182. *The Hydrolysis of Acetic Anhydride. Part VIII.*[1] *A Comparative Study of Pivalic (Trimethylacetic) Anhydride.*

By A. R. Butler and V. Gold.

The spontaneous hydrolysis of pivalic anhydride in aqueous solution at 25° is approximately 30 times slower than that of acetic anhydride. The hydrolysis is catalysed by pivalate ions in a manner comparable to the acetate catalysis of the hydrolysis of acetic anhydride. Pivalic anhydride differs from acetic anhydride in being much less, if at all, sensitive to the catalytic influence of pyridine. This result agrees with the view that the pyridine catalysis involves an association between pyridine and an acyl group and that the association is sterically inhibited by bulky substituents in either of these entities.

Pivalic (trimethylacetic) anhydride is of interest in relation to the mechanism of hydrolysis of anhydrides mainly on account of the bulky substituent groups which distinguish it from acetic anhydride. In the present work the hydrolysis of pivalic anhydride has been compared with that of acetic anhydride: (*a*) as a spontaneous reaction, (*b*) under the influence of the common carboxylate ion, and (*c*) under the influence of pyridine. The extent to which the two reactions resemble each other under these conditions affords a test of the reaction mechanisms suggested in Parts VI and VII of this series.[2,1]

Experimental

Pivalic anhydride (b. p. 70—73°/9 mm.) was prepared by reaction between pivalic acid and acetic anhydride.[3] The absence of significant amounts of acetic anhydride and acetic pivalic anhydride in the product was confirmed by the first-order course of the hydrolyses (see below).

Sodium pivalate was prepared by neutralisation of a warm concentrated solution of pivalic acid with sodium bicarbonate. The solution was further concentrated and allowed to crystallise. The salt was filtered off and dried *in vacuo* (H_2SO_4). It was free from carbonate and bicarbonate.

Determination of Pivalic Anhydride in Solution.—Lees and Saville's determination of acetic anhydride by reaction with a buffered quenching solution of 1-naphthylamine and sodium nitrite[4] was found to be applicable to pivalic anhydride provided that the solutions were kept overnight in the dark while the colour developed. The optical densities (*D*) of the resultant dye solutions at 470 mμ were proportional to the amount of anhydride added to the quenching solution, as shown below for the addition of various small volumes of a 0·2% solution of pivalic anhydride in acetone.

Vol. of soln. (*v*)	0·10	0·20	0·30	0·40	0·50	0·60
D	0·182	0·374	0·582	0·759	0·940	1·13
D/*v*	1·82	1·87	1·94	1·90	1·88	1·88

For kinetic runs (at 25°) the anhydride was added to the reaction medium (10 ml.) as a small volume (*ca.* 0·02 ml.) of a 10% stock solution in acetone so as to produce generally an initial anhydride concentration of *ca.* 10^{-3}M. Portions (1 ml.) were removed at timed intervals and treated with quenching solution. The technique was checked by following one of the spontaneous runs by a conductivity method; the rate constant ($7{\cdot}8 \times 10^{-5}$ sec.$^{-1}$) was in good agreement with the mean value obtained in runs followed spectrophotometrically ($7{\cdot}9 \times 10^{-5}$ sec.$^{-1}$).

In the following Tables first-order rate constants are expressed in the units sec.$^{-1}$, and second-order constants as l. sec.$^{-1}$ mole^{-1}. Spontaneous rates are reported as first-order constants, k_0 (*i.e.*, without introducing the molarity of water into the calculation). All runs were of first-order with respect to anhydride. Observed first-order rate constants in the presence of added substances are designated by the symbol *k*.

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[1] Part VII, Butler and Gold, *J.*, 1961, 4362.

[2] Butler and Gold, *J.*, 1961, 2305.

[3] Ansell, Davis, Hancock, Hickinbottom, Holton, and Hyatt, *J.*, 1955, 2705.

[4] Lees and Saville, *J.*, 1958, 2262.

RESULTS

The symbol Pv represents the pivaloyl group.

Spontaneous rate:

For $[Pv_2O]_{\text{initial}} \simeq 10^{-3}$ M: $7{\cdot}9_6 \times 10^{-5}$, $7{\cdot}7_1 \times 10^{-5}$, $8{\cdot}0_5 \times 10^{-5}$. Mean: $7{\cdot}9_1 \times 10^{-5}$.
For $[Pv_2O]_{\text{initial}} \simeq 5 \times 10^{-4}$M: $8{\cdot}0_3 \times 10^{-5}$.

Effect of added sodium pivalate in the presence of pivalic acid.

[PvOH]	0·005	0·005	0·005	0·005	0·005	0·048	0·048
[NaOPv]	0	0·080	0·128	0·158	0·249	0	0·088
10^5k	$7{\cdot}8_0$	$8{\cdot}4_2$	$9{\cdot}0_2$	$9{\cdot}0_6$	$9{\cdot}5_6$	$7{\cdot}2_9$	$7{\cdot}7_5$
10^5k (calc.) *	7·84	8·44	8·80	9·03	9·71	7·24	7·90

* Calculated from the expression $10^5k = 7{\cdot}91 - 14[\text{PvOH}] + 7{\cdot}5[\text{NaOPv}]$.

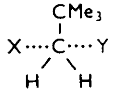
Effect of Pyridine.—This was examined in the presence of pivalic acid–pivalate buffer. In the four experiments at low concentrations of pyridine the fraction of free (*i.e.*, unprotonated) base in the buffer solution employed was determined spectrophotometrically.[2] In the three experiments at high concentrations of pyridine there is no significant reduction in the amount of free base present.

[NaOPv]	0·080	0·128	0·158	0·249	0·045	0·045	0·045
[PvOH]	0·005	0·005	0·005	0·005	0·005	0·005	0·005
$10^4[\text{Py}]_{\text{free}}$	3·23	6·78	3·52	6·56	3,550	6,250	10,400
10^5k_{buffer}	8·42	9·02	9·06	9·56	8·3 *	8·3 *	8·3 *
10^5k	7·82	8·98	9·33	9·36	23·4	42·2	60·6

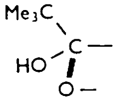
* By interpolation.

DISCUSSION

α-Methylation in acetic anhydride reduces the spontaneous rate of hydrolysis; we find a factor of 33 for the ratio of the reaction velocities of acetic and pivalic anhydride. The sequence of reaction velocities in the series acetic, propionic, isobutyric, pivalic anhydride (1 : 0·52 : 0·32 : 0·03, the first three members being taken from Verkade's work,[5] whose relative value for propionic anhydride is in good agreement with other determinations [6]) is monotonic though not quite regular. A radical change of mechanism is therefore unlikely. At first sight the absence of dramatic steric retardation (*i.e.*, by several powers of ten) in the hydrolysis of a pivaloyl compound, of the kind found in the bimolecular substitution reactions of the structurally closely related neopentyl compounds,[7] may seem surprising. The analogy between the two types of compound cannot, however, be applied to the hydrolytic reactions if the neopentyl compound forms an S_N2 transition state of the configuration (*A*), and the anhydride does not pass through a corresponding



(*A*)



(*B*)

configuration during the course of its hydrolysis, but instead goes over into a tetrahedral structure (*B*). In the more specific mechanism considered by us for the hydrolysis of acetic anhydride [2] steric hindrance is likely to affect only the pre-equilibrium (i), and is expected to be less important than in the neopentyl halide transition state. According to this mechanism, the spontaneous rate constant is given by

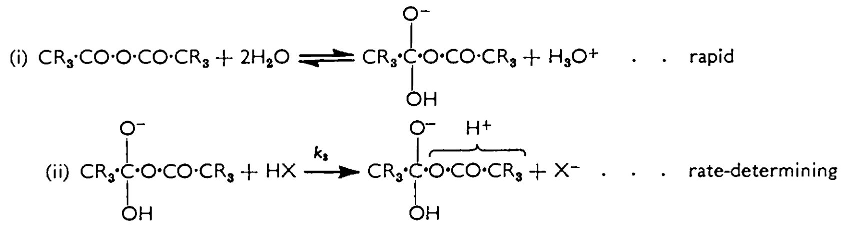
$$k_0 = K_1 k_3^{\text{H}_3\text{O}^+}$$

Verkade, *Rec. Trav. chim.*, 1916, **35**, 79.

[6] Wilsdon and Sidgwick, *J.*, 1913, **103**, 1959; Kilpatrick, *J. Amer. Chem. Soc.*, 1930, **52**, 1410; Vles, *Rec. Trav. chim.*, 1933, **52**, 809.

[7] Dostrovsky and Hughes, *J.*, 1946, 157, 164.

where K_i is the equilibrium constant for (i) and $k_3^{\mathrm{H_3O^+}}$ is the rate constant of step (ii), when $\mathrm{HX} = \mathrm{H_3O^+}$. The rate factor of 33 and the corresponding relative rates for the other methyl-substituted acetic acids are therefore to be attributed to the combined, and probably opposed, effects of methyl-substitution in the two factors of k_0.



$$\text{(i)}\quad \mathrm{CR_3{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CR_3 + 2H_2O \rightleftharpoons CR_3{\cdot}\overset{O^-}{\underset{OH}{C}}{\cdot}O{\cdot}CO{\cdot}CR_3 + H_3O^+}\quad .\ .\ \text{rapid}$$

$$\text{(ii)}\quad \mathrm{CR_3{\cdot}\overset{O^-}{\underset{OH}{C}}{\cdot}O{\cdot}CO{\cdot}CR_3 + HX \xrightarrow{k_3} CR_3{\cdot}\overset{O^-\quad H^+}{\underset{OH}{C}}{\cdot}O{\cdot}CO{\cdot}CR_3 + X^-}\quad .\ .\ .\ \text{rate-determining}$$

The catalytic effect of sodium pivalate on the reaction velocity is small, as is the effect of sodium acetate on the hydrolysis of acetic anhydride.[8] Indeed, both these effects are only of the same order of magnitude as the retarding influence of the two corresponding acids in the hydrolysis reactions for which no specific model has yet been suggested and which can formally (but not very informatively) be represented as medium or activity effects. The mechanistic significance of the carboxylate-ion effect as general base catalysis is, however, more firmly established by comparison of its magnitude with other salt effects.[8] Leaving aside any possible correction of the catalytic constant for such a salt effect the following comparison can be made between the influence of sodium acetate on the hydrolysis of acetic anhydride and that of sodium pivalate on the hydrolysis of pivalic anhydride. For acetic anhydride, $k_{\mathrm{NaOAc}}/k_0 = 4{\cdot}0/2{\cdot}61 = 1{\cdot}53$; for pivalic anhydride, $k_{\mathrm{NaOPv}}/k_0 = 7{\cdot}5/7{\cdot}9 = 0{\cdot}95$. According to this mechanism

$$k_{\mathrm{NaOAc}}/k_0 = k_3^{\mathrm{AcOH}}/k_3^{\mathrm{H_3O^+}}K_{\mathrm{AcOH}}$$

whence we deduce that

$$\begin{aligned}(k_3^{\mathrm{AcOH}}/k_3^{\mathrm{H_3O^+}})_{\mathrm{Ac_2O}}/(k_3^{\mathrm{PvOH}}/k_3^{\mathrm{H_3O^+}})_{\mathrm{Pv_2O}} &= (K_{\mathrm{AcOH}}k_{\mathrm{NaOAc}}/k_0)_{\mathrm{Ac_2O}}/(K_{\mathrm{PvOH}}k_{\mathrm{NaOPv}}/k_0)_{\mathrm{Pv_2O}}\\ &= 1{\cdot}75 \times 10^{-5} \times 1{\cdot}53/(0{\cdot}93 \times 10^{-5} \times 0{\cdot}95) = 3{\cdot}0.\end{aligned}$$

By a calculation analogous to that given previously,[2] the results can further be shown to imply that the Brønsted exponent for proton transfer from acids to the anionic intermediate is slightly greater (0·49) for pivalic anhydride than for acetic anhydride (0·43 or 0·435). The magnitude of the catalytic effect of pivalate ions in the present case is therefore entirely consistent with the suggested mechanism.

By contrast with the similar effects of the common carboxylate ions, the influence of pyridine is entirely different in the two reactions. For acetic anhydride a concentration of free pyridine of $4{\cdot}3 \times 10^{-4}$M is sufficient to produce a catalytic acceleration greater than the velocity of the spontaneous reaction.[1] In the hydrolysis of pivalic anhydride no significant effect can be discerned at such a low concentration of pyridine. Experiments at higher concentrations of pyridine suggest that a doubling of reaction velocity would require a catalyst concentration of *ca.* 1800×10^{-4}M. However, the experiments performed so far do not rule out the possibility that this acceleration is due to hydroxide ions, formed as a consequence of the hydrolytic protonation of pyridine. Accordingly, pyridine is *at least* 400 times less effective with pivalic anhydride than it is with acetic anhydride, but the factor may be even much greater if some catalysis by hydroxide ion occurs at high concentrations of pyridine.

This lower effectiveness of pyridine constitutes a crucial test for the mechanism of pyridine catalysis[1,9,10] suggested for acetic anhydride. We have previously explained

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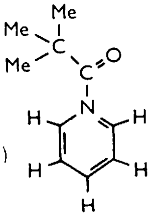
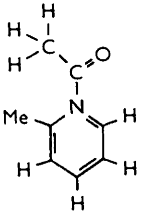
[8] Kilpatrick, *J. Amer. Chem. Soc.*, 1928, **50**, 2891.
[9] Bafna and Gold, *J.*, 1953, 1406.
[10] Gold and Jefferson, *J.*, 1953, 1409.

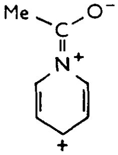
the absence of catalytic efficiency [1,10] in α-substituted pyridine bases as being due to steric hindrance of the formation of α-substituted 1-acetylpyridinium ions, and not to steric hindrance of some other step, such as a proton transfer involving the pyridine base or its conjugate acid. This interpretation requires as a corollary that it should be possible to eliminate or reduce the catalysis by bulky substituents in the acyl portion of the adduct, and the experiments with pivalic anhydride were performed to test this prediction. The results obtained support the proposed model and confirm that the 1-pivaloylpyridinium ion (I) and the 1-acetyl-2-picolinium ion (II) are destabilised by steric hindrance in a similar way.

(I)



(II)





(III)

The absence of pyridine catalysis in the hydrolysis of pivalic anhydride suggests that the effectiveness of this catalyst in other acylation reactions will depend on the structure of the acid anhydride or acyl halide employed.

The existence of steric strain in structures (I) and (II) is not fully explained. Since the steric interference between the acyl group and the α-positions in pyridine is relieved by rotation of the acyl group out of the plane of the heteroaromatic ring, Gold and Jefferson postulated that this rotation was attended by a loss of resonance stabilisation,[10] but this interpretation implies the unexpected significance of structures such as (III) in which two positive charges are located in the ring.

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