

1149. *The Hydrolysis of Carboxylic Anhydrides. Part VI.¹*
Acid Hydrolysis of Cyclic Anhydrides

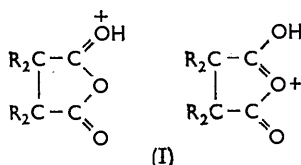
By C. A. BUNTON, J. H. FENDLER, N. A. FULLER, S. PERRY, and J. ROCEK

The extent of perchloric acid catalysis of the hydrolysis of cyclic anhydrides follows the sequence: homophthalic > glutaric, camphoric > *cis*-cyclohex-3-ene-1,2-dicarboxylic, succinic > maleic, phthalic. The sensitivity to acid appears to be related to the bond angle of the ethereal oxygen atom of the anhydride, and if this angle is small acid catalysis may not overcome a negative salt effect. Solubility measurements upon camphoric anhydride show that electrolytes have specific effects upon the initial state of the reaction.

Acid catalysis is more significant in aqueous dioxan than in water, and is greater with hydrochloric acid than with perchloric acid. The acid hydrolysis has a higher activation energy than has the spontaneous hydrolysis. No appreciable oxygen exchange was observed during these hydrolyses in acid.

AQUEOUS mineral acids in moderate concentration retard the hydrolysis of succinic and tetramethyl succinic anhydrides, although they are catalysts at high concentration (*ca.* 10M).^{2,3} Perchloric acid in aqueous dioxan is a catalyst at all concentrations.³ Most univalent salts of strong acids retard hydrolysis of carboxylic anhydrides in water.⁴ A negative salt effect of an acid may overcome its feeble catalysis, but perchloric and hydrochloric acids catalyse the hydrolysis of succinic anhydride in water provided that the ionic strength is maintained by addition of their sodium or lithium salts.³ These observations suggest that the effect of the acids as electrolytes can be reduced, although probably not eliminated, by maintaining the ionic strength of the solution by addition of their sodium or lithium salts.³ Salt effects upon these reactions are specific, but they appear to depend upon the nature of the anion rather than the cation (*cf.* ref. 4), and there is evidence that the specific salt effect of the hydronium ion is similar to the effects of the lithium or sodium ions.⁵ However, even in these acid-salt mixtures, and in aqueous dioxan where these electrolyte effects are smaller than in water,³ the acid catalysis is weaker than that observed for hydrolysis of open-chain anhydrides in comparable conditions.^{1,6,7}

Cyclic carboxylic anhydrides are not especially unreactive in neutral solution unless they contain bulky groups^{8,9} and the relative unreactivity of the succinic anhydrides in acid



could be caused by a low affinity of one of their oxygen atoms towards a proton in the transition state, especially because cyclic anhydrides are less basic than open-chain anhydrides in sulphuric acid.¹⁰ This low basicity might be caused by a resistance to the change in the bond angle of the ethereal oxygen atom which would occur if the positive charge in structure (I) is delocalised.³

Alternatively one might suppose that the first step of acid hydrolysis involves ring opening to give an intermediate which returns to reactant by an acid-catalysed reaction.³ Reversion of such an intermediate could occur readily with cyclic anhydrides.

¹ Part V, C. A. Bunton and J. H. Fendler, *J. Org. Chem.*, 1965, **30**, 1365.

² J. Koskikallio and A. Ervasti, *Suomen Kem.*, 1962, **35B**, 213.

³ C. A. Bunton, J. H. Fendler, N. A. Fuller, S. Perry, and J. Rocek, *J.*, 1963, 5361.

⁴ C. A. Bunton, N. A. Fuller, S. Perry, and I. Pitman, *J.*, 1962, 4478, and references cited.

⁵ F. A. Long, F. B. McDevit, and F. B. Dunkle, *J. Phys. Chem.*, 1951, **55**, 813; C. A. Bunton, D. R. Llewellyn, K. G. Oldham, and C. A. Vernon, *J.*, 1958, 3574.

⁶ (a) V. Gold and J. Hilton, *J.*, 1955, 838, 843; (b) J. Koskikallio, D. Pouli, and E. Whalley, *Canad. J. Chem.*, 1959, **37**, 1360.

⁷ C. A. Bunton and S. Perry, *J.*, 1960, 3070.

⁸ J. Koskikallio, *Ann. Acad. Sci. Fennicae*, 1954, AII, **57**, 1; T. C. Bruice and U. K. Pandit, *J. Amer. Chem. Soc.*, 1960, **82**, 5858; L. Ebersson, *Acta Chem. Scand.*, 1964, **18**, 534.

⁹ C. A. Bunton, N. A. Fuller, S. G. Perry, and V. J. Shiner, *J.*, 1963, 2918.

¹⁰ J. Leisten, *J.*, 1961, 2191.

We have therefore examined the acid hydrolysis of other cyclic anhydrides, seeking a relationship between their geometry and their sensitivity to acid. Anhydrides of 1,3-dicarboxylic acids are more reactive in aqueous acid than those of 1,2-dicarboxylic acids, and succinic anhydride is more reactive in acid than either maleic or phthalic anhydride.

RESULTS

The hydrolyses of glutaric and maleic anhydrides were studied in aqueous acid; the first-order rate constants, $k\psi$, are given in Table 1. Values of $k\psi$ are plotted against concentration

TABLE 1
Hydrolysis in aqueous acid
Glutaric anhydride

At 0°.							
[HClO ₄] (M)	—	0.50	0.90	1.00	2.00	2.95	6.00
10 ⁴ $k\psi$ (sec. ⁻¹)	4.23	3.97	3.67	3.64	3.97	4.93	8.00
[HClO ₄] + [NaClO ₄] = 6.0M							
[HClO ₄] (M)	—	3.00	4.17	4.78	6.00		
10 ⁴ $k\psi$ (sec. ⁻¹)	0.07	2.63	4.16	5.05	8.00		
At 25.1°.							
[HClO ₄] (M)	—	0.23	1.15	1.78	2.39	3.01	
10 ⁴ $k\psi$ (sec. ⁻¹)	27.0	29.2	32.5	36.0	37.7	41.0	
Maleic anhydride							
At 0°.							
[HClO ₄] (M)	—	0.10	0.19	1.06	2.14	4.00	6.2
10 ⁴ $k\psi$ (sec. ⁻¹)	34.8	33.8	31.6	17.3	9.16	3.80	0.97
[HClO ₄] + [NaClO ₄] = 4.0M							
[HClO ₄] (M)	—	1.21	1.57	4.00			
10 ⁴ $k\psi$ (sec. ⁻¹)	5.83	4.08	3.51	3.80			
[HCl] (M)	0.11	1.05	2.85	9.9			
10 ⁴ $k\psi$ (sec. ⁻¹)	36.0	25.3	9.7	0.10			

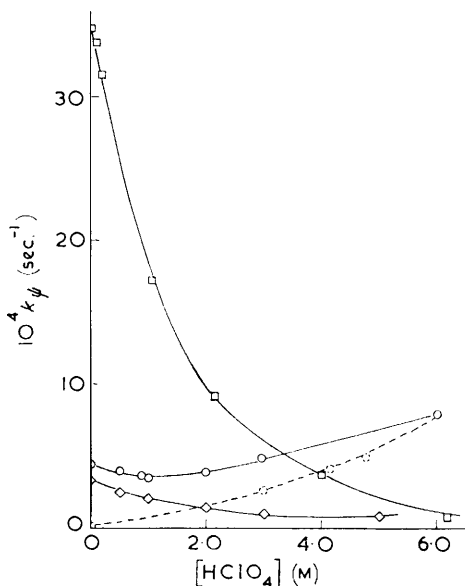


FIGURE 1. Hydrolysis at 0° in aqueous perchloric acid

- Glutaric anhydride.
- ◇ Glutaric anhydride at $\mu = 6.0$.
- ◇ Succinic anhydride.
- Maleic anhydride.

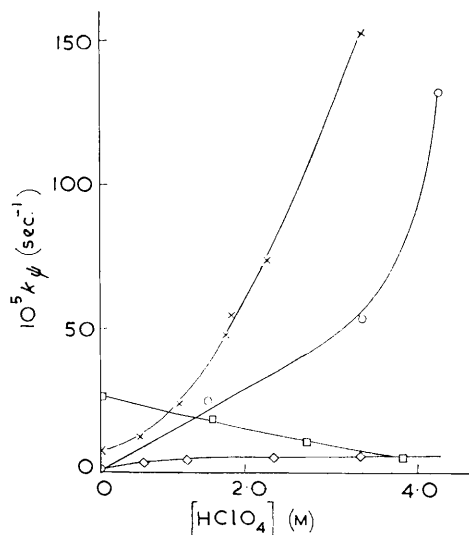


FIGURE 2. Hydrolysis at 0° in dioxan-water 60 : 40 v/v, containing perchloric acid

- Glutaric anhydride.
- ◇ Succinic anhydride.
- Maleic anhydride.
- × Homophthalic anhydride.

TABLE 2
 Hydrolyses in aqueous dioxan

Dioxan-water 60 : 40 v/v		Glutaric anhydride							
At 0°.									
[HClO ₄] (M) ...	—	1.23	3.02	4.21					
10 ⁵ kψ (sec. ⁻¹) ...	1.4	24.3	53.4	132					
At 25.1°.									
[HClO ₄] (M) ...	—	0.52		1.01		1.20	2.45	3.00	
10 ⁵ kψ (sec. ⁻¹) ...	11.1	3.7 *	1.7 †	88.9	177	207 *	225 †	450 566	
At 0°.		Maleic anhydride							
[HClO ₄] (M) ...	—	1.18	2.37	3.50					
10 ⁵ kψ (sec. ⁻¹) ...	26.3	18.3	10.2	5.17					
[HCl] (M).....	1.00	2.00	3.00	4.00	6.00				
10 ⁵ kψ (sec. ⁻¹) ...	27.9	23.3	22.9	20.4	16.3				
At 25.1°.									
[HClO ₄] (M) ...	—	0.10	0.20	0.59	1.22		1.51	2.40 3.00	
10 ⁵ kψ (sec. ⁻¹) ...	165	16.7 †	165	160	151	121	39.9 †	109 83.3 60	
At 25.1°.		Phthalic anhydride							
[HClO ₄] (M) ...	—	0.10	0.20	0.98	1.82	3.02			
10 ⁵ kψ (sec. ⁻¹) ...	42.9	44.4	44.5	38.7	30.0	23.3			
Temp.		Homophthalic anhydride							
		0°						25.1°	
[HClO ₄] (M) ...	—	0.46	0.92	1.42	1.50	1.90	3.00	— 0.50	
10 ⁵ kψ (sec. ⁻¹) ...	7.4	13.0	24.0	48.0	55.3	73.6	153	49.3 200	
At 25.1°.		<i>cis</i> -Cyclohex-3-ene-1,2-dicarboxylic anhydride							
[HClO ₄] (M) ...	—	1.95	3.55	4.42	4.82	6.10	8.06		
10 ⁵ kψ (sec. ⁻¹) ...	15.7	32.5	59.1	73.6	80.3	102	135		
Dioxan-water 12.5 : 87.5 v/v		Camphoric anhydride							
Temp.		72.9°			101°				
[HClO ₄] (M) ...	—	0.32		—	0.21	0.32			
10 ⁵ kψ (sec. ⁻¹) ...	4.7	13.9	22.5	55	81				
With added salts at 101°.									
Salt		NaClO ₄			Et ₄ NBr		MgSO ₄		
[Salt] (M).....	0.45	0.97	1.75	0.22	1.00		1.00		
10 ⁵ kψ (sec. ⁻¹) ...	16.6	13.0	9.45	22.2	16.2		34.3		

* D₂O-dioxan. † [HClO₄] + [LiClO₄] = 3.0M.

of perchloric acid (Figure 1) for glutaric, maleic, and succinic anhydrides. (The rate constants for hydrolysis of succinic anhydride are taken from ref. 3.) Added salts of monobasic acids retard hydrolysis (Table 1 and ref. 3).

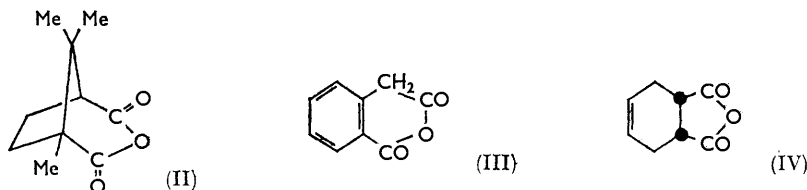
The acid hydrolyses of all the anhydrides were studied in dioxan-water 60 : 40 v/v (Table 2 and Figure 2). Perchloric acid catalysed all the hydrolyses, except those of maleic and phthalic anhydrides. However, even with maleic anhydride acid catalysis could be realised in aqueous dioxan at 25°, provided that the perchlorate ion concentration was maintained by addition of lithium perchlorate. The acid hydrolysis of glutaric anhydride in aqueous dioxan is very much faster than the spontaneous hydrolysis and therefore for this special case the contribution of the spontaneous hydrolysis can be neglected, and we estimate the solvent deuterium isotope effect upon the acid hydrolysis, $k_{H_2O}/k_{D_2O} \approx 0.85$ (Table 2). In water the spontaneous hydrolysis makes a large contribution to the overall reaction, and it then becomes difficult to separate

the isotope effect upon the acid hydrolysis from the large isotope effect upon the spontaneous hydrolysis,^{9,11} where $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} \approx 3$.

For glutaric and camphoric anhydrides we calculated approximate values of the entropy, ΔS^* , and energy, E , of activation of acid hydrolysis in aqueous dioxan. The observed rate constants $k\psi$ were corrected for the small contribution of the spontaneous hydrolysis on the assumption that the salt effects upon it could be neglected. The uncertainties so introduced are small for these particular reactions, because the contribution of the spontaneous hydrolysis is relatively small, and in any event salt effects upon anhydride hydrolysis are smaller in aqueous dioxan than in water.^{3,4} (It would be difficult to calculate meaningful energies and entropies of activation for the acid hydrolyses of those cyclic anhydrides for which the spontaneous hydrolysis makes a large contribution to the overall reaction.)

For glutaric anhydride in dioxan-water 60 : 40 v/v $\Delta S^* = -22$ e.u., and $E = 15.5$ kcal. mole⁻¹, and for camphoric anhydride $\Delta S^* = -28$ e.u., and $E = 17$ kcal. mole⁻¹. These values are approximate because of this correction, but they are in the general range found for acid hydrolyses of other anhydrides, and the energy of activation is greater for the acid than for the spontaneous hydrolysis, as for other anhydrides.^{1,3,6b,7} The negative entropy of activation is in the range generally associated with A-2 hydrolyses.¹²

Added uni-univalent salts retard the spontaneous hydrolysis of these cyclic anhydrides (Table 1, cf. refs. 3 and 4) but the electrolyte effects of added acids can be reduced by maintaining the ionic strength constant with added sodium salt (Table 1 and Figure 1). We then



generally observed some acid catalysis. Salt effects upon the spontaneous hydrolysis of acetic anhydride in water are specific, and are exerted in part upon the initial state,⁴ and therefore we measured the salt effects upon the spontaneous hydrolysis of camphoric anhydride (II) in dioxan-water 12.5 : 87.5% v/v (Table 2). This solvent mixture was chosen because it has a high water content, and the solubility of the anhydride is convenient for rate and solubility measurement, and hydrolysis is relatively slow. The solubility experiments (Table 3) show

TABLE 3

Salt effects upon the activity coefficient of camphoric anhydride. In dioxan-water 12.5 : 87.5 v/v at 25°

Salt	NaClO ₄						Et ₄ NBr				MgSO ₄	
	0.5	0.7	0.9	1.0	1.1	1.65	0.6	0.9	0.95	1.25	0.35	1.2
[Salt] (M)	0.8	0.75	0.8	0.7	0.65	0.6	1.0	0.95	1.0	0.95	1.25	1.65
<i>f_s</i>												

TABLE 4

Oxygen exchange during hydrolysis

At 0°, and in dioxan-water 60 : 40 v/v containing 3M-HClO₄, unless specified

*N*_{H₂O} = 1.33 atom-% excess.

Anhydride	Succinic *	Maleic	Phthalic †	Camphoric ‡
% Reaction	75	68	75	68
<i>N</i> Atom-% excess	0.00 ₃	0.00 ₃	0.00	0.01 ₃

* 1.9M-HClO₄ in water. † 25.1°. ‡ 0.3M-HClO₄ in dioxan-water 12.5 : 87.5 v/v, at 101°.

that magnesium sulphate "salts-out" the anhydride, *i.e.*, increases its activity coefficient, *f_s*. Tetraethylammonium bromide has little effect upon solubility, but sodium perchlorate

¹¹ A. R. Butler and V. Gold, *J.*, 1961, 2305; 1962, 2212.

¹² L. L. Schaleger and F. A. Long in "Advances in Physical Organic Chemistry," ed. V. Gold, Academic Press, New York, 1963, vol. 1, p. 1.

increases it, *i.e.*, decreases f_s . Some of the kinetic salt effect is associated with changes in the activity coefficient of the initial state, because sodium perchlorate decreases f_s and the rate of hydrolysis, tetraethylammonium bromide has little effect, and magnesium sulphate increases both. However, all the salts destabilise the transition state, *i.e.*, increase its activity coefficient. These results are very similar to those found for the hydrolysis of acetic anhydride in water.⁴

Oxygen Exchange.—These cyclic anhydrides do not undergo appreciable oxygen exchange during acid hydrolysis. Table 4 gives the results of experiments using isotopically normal anhydride in enriched water. The anhydrides were converted into their monoanilides for isotopic analysis (except for camphoric anhydride which was isolated directly). The isotopic abundances of the water, $N_{\text{H}_2\text{O}}$, and the anhydride, N , are in atom-% excess above normal. For camphoric anhydride the ratio of the rate of hydrolysis to that of exchange is greater than 80, and much larger for the other anhydrides.

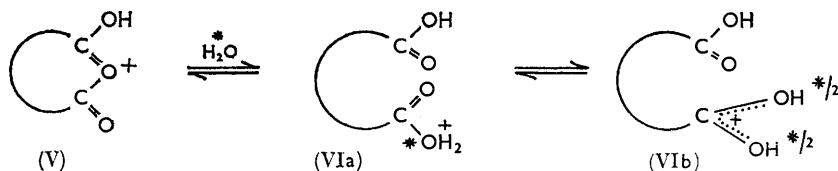
DISCUSSION

The sensitivity of the monocyclic anhydrides to acid follows the approximate sequence, glutaric > succinic \approx tetramethylsuccinic > maleic (Tables 1 and 2, Figures 1 and 2, and ref. 3).

In water the hydrolysis of maleic anhydride is retarded by both perchloric and hydrochloric acids, even in conditions where they assist the hydrolysis of the other cyclic anhydrides. The rate of hydrolysis decreases steadily with addition of acid, up to *ca.* 10M concentration, which was the highest used. Similarly we observe no acid catalysis even when we maintain the electrolyte concentration at 4M by addition of sodium perchlorate to the perchloric acid. On the other hand perchloric acid at first hinders, but then assists, the hydrolysis of succinic anhydride,^{2,3} and reaction rate increases steadily with increasing acid concentration at constant ionic strength.³ For glutaric anhydride the region of anticatalysis is smaller, and at 0° there is a small initial rate decrease with addition of perchloric acid to the water, with a shallow rate minimum at *ca.* 1M-acid, but there is a smooth catalysis at 25°, and at 0° if the electrolyte concentration is kept constant.

This general pattern is followed in aqueous dioxan, although in this solvent the acid hydrolysis is assisted relatively to the spontaneous hydrolysis, and anticatalysis by perchloric acid is observed only with maleic and phthalic anhydrides. (Even here we observed an acid-catalysed hydrolysis of maleic anhydride by maintaining a constant concentration of perchlorate ion, and so suppressing the spontaneous hydrolysis.) Both mono- and bicyclic anhydrides behave similarly, in that 1,3-dicarboxylic anhydrides are more sensitive to acid than are the succinic anhydrides, and maleic and phthalic anhydrides are less. The acid catalysis of the hydrolyses of homophthalic (III) and *cis*-cyclohex-3-ene-1,2-dicarboxylic anhydrides (IV) contrasts sharply with the acid anti-catalysed hydrolysis of phthalic anhydride (Table 2).

Therefore there is a correlation between sensitivity to acid, and size and configuration of the anhydride ring, for both mono- and bi-cyclic anhydrides, but flexibility of the anhydride ring system does not affect the sensitivity to acid, *e.g.*, camphoric anhydride (II)

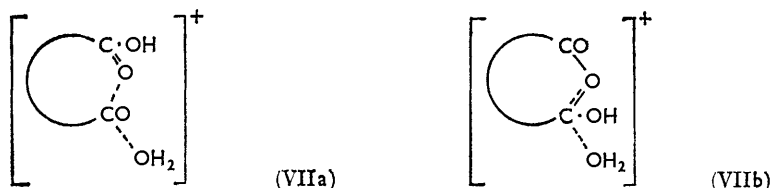


has a rigid structure, but nonetheless its hydrolysis is acid-catalysed. We therefore discard the tentative suggestion that the absence of acid catalysis might be caused by a rapid recyclisation of an intermediate formed by ring opening of the anhydride.³ The absence of oxygen exchange is further evidence against a rapid recyclisation. If attack of a water molecule upon the conjugate acid (V) opened the anhydride ring to give an intermediate (VIa, b) which then cyclised, we might observe exchange, because of isotopic

scrambling of the oxygen atoms in structure (VI), provided that proton transfer is fast enough to allow isotopic equilibration within the lifetime of compound (VI).

Maleic and phthalic anhydrides are more reactive than the other cyclic anhydrides in neutral solution because one carbonyl group can activate another by electronic relay through the double bond. This electronic effect apparently does not assist the acid hydrolysis. Hydrolysis by the *A-2* mechanism involves both protonation of an oxygen atom, and nucleophilic attack upon a carbonyl carbon atom, and electron-withdrawal should hinder protonation. Therefore the insensitivity of maleic and phthalic anhydrides to acidic catalysts could be caused by electronic relay through the double bond, as well as by the reduced bond angle of the ethereal oxygen atom.

The explanations that were advanced for the insensitivity of succinic and tetramethylsuccinic anhydrides to aqueous acid can be applied to all these cyclic anhydrides, *viz.*, that the transition state for acid hydrolysis (VIIa or b) is stabilised by electron release from the ethereal oxygen atom, but that cyclisation suppresses electron release by inhibiting a covalency increase of this oxygen atom.³ Therefore in water the acid catalysis may not be large enough to overcome the negative salt effect of the acid. However in aqueous dioxan the spontaneous hydrolysis is slower than in water, and salt effects are also smaller,⁴ and acid catalysis is observed more readily.



It seems that ring opening has not made much progress in the transition state for the hydrolyses of these cyclic anhydrides. This conclusion is supported by the negative values of the entropy of activation, which are in the range associated with *A-2* reactions.¹² If ring opening was important we should expect the entropies of activation to be more positive for the acid hydrolyses of the cyclic than of the open chain anhydrides. The effect of ring opening upon the entropy of activation of *A-2* hydrolyses of epoxides has been discussed by Whalley.¹³ The entropy of activation is more negative, and the energy larger, for the acid (and spontaneous) hydrolysis of camphoric, as compared with glutaric or open-chain anhydrides,^{1,6,7,9} because the methyl groups exert considerable steric hindrance to nucleophilic attack.

The hydrolysis of these cyclic anhydrides is generally faster in hydrochloric acid than in perchloric acid (Table 1 and Figure 1). This acid specificity is also shown in the hydrolyses of acetic and trimethylacetic anhydrides.¹ It is almost certainly caused by the greater negative salt effect of the perchlorate over the chloride ion, which is generally observed for anhydride hydrolysis, and depends, at least in part, upon the effect of the electrolyte upon the activity coefficient of the anhydride.⁴

Although these cyclic anhydrides are relatively insensitive to acid their acid hydrolyses appear to follow conventional *A-2* mechanisms. The solvent deuterium isotope effect $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} \approx 0.85$ is closer to unity than is generally observed for *A-2* reactions of oxygen compounds, but these isotope effects vary widely with differences of substrate and reaction conditions.¹⁴

EXPERIMENTAL

Materials.—The preparation and purification of the anhydrides and the solvents have been described.⁹

¹³ E. Whalley in "Advances in Physical Organic Chemistry," ed. V. Gold, Academic Press, New York, 1964, vol. 2, p. 93.

¹⁴ J. G. Pritchard and F. A. Long, *J. Amer. Chem. Soc.*, 1956, **78**, 6008; 1958, **80**, 4162; P. Salomaa, L. L. Schaleger, and F. A. Long, *ibid.*, 1964, **86**, 1; C. A. Bunton and V. J. Shiner, *ibid.*, 1961, **83**, 3207.

Kinetics.—The methods have been described.^{1,3,7} For hydrolyses in dilute acid aniline was added to portions of the reaction mixture, and the acid was then titrated against standard alkali under nitrogen. (Camphoric anhydride reacts slowly with aniline;¹⁵ we therefore titrated the liberated acid quickly with 0.05N-sodium hydroxide.) For higher concentrations of mineral acid reaction was followed dilatometrically or spectrophotometrically using a Cary 14 spectrophotometer.

Oxygen Exchange.—Isotopically normal anhydride (0.5 g.) was dissolved in sufficient isotopically enriched solvent to make its concentration *ca.* 0.1M. The extent of reaction was calculated from interpolated values of the rate constants of hydrolysis. After partial hydrolysis the unreacted anhydride was extracted with chloroform, the chloroform layer was washed with water, and the anhydride was converted into its monoanilide by addition of excess of aniline.⁹ The anilide was recrystallised from chloroform to constant m. p. Camphoric anhydride was not converted into its anilide, but was purified by dissolving it in ether, washing the ethereal solution with dilute NaHCO₃, drying it (Na₂SO₄), and recrystallising the anhydride from benzene. The isolated anilides (or anhydride) were heated *in vacuo* with guanidine hydrochloride and phenylenediamine hydrochloride, and the evolved carbon dioxide was analysed mass spectrometrically.

Solubility Measurements.—Saturated solutions of camphoric anhydride in dioxan–water 12.5 : 87.5 v/v were prepared by shaking the solvent with powdered anhydride for 1 hr. at 25°. The solution was then filtered and a portion was titrated with 0.05N-sodium hydroxide under nitrogen to determine the concentration of any camphoric acid which had been formed by hydrolysis of the anhydride. The amount of unreacted anhydride was determined by heating another portion at 100° for 24 hr., in a sealed tube, and titrating the camphoric acid which was formed. A saturated solution of camphoric anhydride, at 25°, in dioxan–water 12.5 : 87.5 v/v is 8×10^{-3} M, and in dioxan–water 60 : 40 v/v is 4.5×10^{-2} M.

We thank the D.S.I.R. for a grant (N. A. F.), and the National Science Foundation for partial support of this work.

DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA,
SANTA BARBARA, CALIFORNIA.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES, UNIVERSITY COLLEGE, GOWER STREET,
LONDON W.C.1. [Received, April 20th, 1965.]

¹⁵ S. Siggia and J. G. Hanna, *Analyt. Chem.*, 1951, **23**, 1717.
