613. *The Acid-catalysed Hydrolysis of Carboxylic Anhydrides.*

By C. A. Bunton and S. G. Perry.

The rates of hydrolysis of five carboxylic anhydrides have been measured, and the positions of bond fission of two unsymmetrical anhydrides determined by use of ^{18}O.

Hydrolyses of acetic, of acetic benzoic, and of benzoic anhydride in aqueous dioxan containing perchloric acid are by the *A*-2 mechanism, and of acetic mesitoic and of mesitoic anhydrides predominantly by the *A*-1 mechanism. Because the hydrolysis of acetic anhydride in aqueous acid is by the *A*-1 mechanism there appears to be a mechanistic change with changing solvent.

The application of the Zucker–Hammett hypothesis to these problems is discussed.

Hydrolysis of open-chain carboxylic anhydrides is less sensitive to mineral acids than is that of carboxylic esters and amides. Early work did not clearly establish acid-catalysis,[1] although it has long been known that many acetylations by acetic anhydride are catalysed by sulphuric acid.[2] Acid-catalysis of the hydrolysis was proved by Kilpatrick.[3] Acid-hydrolysis of acetic anhydride in water is h_0-dependent, and acetyl chloride is not an intermediate when hydrochloric acid is the catalyst;[4] it is, however, an intermediate in acetylations by acetic anhydride in acetic acid containing hydrogen chloride.[5]

Our work was a kinetic study of the hydrolyses of several carboxylic anhydrides in aqueous dioxan (and where solubility permitted in water) together with a determination of the positions of bond fission for hydrolyses of some unsymmetrical anhydrides.

Results.

Kinetics.—The rates of hydrolysis of several anhydrides in aqueous dioxan, with added perchloric acid, have been measured. The range of acid concentration was sufficient for h_0 to diverge appreciably from the stoicheiometric acidity. The ionic strength of the reacting solutions was varied by addition of lithium perchlorate. The temperature coefficients of these hydrolyses, and of that of acetic anhydride in water, were measured. The values of H_0 in aqueous dioxan–perchloric acid are known.[6] Those for this system with added salts were determined in related work.[7] In all experiments the anhydride concentration was *ca.* 0·08M. The first-order rate coefficients, k_1, are tabulated, together with k_1^A, the first-order rate coefficient for the acid-catalysed component of hydrolysis: $k_1^A = k_1(\text{overall}) - k_1(\text{neutral})$. In most experiments the correction for the neutral rate is small.

The kinetic data are tabulated in Table 1—5; the last two lines of each table show the variations of rate with acidity. Figs. 1 and 2 illustrate these variations for similar hydrolyses of acetic and acetic benzoic anhydride. Table 6 summarises the results.

Bond Fission.—These experiments were done by isolating the less soluble acid formed by hydrolysis of a mixed anhydride in a solvent containing water enriched in ^{18}O. The bond fission is calculated (see Table 7) on the assumption that attack by a water molecule upon either acyl carbon atom would introduce one labelled oxygen atom into the acid product, which would therefore be 50% enriched. This is not strictly correct, because anhydrides may exchange their carbonyl-oxygen atoms with those of water during acid-hydrolysis. However, the extent of this exchange is small for hydrolysis of benzoic anhydride in initially neutral aqueous dioxan.[8]

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[1] Rivett and Sidgwick, *J.*, 1910, **97**, 1677; Wilsdon and Sidgwick, *J.*, 1913, **103**, 1959; Szabo, *Z. phys. Chem.*, 1922, **122**, 405; Olivier and Berger, *Rec. Trav. chim.*, 1927, **46**, 609.

[2] Burton and Praill, *Quart. Rev.*, 1952, **6**, 302.

[3] Kilpatrick, *J. Amer. Chem. Soc.*, 1928, **50**, 2891; 1930, **52**, 1410.

[4] Gold and Hilton, *J.*, 1955, 838, 843.

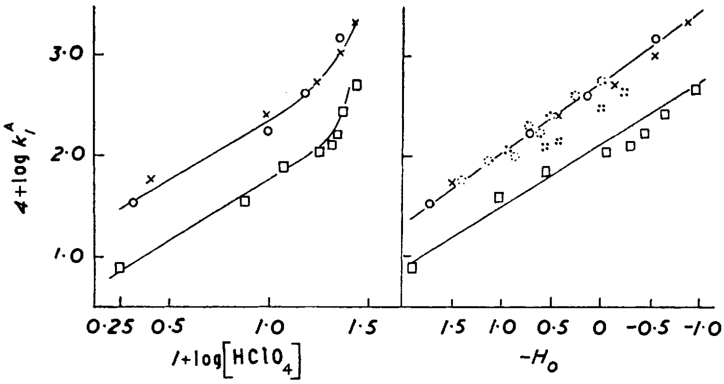
[5] Satchell, *Chem. and Ind.*, 1958, 1442.

[6] Bunton, Ley, Rhind-Tutt, and Vernon, *J.*, 1957, 2327.

[7] Perry, Thesis, London, 1958.

[8] Bunton, Lewis, and Llewellyn, *Chem. and Ind.*, 1954, 1154.

FIG. 1. FIG. 2.



Variation of rate of hydrolysis of acetic and acetic benzoic anhydride with concentration of acid in aqueous dioxan at 0°.

Acetic anhydride: ×, dioxan–water, 40 : 60 (v/v)
⁙, ,, ,, ,, with lithium perchlorate added
○, dioxan–water, 60 : 40 (v/v)
◌, ,, ,, ,, with lithium perchlorate added
Acetic benzoic anhydride: □, dioxan–water, 60 : 40 (v/v)

TABLE 1. *Acetic anhydride.*

(a) *Dioxan–water* 60 : 40 (v/v).

Temp.	0°				13·26°	25·08°	
[HClO$_4$] (M)	0·26	1·02	1·55	2·28	1·00	0·26	0·99
10^2k_1 (min.$^{-1}$)	0·41	1·85	4·23	15·2	7·36	4·37	2·31
$4 + \log k_1^A$	1·53	2·25	2·62	3·18	—	2·60	3·36
H_0	1·73	0·71	0·15	—0·54	—	1·73	0·76
$4 + \log k_1^A + H_0$	3·26	2·96	2·77	2·64	—	4·39	4·12
$4 + \log k_1^A - \log\,[\text{HClO}_4]$	2·22	2·24	2·43	2·72	—	3·19	3·36

In initially neutral solution $10^2k_1 = 0{\cdot}073$ at 0° and 0·396 (min.$^{-1}$) at 25·08°.

Effect of added salts. (i) At 0°.

[HClO$_4$] (M)	0·50				1·00			
[LiClO$_4$] (M)	0·0	0·50	1·00	1·50	0·0	0·50	1·00	1·50
10^2k_1 (min.$^{-1}$)	0·65	0·91	1·06	1·73	1·82	2·53	4·09	5·76
$4 + \log k_1^A$	1·76	1·96	2·02	2·24	2·26	2·40	2·61	2·76
H_0	1·35	1·13	0·87	0·62	0·72	0·51	0·25	0·0
$4 + \log k_1^A + H_0$	3·11	3·09	2·89	2·86	2·98	2·91	2·86	2·76
$4 + \log k_1^A - \log\,[\text{HClO}_4]$	3·50	2·26	2·32	2·54	2·26	2·40	2·61	2·76

(ii) At 25·08°.

[HClO$_4$] (M)	0·50				1·00		
[Et$_4$NBr] (M)	0·0	0·50	1·00	1·50	0·0	0·50	0·67
10^2k_1 (min.$^{-1}$)	8·50	8·06	6·33	4·82	23·3	20·1	18·7
$4 + \log k_1^A$	2·93	2·91	2·80	2·68	3·37	3·30	3·27
H_0	1·35	1·44	1·50	1·56	0·72	0·82	0·84
$4 + \log k_1^A + H_0$	4·28	4·35	4·30	4·24	4·09	4·12	4·11
$4 + \log k_1^A - \log\,[\text{HClO}_4]$	3·23	3·21	3·10	2·98	3·37	3·30	3·27

(b) *Dioxan–water* 40 : 60 (v/v).

Temp.	0°					4·80°	13·0°
[HClO$_4$] (M)	0·25	1·02	1·72	2·32	2·80	1·00	1·00
10^2k_1 (min.$^{-1}$)	0·91	3·01	5·76	11·1	22·7	4·73	10·7
$4 + \log k_1^A$	1·75	2·42	2·73	3·03	3·35		
H_0	1·48	0·42	−0·14	−0·55	−0·87		
$4 + \log k_1^A + H_0$	3·2	2·84	2·59	2·48	2·48		
$4 + \log k_1^A - \log\,[\text{HClO}_4]$	1·51	2·41	2·50	2·66	2·90		

In initially neutral solution $10^2k_1 = 0{\cdot}349$ at 0°, and 2·15 (min.$^{-1}$) at 25·08°.

TABLE 1. (*Continued.*)

Effect of added salt. $LiClO_4$ at 0°.

$[HClO_4]$ (M)	0·50				1·00		1·50	
$[LiClO_4]$ (M)	0·0	0·50	1·00	1·50	0·0	1·00	0·0	0·50
10^2k_1 (min.$^{-1}$)	1·40	1·48	1·61	1·86	2·80	3·40	4·70	4·87
$4 + \log k_1^A$	2·02	2·05	2·10	2·17	2·39	2·48	2·67	2·66
H_0	0·98	0·84	0·60	0·37	0·43	−0·01	−0·04	−0·23
$4 + \log k_1^A + H_0$	3·00	2·90	2·70	2·54	2·82	2·47	2·60	2·43
$4 + \log k_1^A - \log [HClO_4]$	2·32	2·35	2·41	2·47	2·39	2·48	2·46	2·48

(c) *Water.*

(i) $[HClO_4] = 0·95$M

Temp.	0·0°	4·80°	15·1°
10^2k_1 (min.$^{-1}$)	4·86	8·22	25·4

In initially neutral solution $10^2k_1 = 2·81$ min.$^{-1}$ at 0°; values at other temperatures are known.[4]

(ii) $[HClO_4] + [NaClO_4] = 4·0$M; at 0°.

$[HClO_4]$ (M)	0·0	0·50	1·53	2·48	4·00
10^2k_1 (min.$^{-1}$)	0·26	3·75	14·0	29·9	144
$4 + \log k_1^A$	—	2·54	3·14	3·48	4·16
H_0	—	−0·80	−1·19	−1·44	−1·72
$4 + \log k_1^A + H_0$	—	1·74	1·95	2·04	2·44
$4 + \log k_1^A - \log [HClO_4]$	—	2·84	2·95	3·08	3·56

(d) *Hydrolysis in deuterium oxide.* Dioxan–water 60 : 40 (v/v) at 0°.

$[HClO_4] = 0·98$M. Protio, $10^2k_1 = 1·64$ min.$^{-1}$; deutero, $10^2k_1 = 2·37$ min.$^{-1}$.
$k_1(D_2O)/k_1(H_2O) = 1·45$ (deuterium oxide in water = 90%).

(e) *Results of hydrolyses at constant ionic strength at 0°.*

(i) Dioxan–water 40 : 60 (v/v).

μ	1·00		1·50			2·00			
$[HClO_4]$ (M)	0·50	1·00	0·50	1·00	1·50	0·50	1·00	1·50	2·00
$4 + \log k_1^A - \log [HClO_4]$	2·35	2·39	2·41	2·48	2·46	2·47	2·48	2·48	2·53

(ii) Dioxan–water 60 : 40 (v/v).

μ	1·00		1·50			2·00		
$[HClO_4]$ (M)	0·50	1·00	0·50	1·00	1·50	0·50	1·00	1·50
$4 + \log k_1^A - \log [HClO_4]$	2·26	2·26	2·32	2·40	2·41	2·54	2·61	2·63

TABLE 2. *Acetic benzoic anhydride.*

(a) *Dioxan–water* 60 : 40 (v/v) at 0°.

$[HClO_4]$ (M)	0·18	0·74	1·19	1·77	2·01	2·13	2·34	2·71
10^3k_1 (min.$^{-1}$)	1·29	4·45	7·98	12·0	13·8	16·6	29·0	50·0
$4 + \log k_1^A$	0·88	1·59	1·87	2·06	2·12	2·21	2·45	2·69
H_0	1·92	1·04	0·55	−0·05	−0·30	−0·41	−0·62	−0·94
$4 + \log k_1^A + H_0$	2·80	2·63	2·42	2·01	1·82	1·80	1·83	1·75
$4 + \log k_1^A - \log [HClO_4]$	1·63	1·72	1·75	1·81	1·82	1·88	2·08	2·26

(b) *Dioxan–water* 60 : 40 (v/v) at 25·08°.

$[HClO_4]$ (M)	0·24	0·75	1·19	1·80
10^3k_1 (min.$^{-1}$)	13·8	40·4	63·2	171
$4 + \log k_1^A$	2·04	2·57	2·78	3·23
H_0	1·74	1·02	0·55	−0·10
$4 + \log k_1^A + H_0$	3·78	3·59	3·33	3·13
$4 + \log k_1^A - \log [HClO_4]$	2·66	2·70	2·70	2·98

In initially neutral solution $10^3k_1 = 0·54$ at 0° and 2·91 (min.$^{-1}$) at 25·08°.

TABLE 3. *Benzoic anhydride.*

Dioxan–water 60 : 40 (v/v).

Temp.	20·1°	25·08°							35·0°
[HClO$_4$] (M)	1·55	0·10	0·26	0·93	1·69	2·49	2·54	2·94	1·55
10^4k_1 (min.$^{-1}$)	13·1	2·34	4·48	16·1	24·3	31·9	37·1	58·8	61·0
$4 + \log k_1^A$	—	0·004	0·50	1·17	1·36	1·49	1·55	1·76	—
H_0	—	(2·2)	1·72	0·80	0·02	−0·74	−0·79	−1·13	—
$4 + \log k_1^A + H_0$	—	(2·2)	2·22	1·97	1·38	0·75	0·76	0·63	—
$4 + \log k_1^A - \log [HClO_4]$	—	1·00	1·09	1·20	1·13	1·09	1·15	1·29	—

In initially neutral solution $10^4k_1 = 1·33$ min.$^{-1}$ at 25·08° and $2·40 \times 10^{-4}$ at 35·0°.

TABLE 4. *Acetic mesitoic anhydride.*

(a) *Dioxan–water* 60 : 40 (v/v) *at* 0°.

[HClO$_4$] (M)	0·26	0·85	0·98 *	1·20	1·21	1·48	1·73	2·01	0·84 †
10^3k_1 (min.$^{-1}$)	2·41	11·6	48·5	28·0	31·0	48·0	133	240	180
$4 + \log k_1^A$	1·20	2·03	2·69	2·43	2·49	2·67	3·12	3·38	—
H_0	1·75	0·90	0·21	0·50	0·50	0·23	−0·02	−0·30	—
$4 + \log k_1^A + H_0$	2·95	2·93	2·90	2·93	2·99	2·90	3·10	3·08 —	—
$4 + \log k_1^A - \log [HClO_4]$	1·79	2·20	2·70	2·35	2·41	2·50	2·88	3·08	—

In initially neutral solution $10^3k_1 = 0·81$ at 0° and 4·33 (min.$^{-1}$) at 25·08°.

* [LiClO$_4$] = M. † At 25·08°.

TABLE 5. *Mesitoic anhydride.*

Dioxan–water 60 : 40 (v/v).
[HClO$_4$] = 0·3M when present.

Temp.		44·9°	60°	101°
10^2k_1 (min.$^{-1}$)	Initially neutral	—	0·31	3·52
	Acid	3·6	17·0	*

* $t_{½} < 0·5$ min.

TABLE 6. *Position of bond fission in acid-hydrolyses. Dioxan–water* 60 : 40 (v/v) *at* 25·08°. *Isotopic abundances are in atom % excess above normal.*

[HClO$_4$] (M)	Isotopic abundances Solvent	Product	Control	Acetyl–oxygen fission (%)
Acetic benzoic				
0	2·37	0·03 (benzoic)	0·01	100
0·59	2·23	0·02 ,,	0·02	,,
3·0	1·57	0·03 ,,	0·02	,,
5·0	0·89	0·01 ,,	0·00	,,
Acetic *p*-nitrobenzoic				
0	2·37	0·04 (*p*-nitrobenzoic)	0·04	100
3·0	1·57	0·05 ,,	0·06	,,
Acetic mesitoic				
0	2·37	0·02 (mesitoic)	0·03	100
1·0	2·13	0·75 ,,	0·01	30
3·0	1·57	0·46 ,,	0·03	40

TABLE 7. *Solvolyses in perchloric acid at* 0°.

Anhydride	Solvent	Slope of Hammett plot	ΔH * (kcal. mole^{-1})	ΔS * (e.u.)	Bond fission	Mechanism
Acetic	Dioxan–water					
	60 : 40 (v/v)	*ca.* 0·7	16·5	−16·1	—	*A*-2(?)
	40 : 60 (v/v)	*ca.* 0·7	15·4	−19·3	—	*A*-2(?)
	Water	*ca.* 1 [4]	21·4	+2·2	—	*A*-1
Benzoic	Dioxan–water:					
	60 : 40 (v/v)	Rate ∝ [HClO$_4$]	18·8	−18·9	—	*A*-2
Mesitoic	,,	—	21·8	−8·6	—	*A*-1(?)
Acetic benzoic	,,	*ca.* 0·6	15·7	−22·4	Ac–O	*A*-2
Acetic *p*-nitrobenzoic	,,	—	—	—	,,	*A*-2
Acetic mesitoic	,,	1·1	18·1	−3·8	Ar·CO–O	*A*-1

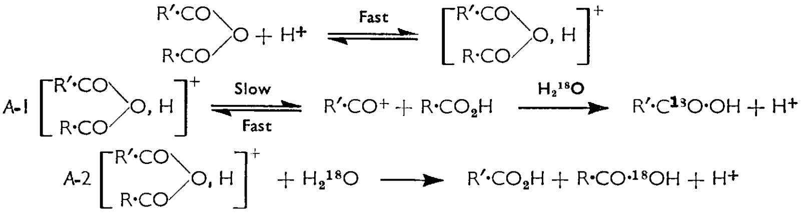
DISCUSSION

The mechanisms of the acid-catalysed hydrolyses of these open-chain carboxylic anhydrides are considered in terms of three mechanistic tests: the Zucker–Hammett hypothesis,[9] the values of the entropies of activation (ΔS^*),[10] and the position of bond fission in the hydrolysis of an unsymmetrical anhydride.

Application of the Zucker–Hammett hypothesis depends upon the observation that the rates of many acid-catalysed hydrolyses depend either on concentration, *i.e.*, Rate $\propto$ [stoicheiometric acid], or h_0, *i.e.*, Rate $\propto h_0$.[11]

We should expect that bimolecular nucleophilic attack would occur less readily if an aromatic ring were attached to the acyl (carbonyl) carbon atom, whereas unimolecular formation of an acylium ion is favoured by substituents, such as an aryl group, which can stabilise the positive charge.[12]

We assume that the perchloric acid is a specific hydrogen-ion catalyst for all the anhydrides, for the relative rates of hydrolysis of acetic anhydride in protium and deuterium solvents (Table 1), suggest this. Our experiments give no information on the location of the proton in the conjugate acid; nor do they differentiate between *A*-2 mechanisms in which the approach of the water molecule precedes bond-breaking and those in which the two processes are synchronous.[13] We represent the uni- and bimolecular mechanisms in their simplest ways:



Acetic Mesitoic Anhydride.—We discuss this compound first because the evidence is simple. The lowest two lines of Table 4 show that the hydrolysis is dependent on h_0, *i.e.*, $\log k_1^A + H_0$ is approximately constant, whereas $\log k_1^A - \log [HClO_4]$ increases sharply as $[HClO_4]$ increases. (A plot of $\log k_1^A$ against $-H_0$ has a slope of 1·1, and the point for a mixture of perchloric acid and sodium perchlorate fits well.) The value of ΔS^* (for M-$HClO_4$) is $-3{\cdot}8$ e.u., close to that expected for an *A*-1 mechanism.[10] The bond fission is predominantly mesitoyl-oxygen (Table 7). This, with the kinetic evidence, suggests that the main reaction route is formation of a mesitoylium ion from the conjugate acid of acetic mesitoic anhydride. We know that this ion is formed from mesitoic acid and its esters in strong acids, under conditions in which the acetylium ion is not formed,[12] and we should expect that bimolecular attack would be preferentially upon the acetyl group [this is so for neutral hydrolysis (Table 7)].

There is isotopic evidence for some acetyl–oxygen bond fission in the acid hydrolysis, because the mesitoic acid has $<50\%$ of the enrichment of the water;[12] however, some mesitoic acid in the anhydride could be responsible for part of this effect.

Acetic Benzoic Anhydride.—The hydrolysis of this compound is discussed next because our three mechanistic tests agree in suggesting an *A*-2 mechanism. The acetyl–oxygen bond is broken in both acid and neutral hydrolysis (Table 7). This suggests bimolecular

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[9] Zucker and Hammett, *J. Amer. Chem. Soc.*, 1939, **61**, 2779, 2785, 2791.

[10] Taft, *ibid.*, 1952, **74**, 5374; Long, Pritchard, and Stafford, *ibid.*, 1957, **79**, 2362; Glasstone, Laidler and Eyring, "Theory of Rate Processes," McGraw Hill Book Co., New York, 1941, p. 195.

[11] Long and Paul, *Chem. Rev.*, 1957, **57**, 935; Taft, Deno, and Skell, *Ann. Rev. Phys. Chem.*, 1958, **9**, 303.

[12] Treffers and Hammett, *J. Amer. Chem. Soc.*, 1937, **59**, 1758; Gillespie and Leisten, *Quart. Rev.*, 1954, **8**, 52.

[13] Bender, *J. Amer. Chem. Soc.*, 1951, **73**, 1626.

mechanisms, because nucleophilic attack will be preferentially upon the acetyl carbon atom. The acid-hydrolysis is not dependent on h_0 (last but one line of Table 2, and Figs. 1 and 2). A plot of log k_1^A against $-H_0$ is approximately linear (Fig. 2), but the slope is low (*ca.* $-0{\cdot}6$). A plot of log k_1^A against log $[HClO_4]$ is not linear over the whole range of acidity; it is linear, with slope *ca.* 1·2 up to *ca.* 1·2M-perchloric acid. At higher concentrations of acid the curve steepens rapidly. Such deviations are well known for *A*-2 reactions,[11,14] and the behaviour of acetic benzoic anhydride is very similar to that of cyclic sulphites.[15] The entropy of activation is *ca.* 20 e.u. more negative than that for the acid-hydrolysis of acetic mesitoic anhydride, and its value (−22·4 e.u.) is similar to those found for *A*-2 reactions.[10]

The rate of hydrolysis is *ca.* one-third of that of acetic anhydride under comparable conditions. This is reasonable, because this anhydride has two equally reactive points of reaction. It seems therefore that bimolecular nucleophilic attack upon the acetyl group is little affected by replacement of an acetate by a benzoate group.

The rates of hydrolysis of acetic *p*-nitrobenzoic anhydride were not measured, but the acetyl–oxygen bond fission (Table 7) suggests a bimolecular mechanism for acid hydrolysis.

Benzoic Anhydride.—Bond-fission experiments cannot be applied to the hydrolysis of this anhydride; therefore we revert to quasi-thermodynamic arguments based upon the Zucker–Hammett hypothesis and the value of ΔS^*. Also, we could not use water as a kinetic solvent, because of the low solubility of the anhydride.

In dioxan–water 60 : 40 (v/v) the hydrolysis is clearly not h_0-dependent (Table 3). A plot of log k_1^A against $-H_0$ is curved, with a slope of *ca.* 0·3 at the highest acidity. A plot of log k_1^A against log $[HClO_4]$ is linear over the acidity range measured (<3M), with slope 1·1. This concentration-dependence suggests that the reaction is of *A*-2 type, in accord with a value of ΔS^* of −18·9 e.u.[10]

Acetic Anhydride.—The aqueous hydrolysis of this anhydride is h_0-dependent for several acids, over a wide range of acidity, and it was concluded that this is an *A*-1 reaction.[4] The value of the entropy of activation, $\Delta S^* = +2{\cdot}2$ e.u. (Table 7), supports this, and we find also that the rates of hydrolysis in mixtures of perchloric acid and sodium perchlorate (Table 1) fit reasonably well on a plot of log k_1^A against $-H_0$ for perchloric acid. (In making this comparison we have altered the H_0 values used by Gold and Hilton [4] to fit a recalculated scale.[16])

The evidence on the mechanism of acid hydrolysis in aqueous dioxan is much less clear cut. For both dioxan–water solvents plots of log k_1^A against $-H_0$ are linear (and almost coincident), but with slopes of *ca.* 0·7 (Fig. 2). The values for mixtures of perchloric acid and lithium perchlorate fit well on this straight line for the less aqueous solvent. Plots of log k_1^A against log $[HClO_4]$ are also linear up to $[HClO_4] \approx 1{\cdot}2$M, and they too are almost coincident: at higher acidities they steepen sharply (Fig. 1). The kinetic salt effects of lithium perchlorate and tetraethylammonium bromide are in the same order as their salt effects upon h_0;[16] however, in mixtures of perchloric acid and lithium perchlorate the hydrolyses in aqueous dioxan are almost wholly concentration-dependent (Table 1). Thus these kinetic salt effects are of little value in elucidating the mechanism of this hydrolysis in aqueous dioxan, and the rapidity of the hydrolysis prevents our measuring the activity coefficients of the anhydride in these kinetic solvents and so applying the refined treatment which McIntyre and Long used for the acid-hydrolyses of acetals.[17]

Comparison with the hydrolyses of acetic benzoic and dibenzoic anhydride in aqueous dioxan, and consideration of the entropies of activation suggest that the mechanism is not of *A*-1 type in aqueous dioxan; *e.g.*, in dioxan-water 60 : 40 (v/v), $\Delta S^* = -16{\cdot}1$ e.u.; and in 40 : 60 (v/v), $\Delta S^* = -19{\cdot}3$ e.u. Further the ratio k_D/k_H is 1·45 (for hydrolysis in

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[14] Bell, Dowding, and Noble, *J.*, 1955, 3106.

[15] Bunton, de la Mare, and Tillett, *J.*, 1958, 4754; *J.*, 1959, 1766.

[16] Paul and Long, *Chem. Rev.*, 1957, **57**, 1.

[17] McIntyre and Long, *J. Amer. Chem. Soc.*, 1954, **76**, 3240.

dioxan–water 60 : 40 v/v), in the range which is often found for A-2 reactions; the usual values[18] for A-1 reactions are >2. This kinetic isotope effect is not conclusive evidence because it has not yet been applied to many known mechanisms in mixed solvents.

It seems probable that the hydrolysis of acetic anhydride in aqueous dioxan is an example of a bimolecular reaction in which the activity coefficient ratio f_s/f_{x^*} varies with acidity approximately as does f_B/f_{BH^+} [where S is the initial and x* the transition state (containing S, H^+ and H_2O), and B is a Hammett base]. To this extent these hydrolyses are very similar to those of dialkyl sulphites in aqueous acid.[15]

Mesitoic Anhydride.—A few experiments were made on the acid hydrolysis of this anhydride. Our experimental method could not be used with $[HClO_4] > 0{\cdot}3$M, and we do not know whether the acid-hydrolysis is concentration- or h_0-dependent.

Bimolecular attack would be very hindered sterically, and mesitoic anhydride reacts sufficiently slowly with alkali for the hydrolysis to be followed by acid–base titration. The value of the entropy of activation is $-8{\cdot}6$ e.u., and similar to those found for A-1 reactions.[10] These results suggest a unimolecular mechanism for acid-hydrolysis. However, this compound is much less reactive than acetic mesitoic anhydride (Tables 4 and 5). This may be due to a steric hindrance of solvation of the forming mesitoyl cation, and the energy of activation is higher than for other anhydrides.

Comparison between our results for the hydrolysis of acetic anhydride in aqueous dioxan, and those of Gold and Hilton for the aqueous hydrolysis[4] suggests a mechanistic change with changing solvent. Such a change is observed for acetylation by acetic anhydride when the solvent is changed from aqueous hydrochloric acid to acetic acid containing hydrogen chloride.[5] If this interpretation is correct there must be some intermediate solvent composition at which the two mechanisms either coexist or merge. Objection has been raised to the view that uni- and bi-molecular mechanisms can merge;[19] and evidence has been presented suggesting that an alkyl halide can undergo simultaneous uni- and bi-molecular substitution.[20] It is unfortunate that we could not study the hydrolyses of benzoic anhydride and acetic benzoic anhydride in water, because if there is a mechanistic change in the acid hydrolysis of acetic anhydride caused by a change in solvent composition, it should also appear with other compounds.

The relative rates of the A-2 hydrolyses of these anhydrides are: acetic $>$ acetic benzoic $\approx$ acetic mesitoic $>$ benzoic. This order is similar to that for other reactions of the $A_{Ac}2$ type. The relative resistance of the benzoyl group to nucleophilic attack is evident. Because of the way in which the uni- and bi-molecular components of hydrolysis vary with acidity, solvent, and temperature, it is not useful to quote relative rates for these compounds. Table 6 summarises our experimental observations and our conclusions as to the predominant reaction mechanism.

Applicability of the Zucker–Hammett Hypothesis.—There are a number of reactions which are thought to have the A-2 mechanism but have kinetic forms close to that predicted for A-1 reactions by the Zucker–Hammett hypothesis. The rate equation (due to Brönsted) for an A-2 reaction can be written:

$$v \propto [H_3{}^+O][S]f_S \cdot f_{H_3{}^+O}/f_{x^*} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Proportionality between rate and acid-concentration, as predicted by the Zucker–Hammett hypothesis, requires the activity-coefficient term to be independent of acidity; the frequent breakdown of this relation is sometimes ascribed to differences in the molecular geometry of reacting substrates which may affect this activity-coefficient ratio.

The rate equation (1) for bimolecular reaction between a water molecule and a conjugate acid can be written in another form,

$$v \propto [S][H_2O] \cdot f_{H_2O} \cdot f_{HS^+}/f_{x^*} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1a)$$

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[18] Pritchard and Long, *ibid.*, 1958, **80**, 4162.

[19] Gold, *J.*, 1956, 4633.

[20] Kohnstam, Queen, and Shillaker, *Proc. Chem. Soc.*, 1959, 157.

Constancy of the quotient $f_{H_2O} \cdot f_{HS^+}/f_{X^*}$ would lead to a proportionality between rate and h_0 (when the small variation in the concentration of water is neglected). This approximation is similar to that applied to equation (1) in the original form of the Zucker–Hammett hypothesis; but it does not generally conform to the experiments.

We therefore consider another possible rearrangement of equation (1) for an A-2 reaction, by removing the terms which involve the activity or concentration of water. The term $-H_0 - \log [HX] + 4 \log a_{H_2O}$ (where HX is a strong acid) is approximately independent of acid concentration in water for [HX] < 8M.[21] Therefore equation (1*a*) can be written in the logarithmic form:

$$\log v/[S] \simeq -\tfrac{3}{4}H_0 + \tfrac{1}{4}\log [HX] + \log f_{HS^+}/f_{X^*} + \text{Constant} \quad . \quad . \quad (1b)$$

This should also apply to hydrolyses in aqueous dioxan, provided that the omission is justified in this solvent, as it should be at low concentrations of acid.

Plots of $\log k_1^A$ against $(-\tfrac{3}{4}H_0 + \tfrac{1}{4}\log [HClO_4])$ for the hydrolyses of acetic anhydride and acetic benzoic anhydride are straight lines, of slopes 0·8 and 0·75 respectively; the points for the different solvents coincide. This suggests that the activity coefficients of the conjugate acids and the transition states vary similarly with acidity. This approximation differs from that usually applied to A-2 reactions (equation 1), but it fits our system better: it may be reasonable provided that the water molecule is not closely bound to the reaction centre in the transition state. This distance between the reaction centre and the oxygen atom, in the transition state, will be small for unreactive conjugate acids, and will increase as the reactivity of the conjugate acid increases. Therefore, the more reactive (more electrophilic) the conjugate acid, the less closely is the water molecule involved in the transition state, and the more divergent is the kinetic form from concentration-dependence in favour of h_0-dependence. We might therefore expect that, for any given class of compounds reacting by A-2 mechanisms, the more reactive members will show behaviour intermediate between dependence on concentration of acid and on h_0.

Such evidence as exists is in agreement with this. In our experiments the rate of hydrolysis of the comparatively unreactive benzoic anhydride depends on acid concentration, whereas the more reactive acetic anhydride and acetic benzoic anhydride are approximately h_0-dependent. Hydrolysis of the comparatively unreactive alkyl benzoates (and substituted benzoates) is concentration-dependent [22] ($A_{Ac}2$ mechanism), whereas the more reactive aliphatic esters show an intermediate form between dependence upon stoicheiometric acidity and upon h_0.[14] The kinetic behaviour of the cyclic and open-chain dialkyl sulphites, in their A-2 hydrolyses, is intermediate between concentration- and h_0-dependence; here also the kinetic behaviour of the more reactive dialkyl sulphites is closer to h_0-dependence.[15]

In the extreme situation—an A-1 mechanism—the water molecule is considered to have the rôle of solvating the reactants and the transition state. The activity of water does not enter explicitly into the rate equation, and the rate follows h_0, except for deviations due to the lack of identity between f_S/f_{X^*} and f_B/f_{HB^+}.

In this discussion of the mechanism of acid-catalysed reactions we postulate a continuous change in the structures of the transition state with changes in the structure of the substrate; we also assume implicitly that the structure of the transition state changes, for a given substrate, with a change in environment, *e.g.*, with change in the concentration of acid or of solvent. It seems to us that it is very difficult to translate the rate equation deduced by Brönsted into molecular terms for these acid-catalysed solvolyses.

For the A-2 mechanism the activity of water appears explicitly in the equation, and the ratio of activity coefficients will also depend upon the solvent. For the A-1 mechanism the activity of water does not appear explicitly in the rate equation. This implies a discontinuity in mechanism, whereas our experiments on the hydrolyses of carboxylic

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[21] Bascombe and Bell, *Discuss. Faraday Soc.*, 1957, **24**, 158.

[22] Chmiel and Long, *J. Amer. Chem. Soc.*, 1956, **78**, 3326.

anhydrides suggest a merging of uni- and bi-molecular mechanisms with changes in structure and solvent composition.

EXPERIMENTAL

Materials.—" AnalaR " acetic anhydride was distilled from magnesium turnings, the fraction boiling between 137·8° and 138·2° being collected.

Commercial benzoic anhydride was freed from benzoic acid by washing it with aqueous sodium hydrogen carbonate and then water, dried, and after several recrystallisations from benzene–light petroleum ether had (constant) m. p. 42°.

Mixed anhydrides containing the acetyl radical were prepared by means of keten.[23] Keten (from pyrolysis of acetone) was passed into a dry ethereal solution of the carboxylic acid (*ca.* 1 g.), then the ether was removed. The purity of the oily products was assessed in three ways: (1) Titration against alkali gave the total amount of carboxylic acid + anhydride. (2) A known amount was dissolved in dry dioxan; aniline was added to a portion, and water to another. After a time sufficient for reaction each portion was titrated against alkali, and the amounts of free acid and anhydride were calculated. (3) Unsymmetrical anhydrides and mixtures of two simple anhydrides were distinguished by kinetic analysis. Hydrolysis was accurately of the first order for 80—90% of reaction for both acetic benzoic and acetic mesitoic anhydride.

Because of the ease of interconversion of an unsymmetrical anhydride into a mixture of symmetrical anhydrides samples were used within a short time of preparation. Acetic benzoic anhydride was a pale yellow oil. Samples contained >94% of anhydride. Acetic *p*-nitrobenzoic anhydride, recrystallised from light petroleum, had m. p. 75·5—77° and contained *ca.* 92% of anhydride. Acetic mesitoic anhydride was a pale yellow oil, containing *ca.* 85% of anhydride, and small quantities of mesitoic acid were isolated by dissolution in ether: the main impurity was mesitoic acid, which would not affect the kinetics but would give low figures for the amount of mesitoyl–oxygen bond fission. Mesitoic anhydride was prepared by heating acetic mesitoic anhydride at 200° for 6 hr.: the product was dissolved in dry ether, and this solution treated with charcoal; the product was then recrystallised from light petroleum to (constant) m. p. 104° (Fuson, Corse, and Rabjohn[24] give m. p. 106—107°). Dioxan was purified as described by Vogel[25] or by refluxing it for several days with sodium metal (until the surface of the molten metal was bright) and fractionating it through a 3 ft. helix-packed column (head and tail fractions rejected).

The kinetic solvent was made up from the appropriate volumes of water and purified dioxan. Allowance was made for the water content of 72% perchloric acid in making up the acid solutions.

Sodium and lithium perchlorate were dried at 150°, tetraethylammonium bromide at 110°. Aniline was purified by distillation from zinc dust.

Kinetics.—Hydrolysis was followed by adding portions to an excess of aniline. The anhydrides rapidly and quantitatively give the anilide and carboxylic acid.[26] The acid, and that produced during hydrolysis, were titrated against alkali. A modification of this procedure was used when appreciable amounts of perchloric acid were used. After reaction with a known small amount of concentrated alkali, the residual acid was titrated with 0·05N-alkali. This method is reliable for acid concentrations up to 3M; *e.g.*, 10^2k_1 for acetic anhydride at 0° in water = 13·4 min.$^{-1}$; the dilatometric method[4] gave $10^2k_1 = 13{\cdot}7$. This general method could not be applied to the hydrolysis of mesitoic anhydride, because the reaction with aniline was too slow. Fortunately reaction with hydroxide is also relatively slow, and therefore the mesitoic acid produced could be titrated directly with alkali. It was not possible, however, to add concentrated alkali sufficient to neutralise most of the acid present, because this did hydrolyse the anhydride, and therefore we could not use concentrations of the catalysing $[HClO_4] > 0{\cdot}3$M.

Tracer Experiments.—The mixed anhydride (*ca.* 0·25M) was allowed to react in a solvent containing $H_2{}^{18}O$. The less soluble (aromatic) acid was isolated by pouring the solution into ice-cold (isotopically normal) water. The aromatic acid was filtered off and recrystallised.

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[23] Williams and Hurd, *J. Org. Chem.*, 1940, **5**, 122; Dunbar and Bolstad, *ibid.*, 1944, **9**, 219.

[24] Fuson, Corse, and Rabjohn, *J. Amer. Chem. Soc.*, 1941, **63**, 2852.

[25] Vogel, " Practical Organic Chemistry," Longmans, Green and Co., London, 1948, p. 175.

[26] Vlés, *Rec. Trav. chim.*, 1933, **52**, 809; Kappelmeier and van Goor, *Analyt. Chim. Acta*, 1948, **2**, 146.

Benzoic and *p*-nitrobenzoic acid were converted into their silver salts, and these were decomposed *in vacuo*; the evolved carbon dioxide was analysed mass-spectrometrically. Mesitoic acid was pyrolysed to carbon monoxide *in vacuo* over red hot carbon in an R.F. induction furnace, the oxide being analysed mass-spectrometrically. Control tests on exchange between the carboxylic acids and water were made.

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