859. *The Hydrolysis of Acetic Anhydride. Part VII.* Catalysis by Pyridine and Methylpyridines in Acetate Buffers.*

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The effect of pyridine, 2- and 3-picoline, and 2,6-lutidine on the rate of hydrolysis of acetic anhydride in acetate buffer has been measured and related to the spectrophotometrically determined concentrations of unprotonated base in solution. There is no detectable catalysis by the 2-substituted bases. The catalytic effect of pyridine is inversely proportional to the concentration of acetate ions in solution, and it is reduced by a factor of 5 ± 1 on replacement of the solvent by deuterium oxide. The results agree with a mechanism in which 1-acetylpyridinium ions are formed reversibly from pyridine and acetic anhydride, the subsequent hydrolysis of these ions being rate-determining.

The pyridine-catalysed hydrolysis of acetic anhydride in aqueous solution was studied by Gold and Jefferson [1] who formulated the mechanism as

$$Ac_2O + Py \underset{-1}{\overset{1}{\rightleftharpoons}} PyAc^+ + OAc^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$PyAc^+ + H_2O \xrightarrow{2} AcOH + PyH^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

the 1-acetylpyridinium ion ($PyAc^+$) being an unstable intermediate. It was then considered that reaction 1 was the rate-controlling step since (in 50% acetone–water) the catalytic coefficient of pyridine was not found to bear an inverse relation to the concentration of acetate ion.

During some recent experiments on the spontaneous and catalysed hydrolysis of acetic anhydride in deuterium oxide it was observed that the pyridine-catalysed hydrolysis was considerably retarded by the change in solvent from ordinary water to deuterium oxide.[2] This result (which is more fully reported in the present paper) prompted us to examine the kinetics of the catalysis by pyridine bases in greater detail, since it appeared improbable that reaction (1) could be subject to a large solvent isotope-effect. A similar rate-controlling transfer of an acetyl cation (from acetic anhydride to a formate ion) is thought to be the mechanism of catalysis by formate ions [3] and, as expected for such a mechanism, only a very small solvent isotope-effect is found in this case.[2,4]

The use of buffer solutions in the experiments now reported permitted observation of the catalysed hydrolyses as first-order reactions, since it ensured the constancy of the concentration of free pyridine (as distinct from protonated pyridine) during each kinetic run. This concentration was determined for each buffer mixture by spectrophotometric measurements similar to those described by Herington.[5] In this way it was possible to assess separately the effect of added acetate ion on the concentration of free pyridine and its effect on the velocity of the pyridine-catalysed hydrolysis at a given concentration of free pyridine.

Experimental

Reagents were purified as described in earlier Parts of the series, with the following exceptions:

2,6-Lutidine was warmed with urea (120 g.) and water (40 ml.) to 80° and the white

* Part VI, *J.*, 1961, 2305.

[1] Gold and Jefferson, *J.*, 1953, 1409.
[2] Butler and Gold, *Proc. Chem. Soc.*, 1960, 15.
[3] Kilpatrick, *J. Amer. Chem. Soc.*, 1928, **50**, 2891; Gold and Jefferson, *J.*, 1953, 1416.
[4] Butler and Gold, *J.*, 1961, 2305.
[5] Herington, *Discuss. Faraday Soc.*, 1950, **9**, 26; Andon, Cox, and Herington, *Trans. Faraday Soc.*, 1954, **50**, 918.

crystalline complex formed was filtered off and washed rapidly with water. Distillation of a mixture of the crystals with water (200 ml.) yielded the water–2,6-lutidine azeotrope (b. p. 96°) from which lutidine separated on addition of solid sodium hydroxide. The lutidine was dried (NaOH) and distilled. The whole procedure was repeated twice more, the final product distilling sharply at 143°. The object of this treatment was the removal of unhindered homologues or isomers since the formation of the urea complex is stated to be specific to 2,6-substituted pyridines.[6]

3-Picoline (200 g.) was freed from isomeric impurities[7] by refluxing it with phthalic anhydride (50 g.) and acetic anhydride (50 g.) for 4 hr. The mixture was poured into water (1 l.), rendered alkaline with sodium hydroxide, and distilled (b. p. of azeotrope with water, 97°). A 2-picoline layer was formed on addition of solid sodium hydroxide. It was separated, dried (NaOH), and distilled (b. p. 143°).

Hydrolysis velocities of acetic anhydride were determined in sodium acetate–acetic acid buffer solutions containing a low concentration of the pyridine base. In order to keep the extent of protonation of the bases to a minimum, the concentration of acetic acid in the buffer solutions was made as low as was compatible with the requirement of constancy of the degree of protonation during the course of a run. (In experiments with 2,6-lutidine—which was catalytically inactive—it was more important to achieve a high rather than a constant concentration of free base, and the concentration of acetic acid in the buffer was almost of the same magnitude as the concentration of acetic acid generated during the hydrolysis.) The reactions were followed by the modified [4] method of Lees and Saville.[8]

The media for kinetic experiments were prepared by diluting 10 ml. of an accurately prepared aqueous solution of a pyridine base to 250 ml. with sodium acetate–acetic acid buffer solution. The degree of protonation of the pyridine bases in these buffer media was determined spectrophotometrically as follows. Three separate aliquot portions (5 ml.) of the above solution of pyridine base in buffer solution were separately diluted to 25 ml. with (i) N-sulphuric

TABLE 1.

Specimen evaluation of α, for pyridine.

$10^5[Py]_{stoich.}$	2·74	5·76	7·76	9·31	11·72
D_{PyH^+}	0·155	0·309	0·417	0·491	0·621
D_{Py}	0·082	0·152	0·191	0·242	0·292
D	0·100	0·207	0·279	0·331	0·418

acid, (ii) N-sodium hydroxide, and (iii) a sodium acetate–acetic acid solution prepared by diluting 960 ml. of the buffer employed in preparing a reaction medium with water to 1 l. The buffer concentration in a solution resulting from dilution (iii) is the same as that in the reaction medium, so that (apart from a temperature effect discussed below) the degree of protonation of the pyridine base in this solution should also equal that in the reaction medium. Dilutions (i) and (ii) cause complete conversion of the pyridine base into the protonated and the unprotonated form, respectively. The optical densities of the diluted solutions were measured in matched 1 cm. quartz cells at a suitable wavelength (252 mμ for pyridine, 270 mμ for 2,6-lutidine, 262 mμ for 2-picoline, and 260 mμ for 3-picoline), a corresponding solution without pyridine base being used in the reference beam of the spectrophotometer. If the optical densities of the solutions resulting from dilutions (i), (ii), and (iii) are designated by the symbols D_{PyH^+}, D_{Py}, and D, respectively, the portion (α) of the pyridine base present in the unprotonated form is given by $\alpha = (D_{PyH^+} - D)/(D_{PyH^+} - D_{Py})$. This determination was repeated for several concentrations of a pyridine base, and the best value of α was evaluated from the slopes of the straight lines obtained by plotting the three optical densities against the stoicheiometric concentration of the pyridine base. The procedure is illustrated for pyridine (Table 1). The slopes of the three lines are: for D, 3590; for D_{PyH^+}, 5310; for D_{Py}, 2550 mole^{-1} l.; whence $\alpha = (5310 - 3590)/(5310 - 2550) = 0{\cdot}62_4$.

The experiments with deuterium oxide involved a scaling-down of the same general procedure.

The optical density measurements were performed with a Beckman DU spectrophotometer, without temperature regulation, and relate to a temperature of 22° ± 3°. We must consider

[6] U.S.P. 2,376,008.
[7] Riethof, Richards, Savitt, and Othmer, *Ind. Eng. Chem., Analyt. Ed.*, 1946, **18**, 458.
[8] Lees and Saville, *J.*, 1958, 2262.

whether the value of α determined at this temperature may be applied to the evaluation of catalytic coefficients at 25°. The temperature-dependence of α at a fixed acetate-buffer composition is governed by the temperature-dependence of the ratio of acid dissociation constants K_{AcOH}/K_{PyH^+}. The temperature-variation of K_{AcOH} is well-known to be very small in this region and that of the dissociation constants of pyridinium and 2-picolinium ions can be evaluated from thermochemical measurements.[9] It follows from these data that the values of α which were measured at 22° ± 3° should be increased by *ca.* 5 ± 5% in order to apply at 25°.

TABLE 2.

Pyridine catalysis.

(a) *Effect of varying pyridine concentration*: $\alpha = 0{\cdot}62_4$

$10^4[Py]_{stoich.}$ (M)	$10^4[Py]_{free}$ (M)	10^3k (sec.$^{-1}$)	$10^3(k - k_{Buffer})$ (sec.$^{-1}$)	$(k - k_{Buffer})/[Py]_{free}$ (sec.$^{-1}$ mole^{-1} l.)
0	0	2·89	—	—
1·99	1·24	3·65	0·76	6·1
2·88	1·80	4·04	1·15	6·4
3·88	2·42	4·44	1·55	6·4
4·91	3·06	4·88	1·99	6·5
6·89	4·30	5·67	2·78	6·5

(b) *Experiments in deuterium oxide*: [AcONa] = 0·015M; $\alpha = 0{\cdot}32_2$

$10^4[Py]_{stoich.}$	$10^4[Py]_{free}$	10^3k	$10^3(k - k_{Buffer})$	$[OAc^-](k - k_{Buffer})/[Py]_{free}$
0	0	$0{\cdot}97_1$	—	—
4·37	1·41	$1{\cdot}44_6$	$0{\cdot}47_5$	0·049

(c) *Effect of varying acetate concentration*:

$10^4[Py]_{stoich.}$	α	$10^4[Py]_{free}$	100[NaOAc]	10^3k	10^3k_{Buffer}	$10^3(k - k_{Buffer})$	$(k - k_{Buffer})/[Py]_{free}$
3·99	0·592	2·36	6·21	4·26	2·84	1·42	6·0
5·86	0·524	3·07	3·66	4·95	2·74	2·21	7·2
4·98	0·494	2·46	3·55	4·64	2·74	1·90	7·7
5·28	0·429	2·26	2·44	4·95	2·70	2·25	10·0
5·85	0·351	2·05	1·82	5·14	2·67	2·47	12·0
5·25	0·318	1·67	1·53	5·41	2·66	2·75	16·5

From graph in Fig. 2: $[OAc^-](k - k_{Buffer})/[Py]_{free} = 0{\cdot}25$.

TABLE 3.

Effect of other pyridine bases.

(a) *2-Picoline*: $\alpha = 0{\cdot}23_0$ (0·23)

$10^4[Pic.]_{stoich.}$	$10^4[Pic.]_{free}$	10^3k
0	0	2·89
4·57	1·05	2·89
7·92	1·82	2·89
11·1	2·55	2·89
13·3	3·06	2·90
16·2	3·72	2·89

(b) *3-Picoline*: $\alpha = 0{\cdot}32_4$ (0·39)

$10^4[Pic.]_{stoich.}$	$10^4[Pic.]_{free}$	10^3k	$10^3(k - k_{Buffer})$	$(k - k_{Buffer})/[Pic.]_{free}$
0	0	2·89	—	—
2·49	0·81	4·49	1·60	20
4·51	1·46	5·96	3·07	21
6·94	2·25	7·72	4·83	21
9·15	2·96	8·90	6·01	20
11·4	3·69	10·60	7·71	21

(c) *2,6-Lutidine*: $\alpha = 0{\cdot}083$

$10^4[Lut.]_{stoich.}$	$10^4[Lut.]_{free}$	10^3k
0	0	2·89
7·88	0·65	2·89
11·5	0·96	2·88
16·2	1·35	2·89
22·6	1·88	2·88

Such a correction has not been applied in the evaluation of the quoted catalytic coefficients which are accordingly subject to a corresponding systematic error. The error is of marginal significance and, in particular, does not affect the conclusions drawn from the series of experiments with pyridine and different concentrations of acetate.

The effect on the reaction of pyridine, 2- and 3-picoline, and 2,6-lutidine was measured at different concentrations of pyridine base. The same buffer solution was used for the first

[9] Levi, McEwan, and Wolfenden, *J.*, 1949, 760.

three bases; that used with 2,6-lutidine was slightly less acidic. The apparent catalytic coefficient of each base in a given medium was evaluated from the slope of the graph (Fig. 1) of the experimental first-order rate coefficient against the concentration of free base (*i.e.*, $[Py]_{free} = \alpha[Py]_{stoich.}$). The rectilinear course of these graphs for pyridine and 3-picoline indicates first-order dependence on the catalyst concentration. All individual runs conformed accurately to the first-order law (*i.e.*, first-order in acetic anhydride).

In the case of pyridine alone, the catalysis was also studied as a function of the concentration of acetate ion. Under these conditions, acetate catalysis makes a different contribution to the reaction velocity at each concentration. The pyridine-catalysed contribution to the rate was therefore evaluated by subtracting from each measured rate constant the rate constant (k_{Buffer}) for the particular buffer medium in the absence of pyridine. These control values were calculated from the previously determined catalytic coefficient for acetate ions.[4] The apparent catalytic coefficient of pyridine $(k - k_{Buffer})/[Py]_{free}$ was plotted against the reciprocal of the concentration of acetate ions in solution (Fig. 2).

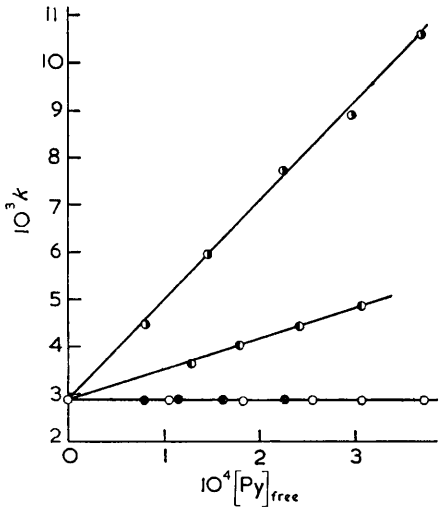

FIG. 1. Dependence of reaction velocity on catalyst concentration.

◐ Pyridine. ○ 2-Picoline. ◑ 3-Picoline. ● 2,6-Lutidine.

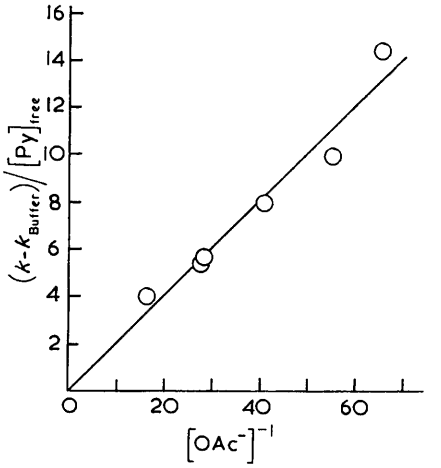

FIG. 2. Dependence of pyridine catalysis upon acetate concentration.

The earlier groups of experiments (Tables 2a and 3) were carried out before the full importance of the concentration of acetate ions in the reaction had been realised, and the buffer solutions used in these experiments were not made up exactly. However, since the first group of experiments on pyridine (Table 2a) and those on the two picolines relate to the same batch of buffer solution, the determined relative values of α should be consistent with the known dissociation constants of these bases.[5] To test this, a second set of values of α has been calculated (given in parentheses in Table 3) on the assumption that our value of α for pyridine is exact and by taking the differences between the pK values of pyridine and the picolines from earlier work.[5]

Discussion

The results now reported indicate (i) that the pyridine-catalysed contribution to the rate of hydrolysis of acetic anhydride is proportional to the concentration of free pyridine in solution (Fig. 1) and inversely proportional to the concentration of acetate ion (Fig. 2), (ii) that the rate of the pyridine-catalysed reaction is depressed on going from ordinary water to deuterium oxide as solvent, and (iii) that the conclusions drawn previously [1] from experiments on unbuffered solutions concerning the relative efficiency of pyridine, 2- and

3-picoline, and 2,6-lutidine as catalysts are at least qualitatively correct. The inverse dependence of the catalysed rate on acetate concentration is not evident on casual examination of our data or from experiments in unbuffered media, since the addition of acetate ions also causes an increase in α (the portion of the pyridine base which remains unprotonated in a given solution) as well as exerting a small catalytic effect of its own.

All three results are consistent with the mechanism described by equations (1) and (2), with the specific condition that the second step is the rate-controlling destruction of an unstable intermediate. The inhibiting effect of acetate represents a common-ion effect on the rapidly established equilibrium (1). This mechanism requires the rate law

$$v = \frac{k_1 k_2}{k_{-1}} \cdot \frac{[\mathrm{Py}][\mathrm{Ac_2O}]}{[\mathrm{OAc^-}]},$$

where [Py] represents the spectrophotometrically determined concentration of unprotonated pyridine in solution, and k_1, k_{-1}, and k_2 are the rate coefficients of the respective steps, the concentration of solvent being taken as unity. The final values of $[\mathrm{OAc}](k - k_{\mathrm{Buffer}})/[\mathrm{Py}]_{\mathrm{free}}$ evaluated in Tables 2(b and c) for water and deuterium oxide as solvent therefore represent the ratio k_1k_2/k_{-1}. The solvent isotope-effect on this ratio [*i.e.*, $(k_1k_2/k_{-1})_{\mathrm{H_2O}}/(k_1k_2/k_{-1})_{\mathrm{D_2O}}$] is found to have a value of 5 ± 1, where the indicated limits of uncertainty express an estimate of the accumulated errors in the final result. The equilibrium constant of reaction (1), *i.e.*, k_1/k_{-1}, is expected to be only slightly affected by the isotopic solvent change, so that the large isotope effect reflects in the main a large value of $(k_2)_{\mathrm{H_2O}}/(k_2)_{\mathrm{D_2O}}$. This isotope effect may arise from causes similar to those suggested as explanation of the solvent isotope-effect in the spontaneous hydrolysis of acetic anhydride,[4] but it is as yet not possible to give an exact interpretation of the value found. A large isotope effect in the hydrolysis of the acetylpyridinium ion is reasonable on the ground that the spontaneous hydrolyses of two similar molecules, 1-acetylimidazole and 1-acetylpyrazole, show similar effects, $k_{\mathrm{H}}/k_{\mathrm{D}}$ being 2·5 in the former case[10] and 3·4 in the latter.[11]

The catalytic effect exerted by the four pyridine bases studied clearly separates them into the two categories previously suggested. According to our earlier work, high catalytic activity is associated with absence of α-substituent groups. The more precise conditions of the present experiments allow more definite conclusions. It now appears that 2-picoline and 2,6-lutidine do not produce any significant catalytic effect. This conclusion is less certain in the second case, owing to the extensive—though by no means complete—protonation of lutidine in the solutions employed. It is more certain and more remarkable that even the blocking of a single α-position in pyridine by a methyl group suffices to inhibit the catalytic power, although, towards protons, 2-picoline is a stronger base than pyridine, the ratio of dissociation constants[5] being 5·5. A very small catalytic effect would escape detection, but our measurements indicate that the catalytic coefficient of 2-picoline must be smaller than that of pyridine by a factor exceeding *ca.* 100, *i.e.*, the standard free energies of activation must differ by at least *ca.* 2·8 kcal. mole^{-1}. This factor is thought to reflect in the main the steric effect of α-substitution on the equilibrium constant of reaction (1), and a comparison with other addition reactions of pyridine and 2-picoline which are subject to steric effects may be cited. The dissociation constant of the 2-picoline–trimethylboron adduct is so much greater than that of the corresponding pyridine complex that its value could not be obtained by measurement of the dissociation pressure.[12] In nitrobenzene solution the addition reaction of trimethylboron with 2-picoline is less exothermic than that with pyridine by 5·3 kcal. mole^{-1} and, after allowance for an electronic effect, it is estimated that the steric effect of the 2-methyl group is responsible for a change of *ca.* 5·9 kcal. mole^{-1}. A similar, but smaller, steric

[10] Jencks and Carriuolo, *J. Biol. Chem.*, 1959, **234**, 1272.
[11] Hüttel and Kratzer, *Chem. Ber.*, 1959, **92**, 2014.
[12] Brown and Barbaras, *J. Amer. Chem. Soc.*, 1947, **69**, 1137.

effect on the enthalpy change is deduced in the reaction with boron trifluoride (*ca.* 2·2 kcal. mole^{-1}) and diborane (*ca.* 1·3 kcal. mole^{-1}).[13] If these effects on the enthalpy changes on addition are reproduced in the Gibbs free energies, the results may be compared with the difference in catalytic power in our reaction, and with the difference in free-energy changes on addition of an acetyl cation to pyridine and 2-picoline. The minimum figure of 2·8 kcal. mole^{-1} could therefore be interpreted as implying that the steric requirements of the acetyl group in the 1-acetylpyridinium ion exceed those of $-\overline{B}F_3$ and $-\overline{B}H_3$ in the corresponding adducts.

KING'S COLLEGE, STRAND, LONDON, W.C.2. [*Received, April 4th,* 1961.]

[13] Brown, *J. Chem. Educ.*, 1959, **36**, 424; Gold, in "Progress in Stereochemistry," Vol. III, ed. Klyne and de la Mare, Butterworths, London, in the press.