The Hydrolysis of Carboxylic Anhydrides. V.[1,2]
The Acid Hydrolysis of Acetic and Trimethylacetic Anhydride

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Received November 10, 1964

The acid hydrolysis of trimethylacetic anhydride follows an A-2 mechanism in both water and aqueous dioxane and is slower than that of acetic anhydride. These observations suggest that the acid hydrolysis of acetic anhydride also follows an A-2 mechanism. Perchloric, sulfuric, and hydrochloric acid catalyze hydrolysis to different extents, and plots of the logarithms of the rate constants against log $[H^+]$ or H_0 are curved. No evidence was found for A-1 mechanisms.

There has been considerable uncertainty as to the mechanism of hydrolysis of acetic anhydride in aqueous acid. Gold and Hilton reported that the rate of hydrolysis in mineral acids was approximately proportional to Hammett's acidity function, H_0, rather than to hydrogen ion concentration,[3] and, using the Zucker–Hammett hypothesis as a criterion,[4a] suggested that reaction followed an A-1 mechanism,[4b] with elimination of an acylium ion (I) as the rate-limiting step,

$$(RCO)_2O + H^+ \overset{\text{fast}}{\rightleftarrows} [RCO_2H{\cdot}CO{\cdot}R]^+ \xrightarrow{\text{slow}} \underset{\text{I}}{RC^+O} + RCO_2H$$

rather than an A-2 mechanism involving nucleophilic attack of water upon the conjugate acid.

$$[RCO_2H{\cdot}CO{\cdot}R]^+ + H_2O \longrightarrow 2RCO_2H + H^+$$

The observation that hydrochloric acid catalyzed hydrolysis by virtue of its acidity, and not because of the nucleophilicity of its chloride ion, appeared to support this suggestion.[3] (Hydrogen chloride does, however, react with acetic anhydride in aprotic solvents.[5]) The entropy of activation for hydrolysis in perchloric acid was erroneously thought to be in the range associated with A-1 hydrolyses, because no allowance was made for the electrolyte effect of the perchlorate ion upon the spontaneous hydrolysis.[6]

However, there is considerable evidence that acid hydrolyses of acetic, benzoic, and acetic benzoic anhydride in aqueous dioxane, and acetic anhydride in aqueous acetone, follow A-2 mechanisms.[6,7]

Therefore either the mechanism of acid hydrolysis of acetic anhydride is different in water and aqueous organic solvents, or the experimental evidence, or its application, is suspect, and Bunnett notes that the acid hydrolysis of acetic anhydride in water shows no simple relation between rate at a given acidity and water activity,[8] suggesting that the tests based on the Zucker–Hammett hypothesis, or variants of it, may be unsatisfactory.

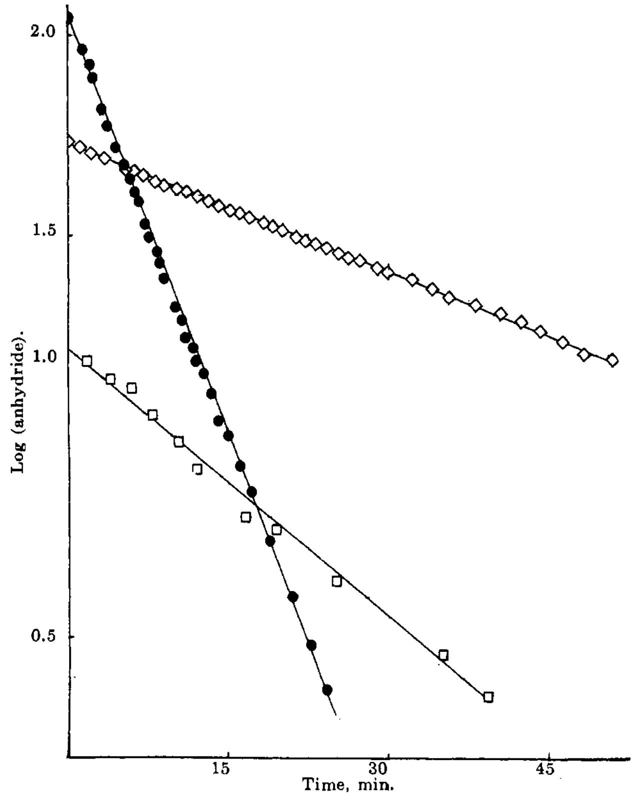

Figure 1.—Plot of log (anhydride) + constant *vs.* time: □, trimethylacetic anhydride, 2.48 *M* $HClO_4$, 25.0°, followed colorimetrically; ●, acetic anhydride, 2.43 *M* $HClO_4$, 0°, followed spectrophotometrically; ◇, acetic anhydride, neutral, 0°, followed dilatometrically.

If the acid hydrolysis of acetic anhydride follows an A-1 mechanism in water trimethylacetic anhydride should follow the same mechanism, and both anhydrides should have similar reactivities in aqueous acid. On the other hand, if A-2 mechanisms are followed, steric hindrance should make trimethylacetic anhydride the less reactive compound, as it is for the spontaneous hydrolysis, which follows a bimolecular mechanism.[9] All our evidence shows that acid hydrolysis of trimethylacetic anhydride follows an A-2 mechanism in water and aqueous dioxane, and because this anhydride is always much less reactive than acetic anhydride we concluded that both compounds follow A-2 mechanisms. Reinvestigation of the acid hydrolysis of acetic anhydride in water supports these conclusions.

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(1) Part IV: C. A. Bunton, J. H. Fendler, N. A. Fuller, S. G. Perry, and J. Rocek, *J. Chem. Soc.*, 5361 (1963).

(2) Presented in part at the Symposium on Reactions in Strong Acids, Division of Organic Chemistry, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept. 1963. (b) This work was supported in part by Grant G.P. 2889 from the National Science Foundation.

(3) V. Gold and J. Hilton, *J. Chem. Soc.*, 838, 843 (1955).

(4) (a) F. A. Long and M. A. Paul, *Chem. Rev.*, **57**, 935 (1957). (b) The usage of the terms A-1 and A-2 follows that described in ref. 4a.

(5) D. P. N. Satchell, *Quart. Rev.* (London), **17**, 160 (1963).

(6) C. A. Bunton and S. G. Perry, *J. Chem. Soc.*, 3070 (1960).

(7) J. Koskikallio, D. Pouli, and E. Whalley, *Can. J. Chem.*, **37**, 1360 (1959).

(8) J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4956 (1961), and accompanying papers.

(9) A. R. Butler and V. Gold, *J. Chem. Soc.*, 976 (1962).

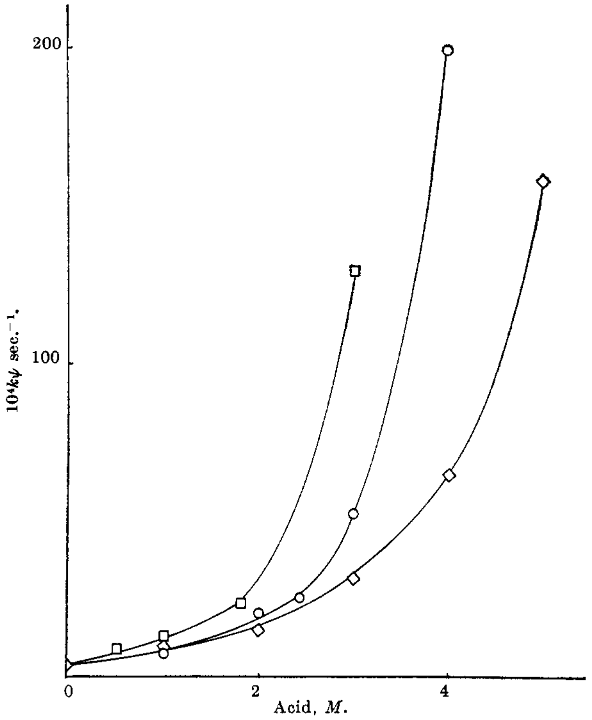

Figure 2.—Plot of k_ψ *vs.* acid concentration for acetic anhydride at 0°: ◇, HCl; □, H_2SO_4; ○, $HClO_4$.

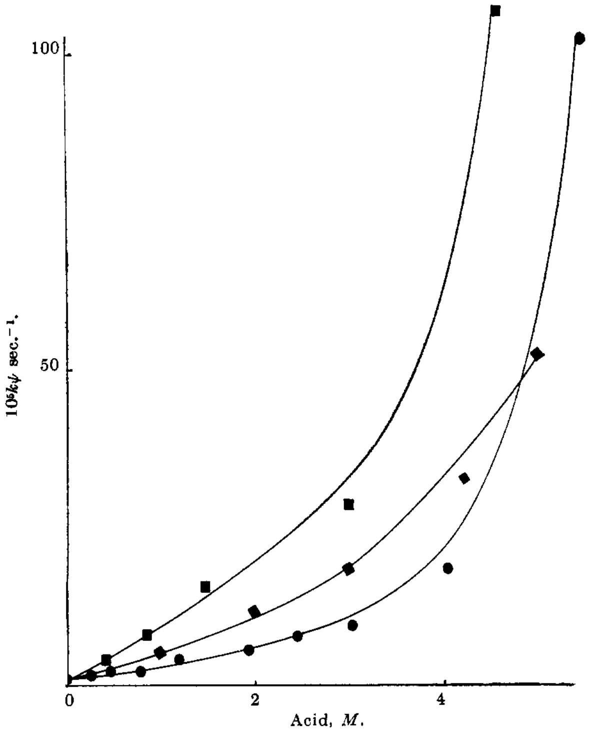

Figure 3.—Plot of k_ψ *vs.* acid concentration for trimethylacetic anhydride at 0°: ◆, HCl; ■, H_2SO_4; ●, $HClO_4$.

Experimental

Materials.—Acetic anhydride (AnalaR grade) was refluxed over magnesium turnings and then fractionally distilled, b.p. 138°. Trimethylacetic anhydride was prepared from the acid and acetic anhydride[9] and purified by fractional distillation, b.p. 66° at 10 mm. The aqueous dioxane solvent was made up from distilled water and purified dioxane.[6]

Kinetics.—Hydrolysis was generally followed spectrophotometrically or colorimetrically, although dilatometry was used to follow the spontaneous hydrolysis of acetic anhydride in water and all the hydrolyses in aqueous dioxane. Our rate constants for the spontaneous (but not the acid) hydrolyses agree with those of others,[6,9] where comparison can be made. The dilatometric method has been described.[3,6] For the colorimetric determination of anhydride concentration, the procedure of Butler and Gold was followed,[9] except that the color was allowed to develop overnight in the dark and that, for the acid hydrolyses, calcium carbonate was used to neutralize the acid. The excess calcium carbonate was removed by filtration. A Hilger Spekker colorimeter with 601 filters was used.

Hydrolysis can be followed spectrophotometrically at 240–245 mμ, where the absorption of the anhydrides is much greater than that of the acids. The cell holder of a Unicam SP 500 or Cary 14 spectrophotometer was maintained at a constant temperature by circulating water or a salt solution. The anhydride concentration was *ca.* 10^{-4} *M* for the runs followed colorimetrically or spectrophotometrically and *ca.* 0.05 *M* for those followed dilatometrically. Examples of runs are shown in Figure 1. For the colorimetric method log O.D. is plotted against time. For the spectrophotometric method log $(\mathrm{O.D.}_t - \mathrm{O.D.}_\infty)$ is plotted (O.D. is measured at 240 mμ), and for dilatometry log $(h_t - h_\infty)$ is plotted (h is the height of the liquid column).

Some of our rate constants for the acid hydrolysis of acetic anhydride differ from those of Gold and Hilton.[3] Gold and Hilton used dilatometry at low acid concentrations and a thermal maximum method at high. At intermediate acid concentrations, where $t_{1/2} \simeq 1$ min., the reaction is inconveniently slow for the thermal maximum method, and inconveniently fast for dilatometry, and the authors point out that there is uncertainty in some of their rate constants.[3]

Tracer Experiments.—Both acetic and benzoic anhydride were examined. The procedures have been described.[10] The solvent was enriched in ^{18}O, and after partial hydrolysis aniline was added, the anilide was isolated, and its ^{18}O content was determined. The results are in Table I.

TABLE I

OXYGEN EXCHANGE

Anhydride	Conditions	Temp., °C.	% reaction	Isotopic abundance (atom % excess)	
				Water	Anilide
Acetic	3 *M* aq. $HClO_4$	0	70	0.95	0.00_2
	1 *M* $HClO_4$ in aq. dioxane	0	55	1.03	0.00_1
Benzoic	1 *M* $HClO_4$ in aq. dioxane	25	65	1.03	0.00

Formation of CO.—Trimethylacetic anhydride (1 mmole) was allowed to hydrolyze in 7 ml. of degassed 3 *M* perchloric acid in an evacuated vessel. After complete hydrolysis any gas which might have been evolved was analyzed mass spectrometrically. No CO was detected, and a control experiment showed that a 0.1% yield of CO could have been detected.

Results

The first-order rate constants, k_ψ, for hydrolysis of acetic and trimethylacetic anhydride are in Tables II–IV. The rate constants for the spontaneous and acid hydrolysis follow the expected pattern, in that trimethylacetic anhydride is less reactive than acetic, and that reaction is retarded by addition of organic solvents to water.[3,7,10,11] Except for sulfates, added salts retard the spontaneous hydrolysis of trimethylacetic anhydride (Tables II and III), and the salt order is very similar to that for acetic anhydride.[12]

The rate constants, k_a, for the acid hydrolysis are obtained by subtracting those for the spontaneous hydrolysis, k_n, from the observed first-order rate constants,

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[10] C. A. Bunton, N. A. Fuller, S. G. Perry, and V. J. Shiner, *J. Am. Chem. Soc.*, 2918 (1963).

[11] V. Gold, *Trans. Faraday Soc.*, **44**, 506 (1948); J. Koskikallio, *Ann. Acad. Sci. Fennicae, Ser. A II*, **67**, 1 (1954).

[12] C. A. Bunton, N. A. Fuller, S. G. Perry, and I. Pitman, *J. Chem. Soc.*, 4478 (1962).

TABLE II

HYDROLYSIS OF ACETIC ANHYDRIDE IN AQUEOUS ACIDS AND SALTS

		HCl, M				
		1.00	2.00	3.00	4.00	5.00
10^4k_ψ, sec.$^{-1}$						
0°	4.70	9.96	15.6	31.4	64.0	157
25.0°	26.6	110	234	...	...	...
$4 + \log k_a + H_0{}^a$		0.53	0.35	0.37	0.37	0.42

	HClO$_4$, M					H$_2$SO$_4$, M			
	1.00	2.00	2.43	3.00	4.00	0.50	1.00	1.81	3.00
10^4k_ψ, sec.$^{-1}$									
0°	8.43	20.1	25.6	52.7	119	9.36	17.3	28.6	134
25.0°	114	285	...	...	...	...	173	406	...
$4 + \log k_a + H_0{}^a$	0.33	0.41	0.35	0.45	0.57	0.81	0.84	0.63	0.73

	[NaCl] + [HCl] = 3.0 M				[NaCl] + [HCl] = 4.0 M			
[Acid,], M	...	1.00	2.00	3.00	1.00	2.00	3.00	4.00
10^4k_ψ, sec.$^{-1\,a}$	2.02, 14.9^b	8.81	17.8	31.4	11.4	21.6	38.8	64.0
$4 + \log k_a + H_0{}^a$	...	0.23	0.31	0.32	0.20	0.22	0.23	0.40

	[NaClO$_4$] + [HClO$_4$] = 3.0 M				[NaClO$_4$] + [HClO$_4$] = 4.0 M			
[Acid], M	...	1.00	2.00	3.00	...	1.00	2.00	4.00
10^4k_ψ, sec.$^{-1a}$	0.88, 4.2^b	10.5	27.4	52.7	0.48	14.8	37.1	199
$4 + \log k_a + H_0{}^a$		0.38	0.45	0.48	...	0.37	0.40	0.58

^{a} At 0°. ^{b} At 25.0°.

TABLE III

HYDROLYSIS OF TRIMETHYLACETIC ANHYDRIDE IN AQUEOUS ACIDS AND SALTS

		NaClO$_4$, M			NaCl, M			Na$_2$SO$_4$, M		NaHSO$_4$, M
		0.49	1.21	2.43	1.00	2.00	3.00	1.00	2.00	1.00
10^5k_ψ, sec.$^{-1}$										
0°	0.62	0.41	0.24	0.11	...	...	...	...	...	...
25.0°	7.95	4.95	3.30	1.20	5.12	4.15	...	19.9	21.6	39.5
68.0°	...	...	...	...	207	170	130	...	...	...

	HClO$_4$, M								
	0.24	0.48	0.80	1.22	1.94	2.43	3.04	4.06	4.87
10^5k_ψ, sec.$^{-1}$									
0°	1.66	2.27	2.56	4.10	5.23	7.42	9.43	17.7	92.5
25.0°	...	18.6	...	46.3	...	86.0	...	...	...
$6 + \log k_a + H_0{}^a$	1.57	1.44	1.20	1.16	0.89	0.86	0.68	0.49	0.75

	HCl, M					H$_2$SO$_4$, M						
	1.00	2.00	3.00	4.00	5.00	0 45	0.91	1.00	1.50	2.00	3.00	4.55
10^5k_ψ, sec.$^{-1}$												
0°	5.38	11.9	18.8	30.9	52.7	3.98	8.05	...	16.0	...	28.8	107
25.0°	52.1	119	233	...	...	...	...	99.0	...	241	313	...
$6 + \log k_a + H_0{}^a$	1.47	1.37	1.20	1.07	0.95	1.69	1.75	...	1.54	...	1.05	0.92

^{a} at 0°.

k_ψ. The constants, k_ψ, are plotted against acid concentration in Figures 2 and 3 for both anhydride. The different catalytic powers of the acids are evident, and the rate constants do not follow Hammett's acidity function, as can be seen from the tabulations of $\log k_a + H_0$[13] in Tables II and III. Although plots of $\log k_a$ against $-H_0$ are approximately linear, of slopes 0.7–0.9, they differ for the various acids, sulfuric being the most effective catalyst.

Added sodium perchlorate or chloride speed the acid hydrolysis of acetic anhydride (Table II and ref. 6) as expected, because they also increase the protonating power of the acids.[13a]

These acid hydrolyses fit neither of the limiting forms of the Zucker–Hammett hypotheses,[4a] nor Bunnett's proposed relation of rate to water activity, as he had concluded from inspection of the earlier results.[8] Plots of $\log k_a + H_0$ against $-\log a_{H_2O}$ are curved and differ for the various acids, and some of them show a minimum (Figure 4). The application of his more recent treatment is shown in Figure 5. For many reactions of weakly basic substrates plots of $\log k_a + H_0$ against $\log [H]^+ + H_0$ are linear,[14] and it is suggested that their slopes Φ multiplied by 4.5 give a parameter w^*, which has a significance similar to that of the earlier w-values, which gave an estimate of the dependence of rate on water activity.[8] The plots are not linear (Figure 5) and depend upon the nature of the catalyzing acid. Bunnett's treatments rely upon the assumption that the activity coefficients of the initial and transition states, and of the Hammett indicator and its conjugate acid, depend largely upon the changes in hydration in the reactions considered. This assumption appears to break down for the acid hydrolysis of carboxylic anhydrides in water, and we suggest that the failure of these relations between acidity and reaction rate is caused at least in part by the specific effects of

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(13) The values of H_0 are taken from Paul and Long's review[13a] and, for mixtures of acids and salts, are interpolated. For the acid concentrations used, these values of H_0 agree with the more recent values.[13b] They differ from the values used by Gold and Hilton.[3] (a) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957); (b) M. J. Jorgenson and D. R. Hartter, *J. Am. Chem. Soc.*, **85**, 878 (1963).

(14) A variant of this treatment can be applied to basic substrates: see J. F. Bunnett, ref. 2a.

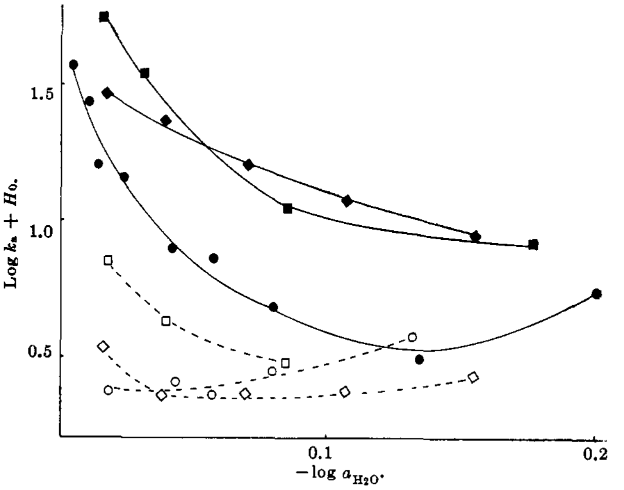

Figure 4.—Plot of log $k_a + H_0$ + constant *vs.* $-\log a_{H_2O}$: trimethylacetic anhydride, ◆—◆, HCl; ■—■, H_2SO_4; ●—● $HClO_4$; acetic anhydride, ◇----◇, HCl; □----□, H_2SO_4; ○----○, $HClO_4$.

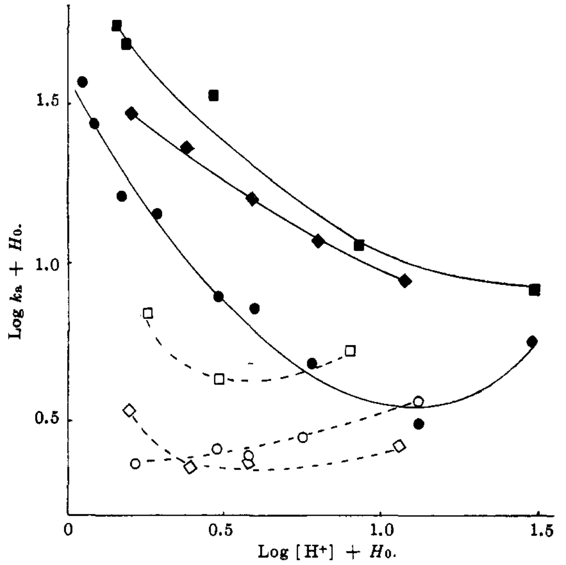

Figure 5.—Plot of log $k_a + H_0$ + constant *vs.* log $[H^+] + H_0$: trimethylacetic anhydride, ◆—◆, HCl; ■—■, H_2SO_4; ●—●, $HClO_4$; acetic anhydride, ◇----◇, HCl; □----□, H_2SO_4; ○----○, $HClO_4$.

the anions of mineral acids upon the initial state.[12] If acids have differential, specific effects upon the activity coefficients of the initial and transition states, perchloric acid, which should decrease the activity coefficient of the initial state,[12] could be a less effective catalyst than hydrochloric or sulfuric acid, although it is not a weaker acid.

A few experiments were done on the acid hydrolysis of trimethylacetic anhydride in dioxane–water (60:40 v./v.), where acid hydrolysis is slower, but more important relative to the spontaneous hydrolysis than in water (Table III and IV); acetic anhydride behaves similarly.[6] The rate constant for hydrolysis of trimethylacetic anhydride in aqueous dioxane increases more rapidly than acid concentration, but more slowly than protonating power as measured by Hammett's acidity function[13a]; acetic anhydride behaves similarly.[6]

TABLE IV

HYDROLYSIS OF TRIMETHYLACETIC ANHYDRIDE IN DIOXANE–WATER

(60:40 v./v. at 25°)

	$HClO_4$, *M*			
	...	0.18	0.24	1.21
10^6k_ψ, sec.$^{-1}$	2.95, 37.9[a]	12.6, 31.5,[b] 28.5[b]	23.6	15.5,[c] 149

[a] 60.5°. [b] H_2SO_4. [c] 0°.

TABLE V

ENERGIES AND ENTROPIES OF ACTIVATION FOR SPONTANEOUS AND ACID-CATALYZED HYDROLYSIS

Solvent	Reagent	*E*, kcal. mole^{-1}	ΔS^*, e.u.
	Acetic Anhydride		
H_2O	...	11[a]	−35[a]
H_2O	2 *M* HCl	18.5	− 8
H_2O	2 *M* $HClO_4$	17.5	−10
H_2O	1.8 *M* H_2SO_4	18	− 8.5
Aq. dioxane	...	11[a]	−43[a]
Aq. dioxane	1 *M* $HClO_4$	16.5[b]	−16[b]
	Trimethylacetic Anhydride		
H_2O	...	16.5	−24
H_2O	2 *M* HCl	15	−26
H_2O	3 *M* HCl	16.5	−20.5
H_2O	2.4 *M* $HClO_4$	15.5	−23
H_2O	3 *M* H_2SO_4	16	−20.5
Aq. dioxane	...	14	−43
Aq. dioxane	1.2 *M* $HClO_4$	14.5	−25

[a] See ref. 10. [b] See ref. 6.

The entropies and energies of activation for hydrolysis in water and dioxane–water (60:40 v./v.) are in Table V. The spontaneous hydrolysis makes an appreciable contribution to the over-all reaction in water, but not in aqueous dioxane, but in allowing for it we must consider that many electrolytes markedly reduce the rate of the spontaneous reaction in water.[12] Therefore, in calculating the entropies and energies of activation for the hydrolysis in aqueous acid, we use a rate constant obtained by deducting the rate constant for hydrolysis in the presence of the sodium salt from that for the over-all reaction in aqueous acid. The rate constants in the salt solution were, if necessary, extrapolated from values at other temperatures or salt concentrations (Tables II–IV and ref. 12). (The correction depends on the assumption that sodium and hydronium ions have similar salt effects upon the spontaneous hydrolysis. It was not applied to hydrolyses in aqueous dioxane, where the contribution of the spontaneous hydrolysis is small, or to hydrolyses catalyzed by sulfuric acid, because sulfates do not retard hydrolysis, and sulfuric acid is a very effective catalyst.) Relatively high acid concentrations (≥ 2 *M*) were used, so that the contribution of the spontaneous hydrolysis is small; however, because of these uncertainties the entropies and energies of activation are given in Table V to the nearest 0.5 e.u. and 0.5 kcal. mole^{-1}, respectively. They are calculated using 1 *M* acid at 25° as the standard state. The entropies of activation are in the range usually associated with A-2 reactions[15] and are similar to those found for the A-2 hydrolysis of acetic anhydride in aqueous dioxane[6] or aqueous acetone.[7]

The energies and entropies of activation for the spontaneous hydrolysis of trimethylacetic anhydride, Table V, are similar to those found for other anhy-

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(15) F. A. Long, J. G. Pritchard, and F. S. Stafford, *J. Am. Chem. Soc.*, **79**, 2362 (1957).

drides; in particular the entropy of activation is highly negative, and the energy relatively small.[10,11]

In the hope of finding further mechanistic evidence we attempted to detect the formation of carbon monoxide during the acid hydrolysis of trimethylacetic anhydride, and oxygen exchange during the acid hydrolysis of acetic anhydride. If the acid hydrolysis of trimethylacetic anhydride followed an A-1 mechanism, an intermediate acylium ion might generate carbon monoxide[16a,b] before capture by a water molecule.

$$\mathrm{Me_3C{-}^{+}CO \longrightarrow Me_3C^{+} + CO}$$

No carbon monoxide was detected (Experimental), but this observation does not prove that the acylium ion was not a reaction intermediate, because in water it might not survive long enough to decompose to carbon monoxide.

Similarly the absence of oxygen exchange between water and acetic or benzoic anhydride during acid hydrolysis (Table I) does not disprove a bimolecular mechanism of hydrolysis, because for many compounds attack upon a carbonyl carbon atom is not accompanied by oxygen exchange[17]; *e.g.*, although the acid hydrolysis of benzoic anhydride follows an A-2 mechanism, there is no oxygen exchange (Table I).

Discussion

Structural Effects and Kinetic Form of Hydrolysis.—Because hydrolysis of trimethylacetic anhydride is slower than that of acetic, in both water and aqueous dioxane, and in the presence or absence of acid, it is probable that all these reactions involve bimolecular attack of a water molecule upon the anhydride, or its conjugate acid, because the methyl groups should sterically, and might inductively, hinder an incoming nucleophile.[9,18] In all conditions the relative rates of hydrolysis of acetic and trimethylacetic anhydride are typical of nucleophile attack upon a carbonyl group.[9,18]

The failure of the relations between reaction rate and acidity may arise because at low acid concentrations there is an appreciable contribution of the spontaneous hydrolysis, but this effect should be unimportant at the higher acidities. Therefore, the anion must be having a specific effect upon the rate of the acid and the spontaneous[12] hydrolysis.

Perchlorates retard the spontaneous hydrolyses of acetic and trimethylacetic anhydride, chlorides retard them slightly, and sulfates speed them (Table III and ref. 12), and part of the retarding effect of perchlorate salts is caused by a decrease in the activity coefficient of the anhydride.[12] Separation of the electrolyte effects upon the initial and transition states of the spontaneous hydrolysis of acetic anhydride shows that perchlorates stabilize the initial state (decrease f_s), whereas chlorides and sulfates destabilize it (increase f_s), but that all the salts destabilize the transition state (increase f_*). This destabilization of the transition state may be caused by the decrease of the water activity by electrolytes.[12]

The Brønsted–Bjerrum rate equation (1) for an A-2 hydrolysis has the form

$$k = k_0 a_{\mathrm{H^+}} a_{\mathrm{H_2O}}{}^{n} (f_s/f_*) \tag{1}$$

It is not obvious what value should be assigned to n, the formal order with respect to water. On Ingold's definition of molecularity, n should equal 1,[19] because only one water molecule is necessarily undergoing covalency change as a nucleophile in forming the transition state, but others are probably involved in kinetically significant proton transfers[8,14,20] or are hydrogen bonded to acidic sites in the transition state.[21]

All the terms in the rate equation (1) depend upon the anion of the acid, but we can usefully compare sulfuric and perchloric acids in moderate concentration, because they show similar variations of water activity[22] and protonating power[13a] (as measured by $-H_0$), but differ in that perchlorate ion markedly decreases the activity coefficient of acetic anhydride.[12] We therefore believe that the catalytic inefficiency of perchloric acid, relative to sulfuric, arises at least in part from the decrease of the activity coefficient of the initial state. To this extent anhydrides behave differently from most other organic substrates, because for most acid hydrolyses rate can be related to acid concentration or protonating power and water activity, irrespective of the anion of the catalyzing acid.[4a,8]

The problem of disentangling the roles of the proton and the water molecules is compounded by the fact that acid concentration, Hammett's acidity function, and the activity of water, are not independent variables,[23] and the activity coefficients of nonelectrolytes, *e.g.*, the substrate, or Hammett bases, should also depend upon electrolyte concentration,[24] as does the water activity.[22]

These specific effects of acids could depend not only upon the mechanism of the reaction and the general chemical nature of the substrate, but also upon the substituent groups; *e.g.*, for the hydrolysis of acetic anhydride the catalytic power of the acids is $[\mathrm{HX}] < 1.5\ M$, $\mathrm{H_2SO_4 > HCl > HClO_4}$, and $[\mathrm{HX}] > 1.5\ M$, $\mathrm{H_2SO_4 > HClO_4 > HCl}$ but for trimethylacetic anhydride it is at all acid concentrations $\mathrm{H_2SO_4 > HCl > HClO_4}$. The use of the Zucker–Hammett hypothesis[4a] or Bunnett's modifications of it[8,14] as mechanistic tests is seriously complicated by these effects, because for any given reaction it is difficult to decide whether relations between rate and acidity arise from the molecularity of the reaction or from specific effects of the acids upon the ratio of the activity coefficients of the initial and transition states (*cf.* ref. 25); *e.g.*, the hydrolysis of the conjugate acid of N-acetylimidazole also shows striking, specific salt

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(16) (a) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 311; (b) G. A. Olah, W. S. Tolgyesi, S. J. Kuhn, M. E. Moffat, I. Bastien, and E. B. Baker, *J. Am. Chem. Soc.*, **85**, 1328 (1963).

(17) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960); M. L. Bender, H. Matsui, R. J. Thomas, and S. W. Tobey, *J. Am. Chem. Soc.*, **83**, 4193 (1961); C. A. Bunton and D. N. Spatcher, *J. Chem. Soc.*, 1079 (1956).

(18) J. N. E. Day and C. K. Ingold, *Trans. Faraday Soc.*, **37**, 686 (1941).

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effects,[26] which are similar to those found for anhydride hydrolysis. In this specific system the electrolyte effect of acids, as distinct from their protonating power, could be investigated, and it was shown that both acids and their salts had specific effects, which depend upon the anion more than on the cation, as for anhydride hydrolysis.[12] Electrolytes also retard (and bases catalyze) the hydrolysis of conjugate acids of imidates,[27] although the system has not been studied so extensively as the hydrolysis of N-acetylimidazole.

We attempted to allow for the specific effect of the anion by using mixtures of the acid and its sodium salt. In doing so we inevitably introduce the differential salt effects of the sodium and hydronium ions, although it is the anion which plays the greater role in determining the salt effect in anhydride hydrolysis and in similar reactions. Mineral acids, except in high concentration, retard the hydrolysis of succinic and tetramethylsuccinic anhydride,[28] because their retardation of the spontaneous hydrolysis outweighs their catalytic power. However, they are catalysts, at all concentrations, provided that the electrolyte concentration is maintained by addition of their sodium or lithium salts. Somewhat similarly with acetic anhydride the rate of hydrolysis increases smoothly with increasing acid concentration if the electrolyte concentration is maintained by addition of the sodium salt. The values of log $k_a + H_0$ for the acid salt mixtures are similar to those for the acids, (Table II), suggesting that at least for acetic anhydride there is a relation between rate of hydrolyis and protonating power of the acid, provided that allowance can be made for the specific electrolyte effect of the anion.

Except at high concentration hydrochloric acid is a better catalyst than perchloric for hydrolysis of trimethylacetic but not acetic anhydride (Figure 3). The effectiveness of hydrochloric acid is almost certainly not caused by the nucleophilicity of the chloride ion,[3,5] because a mixture of perchloric acid and sodium perchlorate is a better catalyst than the corresponding mixture of hydrochloric acid and sodium chloride; in any event sulfuric acid is more effective than the other acids, and it is hard to believe that the hydrogen sulfate ion is a strong nucleophile toward a carbonyl carbon atom. Hydrochloric acid is weaker than sulfuric or perchloric acids at higher molarities.[13a]

There are sharp differences in the Arrhenius parameters for the acid and spontaneous hydrolyses of acetic and trimethylacetic anhydride. In initially neutral water the activation energy for the spontaneous hydrolysis of trimethylacetic in 5 kcal. mole^{-1} greater than that for acetic anhydride, but the effect of the larger activation energy is partially offset by a less negative entropy of activation. The transition state for the spontaneous hydrolysis of acetic anhydride is heavily solvated by water, and thereby stabilized, and the reaction has a low activation energy (*ca.* 11 kcal. mole^{-1}) and a large negative entropy of activation (*ca.* -35 e.u.). The methyl substituents in trimethylacetic anhydride should interfere with the incoming nucleophilic water molecule, as well as the solvating water molecules, and therefore the activation energy is larger and the entropy of activation less negative than for acetic anhydride (Table V). Addition of an organic solvent, *e.g.*, dioxane, retards reaction, because it should stabilize the initial state and decrease the solvation of the transition state. With a decrease in the water content of the solvent, solvation of the transition state by water molecules should provide less driving force for reaction, and steric hindrance to solvation should also become less important; the entropies of activation for the spontaneous hydrolysis of both anhydrides are very similar in aqueous dioxane, and the rate difference is then caused largely by the difference in activation energies.

It is difficult to assign precise significance to the energies and entropies of activation for the acid hydrolyses, because they depend upon the catalyzing acid. However, the energy of activation is greater and the entropy of activation less negative for acetic than for trimethylacetic anhydride. Solvent changes affect the acid hydrolyses of these two anhydrides similarly, in that addition of dioxane to the water makes the entropy of activation more negative (Table V). (The entropy of activation of acid hydrolysis is, however, much less negative than for the spontaneous hydrolysis.)

The entropies of activation are in the general range associated with A-2 reactions, and because protonation provides much of the driving force of the reaction solvation is probably of less importance than in the spontaneous hydrolysis and should play a correspondingly lesser role in determining the entropy of activation; structural factors should become more important. The decrease of rate of saponification of aliphatic esters with increasing alkylation is caused by a decrease in the entropy of activation rather than an increase in the enthalpy of activation,[29] and Humphreys and Hammett note that the rates of acid hydrolysis of these esters and the dissociation constants of the acids also depend upon entropy rather than enthalpy differences. In these reactions attack of the nucleophile and solvation of the ion which is formed reduce the freedom of movement of the alkyl substituent. This factor is probably also important in the acid hydrolyses of these anhydrides, where alkylation reduces reaction rate by making the entropy of activation more negative, but it must be relatively unimportant for the spontaneous hydrolysis.

Although our evidence suggests that the acid hydrolysis of acetic anhydride in water is not an A-1 reaction, the relatively high slopes of plots of log k_a against $-H_0$ and the values of the entropies of activation suggest that the incoming water molecule is not tightly bound in the transition state. Assuming that it is useful to attempt to differentiate between A-1 and A-2 classifications of hydrolysis of esters and related compounds, we should expect the A-2 classification to include a spectrum of mechanism varying from those in which the water molecule is not deeply involved in the transition state, *e.g.*, the acid hydrolysis of acetic anhydride in water, to those in which it is deeply involved, *e.g.*, the acid hydrolyses of the less reactive

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anhydrides,[6] and the entropies of activation would become correspondingly more negative. An alternative possibility is that these variations in kinetic form of the acid hydrolysis and in the entropy of activation arise not from the extent of nucleophilic involvement of the incoming water molecule, but upon the necessity of one or more water molecules being oriented around the transition state, so that they can transfer a proton from one oxygen atom to another and so assist making of a new or breaking of an existing bond.[20] Thus, if breaking of the existing carbon-oxygen bond were less important in forming the transition state for acetic than for trimethylacetic anhydride, we should except fewer water molecules to be involved in the transition state. The entropy of activation should then be less negative, and, as noted by Bunnett, the w-values should be smaller[8] and reaction rate increase more sharply with increasing acidity.

The Hydrolysis of Carboxylic Ortho Esters

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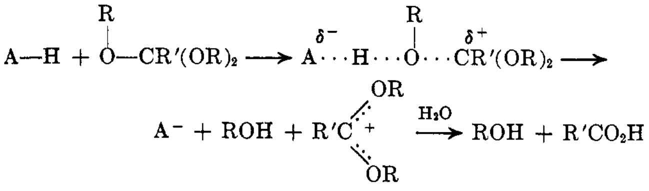
Received October 26, 1964

Estimates of the probable basicities of carboxylic ortho esters suggest that their conjugate acids are not reactive intermediates in their hydrogen ion catalyzed hydrolyses, but that proton transfer to oxygen is involved in the rate-limiting step. The proposed mechanism accords with the relative insensitivity of rate to α-substituents.

In developing his theory of proton acids and bases Brønsted[1] pointed out that general acids, *i.e.* acids other than the solvated hydrogen ion, should be able to catalyze reactions. Both the solvated hydrogen ion and general acids can transfer protons to bases in equilibria, and therefore should be able to transfer protons to basic sites in the transition state of a reaction. Hydrolyses of aliphatic ortho esters were the first general acid catalyzed reactions to be found; although the hydrolysis of ethyl orthoformate is catalyzed specifically by hydronium ions in water,[2] it is catalyzed by both hydronium ion and general acids in aqueous dioxane,[3] and the hydrolysis of most of the other ortho esters is general acid catalyzed even in water.[2]

The general acid catalyzed hydrolysis of an ortho ester could involve a slow proton transfer from the weak acid to an oxygen atom of the ortho ester, concerted with or followed by carbon-oxygen bond cleavage, or a slow carbon-oxygen bond cleavage of a hydrogen-bonded complex of the acid and ester.[4] Both of these mechanisms lead to identical rate laws, and both may be considered examples of bimolecular electrophilic displacements (SE2) upon oxygen, giving dialkoxycarbonium ion intermediates (I). We exclude nucleophilic attack by the conjugate base of the acid upon the conjugate acid of the ortho ester as a possible mechanism, because it is inconsistent with observed structural effects in either the catalyst or the substrate upon reactivity.



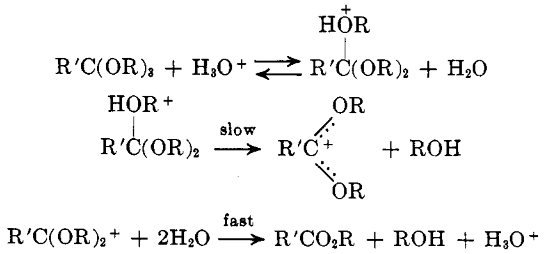
$$A{-}H + \overset{R}{\overset{|}{O}}{-}CR'(OR)_2 \longrightarrow \overset{\delta^-}{A\cdots H}\cdots\overset{R}{\overset{|}{O}}\cdots\overset{\delta^+}{CR'(OR)_2} \longrightarrow$$
$$A^- + ROH + R'C^+(OR)_2 \xrightarrow{H_2O} ROH + R'CO_2H$$

I

Conversion of I to products must be fast, because for both proton and general acid catalyzed reaction there is no evidence for its accumulation in aqueous solution: the reaction can be followed either dilatometrically,[2] *i.e.*, by following a bulk property of the solution, or by following the formation of the carboxylate ester spectrophotometrically,[5a] and the rates of disappearance of methyl orthobenzoate and appearance of methyl benzoate, followed by n.m.r. spectroscopy, are identical.[5b]

Hydrogen ion catalyzed ortho ester hydrolysis almost certainly involves reactive dialkoxycarbonium ion intermediates. Ortho esters are known to form stable dialkoxycarbonium salts,[6] and Fullington and Cordes recently produced convincing evidence for a cationic intermediate by an intervention experiment using hydroxylamine as the trapping agent.[7]

If the usual assumption is made that proton transfer from hydronium ion to an oxygen atom of a substrate cannot be the rate-limiting step of an acid hydrolysis,[8] the most reasonable mechanism of formation of the dialkoxycarbonium ion intermediate is the A-1 mechanism of Winstein and Buckles.[9]



$$R'C(OR)_3 + H_3O^+ \rightleftarrows R'\overset{\overset{+}{HOR}}{\overset{|}{C}}(OR)_2 + H_2O$$
$$R'\overset{HOR^+}{\overset{|}{C}}(OR)_2 \xrightarrow{\text{slow}} R'C^+(OR)_2 + ROH$$
$$R'C(OR)_2^+ + 2H_2O \xrightarrow{\text{fast}} R'CO_2R + ROH + H_3O^+$$

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