can act as a general base; (3) it can act as a nucleophile.

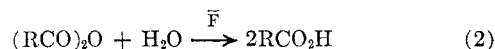
The specific electrolyte effect (1) should be very small, because in concentrations below 1 M salts of the strong acids do not have large kinetic effects upon anhydride hydrolysis. The effects depend markedly upon anion size, and anions of low charge density, *e.g.*, perchlorate, retard hydrolysis, whereas those of high charge density, *e.g.*, sulfate, assist it slightly. Chloride ion is intermediate in behavior, and retards hydrolysis slightly.<sup>15</sup>

Effects 2 and 3 could both be important. Three reactions can be occurring simultaneously.

Spontaneous hydrolysis



General base catalyzed hydrolysis



Nucleophilic-catalyzed hydrolysis



The rate of spontaneous hydrolysis is much smaller than that in the presence of fluoride ion (Table II and Figure 2), and is very much less than the rate of disappearance of acetic anhydride and its contribution will be neglected in the following treatment.

Nucleophilic catalysis is important, and acetyl fluoride builds up during reaction because (i) the rate of disappearance of acetic anhydride followed spectrophotometrically is greater than the rate of hydrolysis followed titrimetrically, and (ii) acetyl fluoride can be detected during hydrolysis.

The next question is whether the fluoride ion catalysis can be accounted for wholly by a nucleophilic catalysis

(reaction 3) or whether there is also an appreciable general base catalyzed component of hydrolysis (reaction 2).

The two-stage nucleophilic catalyzed hydrolysis of acetic anhydride (reaction 3) can be treated very simply by making certain assumptions. We neglect the minor contribution of the spontaneous hydrolysis, and assume that the titratable acidic products come wholly from hydrolysis of intermediate acetyl fluoride. There is no back reaction of acetyl fluoride with acetic acid or acetate ion in our conditions,<sup>10</sup> and therefore the relationship between the instantaneous rate of formation of acid and the standing concentration of acetyl fluoride is

$$\frac{d[\text{acid}]}{dt} = k_2[\text{CH}_3\text{COF}]$$

(By expressing concentrations as mole per cent of total reaction we allow for 1 mole of anhydride giving 2 moles of acids.)

The values of  $k_2$  for the hydrolysis of acetyl fluoride at 0° in aqueous sodium fluoride, are known<sup>10</sup> and from the slopes of plots of titratable acid concentration in mole per cent of total reaction against time, we can calculate the instantaneous concentration of acetyl fluoride. A simple computer program was used to calculate  $d[\text{acid}]/dt$  in the units of mole per cent in reciprocal seconds.

In Table VIII we give as an example the amount of hydrolysis at various times, and the values of  $d[\text{acid}]/dt$  for the reaction of acetic anhydride in 0.30 *M* aqueous sodium fluoride using a pH-Stat to determine the amount of titratable acid at various times. At 0°, in

TABLE VIII

HYDROLYSIS OF ACETIC ANHYDRIDE IN 0.3 <i>M</i> NaF						
Time, sec	Titer <sup>a</sup>	[Acid], <sup>b</sup> <i>M</i>	$d[\text{acid}]/dt$	[CH <sub>3</sub> COF], <sup>c</sup> <i>M</i>	[Ac <sub>2</sub> O], <sup>c</sup> <i>M</i>	Log [Ac <sub>2</sub> O]
0	4	0	...	0	100	2.00
30	8	7.6	0.138	21.2	71.2	1.85
60	14	13.4	0.182	28.0	58.6	1.77
90	22	20.9	0.220	33.8	45.3	1.66
120	28	27.0	0.230	35.4	37.6	1.58
150	35	33.2	0.209	32.2	34.6	1.54
180	42	39.6	0.203	31.2	29.2	1.47
210	48	45.6	0.200	30.8	23.6	1.37
240	54	51.0	0.181	27.7	21.3	1.33
270	59	56.2	0.175	26.8	17.0	1.23
300	63	61.4	0.170	26.1	12.5	1.10
∞	105	100	...	...	...	...

<sup>a</sup> In arbitrary units of chart paper. <sup>b</sup> [CH<sub>3</sub>CO<sub>2</sub>H] + [HF] expressed as per cent of total reaction, and determined by titration. <sup>c</sup> Expressed as per cent of total reaction.

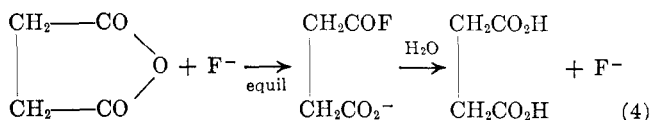
0.3 *M* aqueous sodium fluoride,  $k_2 = 6.5 \times 10^{-3} \text{ sec}^{-1}$  for the hydrolysis of acetyl fluoride.<sup>10</sup> The concentration of unreacted acetic anhydride is given by the instantaneous concentration of acetyl fluoride at time  $t$ , calculated as above, and the amount of acetic or hydrofluoric acid determined experimentally by titration using a pH-Stat and the mass balance relation

$$[\text{Ac}_2\text{O}]_t + [\text{AcOF}]_t + [\text{acid}]_t = 100$$

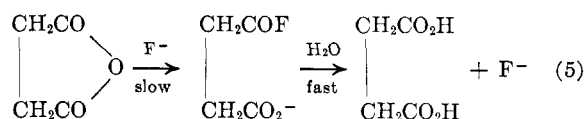
where concentrations are expressed in mole per cent of total reaction. The first-order rate constant ( $k_1$ ) for the over-all disappearance of acetic anhydride in the presence of fluoride ion can therefore be calculated from the rate of hydrolysis followed by titration, on the assumption that all the titratable acid comes from formation and subsequent hydrolysis of acetyl fluoride. If

this is the only route for formation of acid these calculated first-order rate constants ( $k_1$ ) for disappearance of acetic anhydride should agree with the  $k_s$  values for the disappearance of acetic anhydride determined spectrophotometrically. Figure 1 shows a plot of  $\log [\text{Ac}_2\text{O}]$  against time (open points) for which the values of anhydride concentration are given in Table VIII. The agreement between the two sets of rate constants (Table II) shows that most of the reaction does proceed by the formation and subsequent hydrolysis of acetyl fluoride and that a general base catalyzed hydrolysis makes no more than a minor contribution, if any, to the over-all reaction. In these experiments the formation of acid was followed only by the use of a pH-Stat, because the "aniline" method cannot be used to follow the early part of the reaction. The calculations were not made for reaction in 0.1 *M* fluoride ion where there is still an appreciable contribution owing to the spontaneous hydrolysis.

**Hydrolysis of Succinic Anhydride in Water.**—The results for the fluoride ion catalyzed hydrolysis of succinic anhydride are very simple. The rate of appearance of acid followed by titration of acid using the aniline method is the same, where tested, as the rate of disappearance of anhydride followed spectrophotometrically (Table VI) showing that an intermediate does not build up in concentration during the reaction. For succinic anhydride we cannot differentiate between the two possible modes of catalysis by fluoride ion, but if succinyl fluoride is formed by nucleophilic attack upon the anhydride it must either revert very rapidly to reactants and decompose slowly to products (eq 4), or more probably be formed slowly



and react rapidly with water (eq 5).



This second mechanism of nucleophilic catalysis (eq 5) is the more probable, because succinic is less reactive than acetic anhydride toward nucleophiles,<sup>16</sup> and the neighboring carboxyl group should make succinyl fluoride a more readily hydrolyzable compound than acetic anhydride. The slower reaction rate of succinic as compared with acetyl fluoride and the relatively small fluoride ion catalysis in aqueous solutions of fluoride ion are readily understandable in terms of a rate-limiting formation of succinyl fluoride, although our results do not exclude general base catalysis by fluoride ion.

The fluoride ion catalyzed hydrolyses of succinic anhydride can be followed at 0 and 25°, allowing calculation of approximate values of the activation energy and entropy.

For the spontaneous hydrolyses of anhydrides the entropies of activation are always very negative, ca. -35 eu,<sup>6,16,17</sup> because of the orientation of water mole-

(16) J. Koskikallio, *Ann. Acad. Sci. Fennica, Ser. A II*, **57**, 1 (1954).

(17) V. Gold, *Trans. Faraday Soc.*, **44**, 506 (1948).

cules around the transition state. They should be much less negative for attack of an anion upon an unchanged anhydride. In dioxane-water (60:40, v/v) the activation entropies and energies are  $-31$  eu and  $14$  kcal mole $^{-1}$  for the spontaneous hydrolysis,<sup>6</sup> and  $-21$  eu and  $15$  kcal $^{-1}$  for the fluoride ion catalyzed hydrolysis, and in dioxane-water (40:60, v/v) the corresponding values are for spontaneous hydrolysis  $-31$  eu and  $13$  kcal mole $^{-1}$  and for fluoride ion catalyzed hydrolysis  $-14$  eu and  $15$  kcal mole $^{-1}$ . (The entropies are calculated for  $1$  M fluoride ion at  $25^\circ$ .) These values suggest that in this system also we are observing nucleophilic rather than general base catalysis. It has recently been shown that, as would be expected, a general base catalyzed attack of water upon an acyl center has a more negative activation entropy than has nucleophilic attack by an anion upon that center.<sup>8</sup>

**Fluoride Ion Catalyzed Hydrolyses in Aqueous Dioxane.**—Addition of nonpolar organic solvents to water sharply retards the hydrolysis of carboxylic anhydrides, because it stabilizes the initial state and destabilizes the transition state,<sup>6,16,17</sup> but reaction with an anion should be less affected. The fluoride ion catalyzed hydrolyses are favored, relative to the spontaneous hydrolysis, by addition of dioxane (Tables III and VI). These observations are readily understandable in terms of any of these mechanisms, because addition of an aprotic organic solvent should increase both the basicity and the nucleophilicity of the fluoride ion by reducing the ability of the solvent to hydrogen bond to it.<sup>18</sup> As a model for a solvent effect upon a general base catalyzed hydrolysis of an anhydride, we examined the hydrolysis of acetic anhydride in dioxane-water (40:60, v/v) containing acetate ion. In this system there is no nucleophilic catalysis of hydrolysis. For  $1$  M sodium acetate there is a tenfold rate enhancement in aqueous dioxane (Table VII), but only a two-fold one in water.<sup>19</sup>

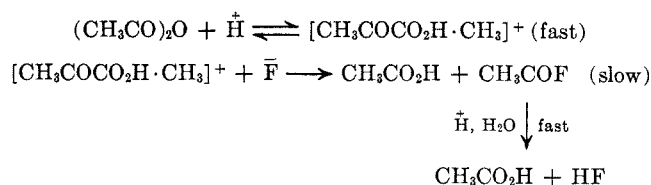
We did not examine the fluoride-catalyzed hydrolyses in aqueous dioxane spectrophotometrically, or by use of a pH stat, because of interference by the organic component of the solvent, but by analogy with the behavior of succinic anhydride in water we assume that no intermediate builds up in concentration during hydrolysis of this anhydride in aqueous dioxane.

For the fluoride ion catalyzed hydrolysis of acetic anhydride in aqueous dioxane we are unable to make any firm mechanistic assignment. The catalysis by fluoride ion is larger than in water, relative to the spontaneous hydrolysis, but this is understandable in terms of either general base or nucleophilic catalysis.

**Catalysis by Hydrogen Fluoride.**—The hydrolysis of acetic anhydride is not catalyzed strongly by mineral acids,<sup>14,20</sup> and small amounts of hydrogen fluoride increase the rate, but there is a leveling off at higher

concentrations of acid. Dilute hydrogen fluoride is a much better catalyst than would be expected in terms of its low protonating power,<sup>21</sup> and a plausible mode of catalysis is attack of fluoride ion upon the conjugate acid of acetic anhydride, followed by a rapid acid-catalyzed hydrolysis of acetyl fluoride (Scheme I).

## SCHEME I



We could not follow this reaction spectrophotometrically and so test this mechanism kinetically, but the rapid hydrolysis of acetyl fluoride in dilute acid suggests that any acetyl fluoride formed as an intermediate would have been hydrolyzed very rapidly.<sup>10</sup> Hydrofluoric acid is weak, and the leveling off of rate at high concentration could be the result of a decreasing extent of acid dissociation and protonating power.<sup>21</sup>

There is some confirmatory evidence for this proposed mechanism from the observation that hydrogen fluoride does not catalyze the hydrolysis of succinic anhydride (Table VI). Mineral acids initially retard the hydrolysis of succinic anhydride, because a negative electrolyte effect overcomes a feeble acid catalysis.<sup>22</sup> The oxygen atoms of cyclic anhydrides are weakly basic, and the relative insensitivity of succinic anhydride toward hydrofluoric acid is understandable if catalysis by it involves attack of fluoride ion upon a conjugate acid.

Sodium hydrogen fluoride will also catalyze the hydrolysis of acetic anhydride (Table V), but our results are insufficient to establish the nature of the catalysis, although there is probably nucleophilic attack by the hydrogen difluoride ion.

**Nucleophilicity of Fluoride Ion.**—From the values of  $k_s$  in Table II we calculate a value of  $2.6 \times 10^{-2}$  sec $^{-1}$  mole $^{-1}$  l. for the second-order rate constant for attack of fluoride ion upon acetic anhydride at  $0^\circ$ . For the corresponding reaction between hydroxide ion and acetate, the second-order rate constant is  $158$  sec $^{-1}$  mole $^{-1}$  l.,<sup>10</sup> showing that hydroxide ion is approximately  $6 \times 10^4$  as reactive as fluoride ion toward acetic anhydride.

**Registry No.**—Acetic anhydride, 108-24-7; succinic anhydride, 108-30-5.

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