251. *The Acetate-catalysed Hydrolysis of* p-*Nitrophenyl Acetate.*

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The rates of the spontaneous and acetate-catalysed hydrolyses of *p*-nitrophenyl acetate have been measured in aqueous solution at 25°. By carrying out the hydrolysis in presence of both acetate and a low concentration of aniline (which would be an effective competitor for any acetic anhydride in solution, to form acetanilide) and analysing the product solution for acetanilide, it has been shown that the acetate-catalysed reaction does not in the main go by way of acetic anhydride as an intermediate.

The hydrolysis of phenyl acetate and of *p*-nitrophenyl acetate (*p*-NPA), catalysed by bases of various kinds (including amines [1] and acetate ions [2]), has been explained in terms of the mechanism [3]

$$\mathrm{ArO{\cdot}Ac} + \mathrm{B} \rightleftharpoons \mathrm{BAc^+} + \mathrm{ArO^-} \qquad \qquad (1)$$

$$\mathrm{BAc^+} + \mathrm{H_2O} \longrightarrow \mathrm{BH^+} + \mathrm{AcOH} \qquad \qquad (2)$$

referred to as nucleophilic catalysis by the base B (where Ar is the *p*-nitrophenyl group).

The implied formation of acetic anhydride in the acetate-catalysed hydrolysis of *p*-nitrophenyl acetate (an ester which can almost be regarded as an unsymmetrical anhydride in view of the acidity of *p*-nitrophenol) is strictly comparable with the mechanism for the acetate-catalysed hydrolysis of acetic propionic anhydride [4] or the chloroacetate-catalysed hydrolysis of acetic chloroacetic anhydride,[5] which have been satisfactorily explained in terms of the intermediate formation of an anhydride of higher reactivity towards water. Although the nucleophilic mechanism therefore appears to be reasonable, it was of interest to test its applicability in the present case by a direct experiment. In particular, the fact that both pyridine- and acetate-catalysis *can* be described in terms of a single mechanism was not regarded as strong support for that mechanism, since with acetic anhydride the evidence points conclusively to the existence of two distinct mechanisms of hydrolysis in the presence of these two catalysts.[6,7] The result is of interest in connection with attempts to systematise the respective roles of base and nucleophilic catalysis in ester hydrolysis.[3,8,9]

The experiments now to be described were designed to establish the intermediacy of acetic anhydride by diverting its further reaction from hydrolysis to acetylation. In dilute aqueous solution aniline competes successfully with water for acetic anhydride, and even in an aniline solution as dilute as 5×10^{-4}M over 80% of any acetic anhydride

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[1] Bruice and Lapinski, *J. Amer. Chem. Soc.*, 1958, **80**, 2265.

[2] (*a*) Bruice and Schmir, *J. Amer. Chem. Soc.*, 1958, **80**, 148; (*b*) Bender and Neveu, *J. Amer. Chem. Soc.*, 1958, **80**, 5388.

[3] Bender and Turnquest, *J. Amer. Chem. Soc.*, 1957, **79**, 1656; Bender, *Chem. Rev.*, 1960, **60**, 53.

[4] Kilpatrick and Kilpatrick, *J. Amer. Chem. Soc.*, 1930, **52**, 1418.

[5] Emery and Gold, *J.*, 1950, 1447.

[6] Gold and Jefferson, *J.*, 1953, 1409; Butler and Gold, *J.*, 1961, 4362.

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

[8] Jencks and Carriuolo, *J. Amer. Chem. Soc.*, 1960, **82**, 1778.

[9] Jencks and Carriuolo, *J. Amer. Chem. Soc.*, 1961, **83**, 1743.

would react to form acetanilide rather than undergo hydrolysis.[10] It is also known that acetanilide would not itself be hydrolysed under these conditions. Our aim was therefore to carry out the acetate-catalysed hydrolysis of *p*-nitrophenyl acetate in the presence of aniline, and to determine the product composition. Put simply, the intermediate formation of acetic anhydride should lead to acetanilide, whereas other catalytic mechanisms might not. In practice, several complications of this simple analysis have to be considered. This technique provides a general and direct method for obtaining evidence concerning the existence of anhydride intermediates, notwithstanding the fact that subsequent hydrolysis of the anhydride may be faster than its formation.

The rate constants for the spontaneous hydrolysis of *p*-nitrophenyl acetate and the catalytic coefficient of acetate ion in water at 25° were re-determined, so that we could specify experimental conditions under which most of the substrate is hydrolysed by the acetate-catalysed route.

EXPERIMENTAL

Kinetic Measurements of Acetate Catalysis.—The hydrolysis of *p*-nitrophenyl acetate (initial concentration $1{\cdot}04 \times 10^{-4}$M) was studied in solutions made by dilution of a stock buffer solution containing 0·479M-sodium acetate and 0·170M-acetic acid with 0·479M-sodium chloride. To start a reaction 0·10 ml. of a 0·104M-solution of *p*-nitrophenyl acetate in dioxan was added from a micro-pipette to 100 ml. portions of acetate buffer at the thermostat temperature (25°). Portions of the mixture were removed at intervals and the progress of the reaction was followed by spectrophotometric observation of the increasing absorption at 320 mμ. Infinity values were obtained by hydrolysis in 0·1M-sodium hydroxide and acidification of the sample before analysis. The reactions followed the first-order law. The ionic strength employed is rather high but largely dictated by the main requirement that the acetate-catalysed rate in the more concentrated solutions should greatly outweigh the spontaneous reaction. Nevertheless, the addition of sodium chloride to maintain the ionic strength constant probably has some compensating effect.

Some results with various concentrations of salts are reported in Table 1.

TABLE 1.

Catalytic effect of sodium acetate.

[NaOAc] (M)	0·0	0·120	0·240	0·360	0·479
[NaCl] (M)	0·479	0·360	0·240	0·120	0·000
10^7k_1 (sec.$^{-1}$)	6·67	13·1	19·2	26·7	33·4
10^7k_1 (calc.*) (sec.$^{-1}$)	6·7	13·3	19·9	26·5	33·1

* Calc. from expression, $10^7k_1 = 6{\cdot}7 + 55$[NaOAc]. The corresponding equation calculated from the results given by Jencks and Carriuolo [8] is $10^7k_1 = 5{\cdot}5 + 85$[KOAc], at constant ionic strength ($I = 1$).

Detection of Acetanilide.—The analytical problem in the competition experiments below is the detection of acetanilide in the presence of the acetate buffer, *p*-nitrophenol, and aniline. The absorption spectra of relevant solutions indicated that acetanilide could be detected by spectrophotometric measurements on acidified solutions at 238 mμ. The optical densities of the following solutions were recorded at this wavelength and at 320 mμ, after two-fold dilution of each solution with M-sulphuric acid. The solution in the reference cell contained aqueous sulphuric acid of the same final concentration (0·5M) together with such a concentration of dioxan as was present in the sample cell. (*p*-Nitrophenyl acetate was added to the medium in the form of a small volume of a stock solution in dioxan.) The measurements can be combined in various ways to check the internal consistency of the results. In all these experiments the buffer contained sodium acetate (0·256M) and acetic acid (0·085M).

Acetate-catalysed Hydrolysis of p-*Nitrophenyl Acetate in Presence of Aniline.*—The two solutions 5 and 6 of Table 2 were prepared and kept at 25°. Samples were removed at timed intervals, diluted as in the first set of kinetic measurements, and examined spectrophotometrically at 238 and 320 mμ. The object of the measurements at 320 mμ was to observe the progress

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[10] Koskikallio, *Suomen Kem.*, 1959, *B*, **32**, 133.

of the reaction, since the absorption at this wavelength (which is mainly due to *p*-nitrophenol) undergoes a very large change during the reaction (Table 3). The measurements at 238 mμ were carried out in order to estimate the amount of acetanilide formed. Only the initial and the final values at this wavelength are of special interest, since the total change is not sufficiently large for the evaluation of an accurate rate constant, although the rate of change is in satisfactory agreement with the result at the longer wave-length.

TABLE 2.

Light absorption of various solutions.

No. of soln.	Compn. before diln. with H_2SO_4	Optical density at 238 mμ	Optical density at 320 mμ	No. of soln.	Compn. before diln. with H_2SO_4	Optical density at 238 mμ	Optical density at 320 mμ
1	Buffer Aniline ($6·62_5 \times 10^{-4}$M)	0·238	0·009	5	*p*-NPA ($1·32 \times 10^{-4}$M) Aniline ($6·62_5 \times 10^{-4}$M)	0·215 *	0·086 *
2	Aniline ,, ,,	0·028	0·009	6	Buffer *p*-NPA ($1·32 \times 10^{-4}$M) Aniline ($6·62_5 \times 10^{-4}$M)	0·418 *	0·089 *
3	Acetanilide ($1·32 \times 10^{-4}$M)	0·693	0				
4	*p*-Nitrophenol ($1·32 \times 10^{-4}$M)	0·275	0·652				

* Immediately after mixing.

From the results in Tables 2 and 3 the acetanilide contribution to the optical density of solution 6 at 238 mμ at the completion of reaction is given by the final value at this wavelength (Table 3: 0·650) *minus* the contributions made by *p*-nitrophenol (Table 2, solution 4: 0·275) and the buffer containing aniline (Table 2, solution 1: 0·238). This value would not be appreciably changed even if a considerable amount of acetanilide were formed during the reaction, since aniline was present in considerable excess over *p*-nitrophenyl acetate, and the contribution of aniline itself to this absorption—as shown by the value for solution 2—is small. The maximum amount of acetanilide which could be formed during the reaction would be equivalent to the initial concentration of ester. This would contribute to the optical density the value for solution 3 in Table 2 (0·693). Therefore the fraction of ester which is converted into acetanilide at the end of reaction in solution 6 is (0·650 — 0·275 — 0·238)/0·693 = 0·20. This fraction of acetanilide includes any that is formed by direct acetylation of aniline by *p*-nitrophenyl acetate under the catalytic influence of acetate ions. The fraction of acetanilide formed from the aryl acetate and aniline in the absence of acetate (solution 5) is analogously calculated to be (0·350 — 0·275 — 0·028)/0·693 = 0·05.

TABLE 3.

Time-variation of optical densities of solutions 5 and 6 (see Table 2).

Time (hr.)	Solution 5 optical density at 238 mμ	Solution 5 optical density at 320 mμ	Solution 6 optical density at 238 mμ	Solution 6 optical density at 320 mμ	Time (hr.)	Solution 5 optical density at 238 mμ	Solution 5 optical density at 320 mμ	Solution 6 optical density at 238 mμ	Solution 6 optical density at 320 mμ
0	0·215	0·086	0·418	0·089	231	0·313	0·380	0·638	0·620
40	0·208	0·159	0·488	0·278	302	0·308	0·433	—	—
88	0·241	0·215	0·540	0·412	494	0·332	0·608	—	—
135	0·280	0·280	0·595	0·525	686	0·347	0·442	—	—
184	0·290	0·330	0·593	0·561	∞	0·350 *	0·659 †	0·650	0·659

* Extrapolated value. † Assumed to be the same as the corresponding value for solution 6.

The optical densities (D) for both solutions at 320 mμ conform to a first-order law. Rate constants were evaluated from the linear graphs of log ($D_\infty - D_t$) against time. Solution 5: $k = 8·5 \times 10^{-7}$ sec.$^{-1}$. Solution 6: $k = 26·8 \times 10^{-7}$ sec.$^{-1}$.

The Efficiency of the Diversion Reaction.—The fraction of acetanilide expected if the acetate-catalysed reaction went through acetic anhydride is calculated as follows:

Total hydrolysis velocity in presence of 0·256M-sodium acetate: $20·8 \times 10^{-7}$ sec.$^{-1}$.

Spontaneous hydrolysis velocity: $6·7 \times 10^{-7}$ sec.$^{-1}$.

Therefore, acetate-catalysed fraction of reaction = (20·8 — 6·7)/20·8 = 0·68.

The percentage (p) of acetic anhydride which would form acetanilide in the reaction medium was determined directly. Acetic anhydride (1 ml. of a 0·13M-stock solution in dioxan) was added dropwise to a stirred solution (1 l.) of composition closely similar to that of solution 1 (sodium acetate 0·257M; acetic acid 0·087M; aniline $5·82 \times 10^{-4}$M). After being kept for *ca.* 2 hr., the solution was analysed for acetanilide by the spectrophotometric procedure described above. The concentration of acetanilide found corresponded to 82% of the acetic anhydride added. This is equivalent to $p = 84\%$ at the slightly higher concentration of aniline employed in the experiment with *p*-nitrophenyl acetate. This result agrees well with a calculation based on Koskikallio's value [10] for the rate of acetylation of aniline by acetic anhydride in aqueous solution and our value for the rate of acetate-catalysed hydrolysis,[7] from which p is found to be 82% on the assumption that the acetylation of aniline is not catalysed by acetate ion (or 86% if the relative importance of acetate catalysis, *i.e.*, the ratio of rate constants for the catalysed and the uncatalysed process, is the same in acetylation and hydrolysis). Taking the experimental value of 84%, we accordingly calculate that a mechanism of acetate-catalysis involving acetic anhydride as an intermediate should, under the conditions of the experiment with solution 6, convert $0{\cdot}68 \times 84 = 57\%$ of the *p*-nitrophenyl acetate into acetanilide. Experimentally only 20% of acetanilide is found.

Direct Acetylation of Aniline by p-*Nitrophenyl Acetate.*—We now calculate whether any part of this figure of 20% is due to direct acetylation of aniline by *p*-nitrophenyl acetate. The first-order rate constants for the changes in optical density of solutions 5 and 6 represent the sum of the rate-constants of all processes of first-order with respect to aryl acetate occurring in the respective solutions. The following such processes are considered. For solution 5: (i) spontaneous hydrolysis of aryl acetate, (ii) aniline-catalysed hydrolysis of aryl acetate ([aniline] = $6{\cdot}62_5 \times 10^{-4}$M), (iii) uncatalysed direct acetylation of aniline by aryl acetate ([aniline] = $6{\cdot}62_5 \times 10^{-4}$M); for solution 6: (i) spontaneous hydrolysis of aryl acetate, (ii) aniline-catalysed hydrolysis of aryl acetate ($[\text{aniline}]_{\text{free}} = 6{\cdot}62_5 \times 10^{-4} \times 0{\cdot}81 = 5{\cdot}36 \times 10^{-4}$M), (iii) uncatalysed direct acetylation of aniline by aryl acetate ($[\text{aniline}]_{\text{free}} = 5{\cdot}36 \times 10^{-4}$M), (iv) acetate-catalysed hydrolysis of aryl acetate, (v) acetate-catalysed direct acetylation of aniline by aryl acetate. The rate constant for 5(i) has the value $6{\cdot}7 \times 10^{-7}$ sec.$^{-1}$ (Table 1). From the amount of acetanilide formed in the experiment with solution 5 it is known that 5% of the total reaction in solution 5 gives acetanilide. On combining this fraction with the total rate constant of the reaction ($8{\cdot}5 \times 10^{-7}$ sec.$^{-1}$) we find the first-order constant for reaction 5(iii) to be $0{\cdot}05 \times 8{\cdot}5 \times 10^{-7} = 0{\cdot}4 \times 10^{-7}$ sec.$^{-1}$. By difference $[(8{\cdot}5 - 6{\cdot}7 - 0{\cdot}4) \times 10^{-7}]$ reaction 5(ii) is calculated to have the first-order rate constant $1{\cdot}4 \times 10^{-7}$ sec.$^{-1}$. The rate constant for reaction 6(v) is calculated similarly, as follows. The rate constant for 6(i) is again $6{\cdot}7 \times 10^{-7}$ sec.$^{-1}$, that for 6(ii) is $1{\cdot}1 \times 10^{-7}$ sec.$^{-1}$ [from the value for 5(ii) and after allowance for the difference in concentration of free aniline in the two cases]. The value for 6(iii) ($0{\cdot}3 \times 10^{-7}$ sec.$^{-1}$) is also obtained from the value of 5(iii) after allowance for this difference in aniline concentration. Results in Table 1 give that reaction 6(iv) contributes $14{\cdot}1 \times 10^{-7}$ sec.$^{-1}$ to the total rate constant. The rate constant for reaction 6(v) is now given by subtracting these contributions from the total rate constant: $(26{\cdot}8 - 6{\cdot}7 - 1{\cdot}1 - 0{\cdot}3 - 14{\cdot}1) \times 10^{-7} = 4{\cdot}6 \times 10^{-7}$ sec.$^{-1}$. The sum of reactions 6(iii) and 6(v) gives the portion of reaction 6 which leads to acetanilide by processes *other* than acetylation of aniline by acetic anhydride. Accordingly, $(0{\cdot}3 + 4{\cdot}6)/28{\cdot}8 = 0{\cdot}18$ represents the fraction of the *p*-nitrophenyl acetate initially present which should give rise to acetanilide in reaction 6 in the absence of the catalytic mechanism involving the intermediate formation of acetic anhydride. In the foregoing analysis the electrolyte effect exerted by the presence of sodium acetate on reactions (i), (ii), and (iii) in solution 6 has been neglected (since it is unknown). On the assumption that the salt effect is of comparable magnitude to that in the hydrolysis of acetic anhydride, this neglect will not put the qualitative conclusion of this work in doubt, but the figure 0·18 is subject to some uncertainty on this account.

DISCUSSION

The results summarised in Table 4 demonstrate that most of the acetate-catalysed hydrolysis of *p*-nitrophenyl acetate must take place by a mechanism that does not involve

TABLE 4.

Summary of results in aniline-competition experiments.

Optical density at 238 mμ expected: (1) in absence of any acetanilide [a]	0·513
(2) for acetate-catalysed hydrolysis going through acetic anhydride [b]	0·908
(3) for direct acetylation by *p*-NPA only [c]	0·638
(4) Observed [d]	0·650

[a] From results in Table 2 (*e.g.*, 1 and 4). [b] 57% of 0·693 (result 3, Table 2) added to 0·513. 18% of 0·693 added to 0·513. [d] Table 3.

the intermediate formation of acetic anhydride. If the acetate-catalysed reaction proceeded entirely by way of acetic anhydride, then the second and fourth entries in the Table should agree, whereas the observed optical density agrees much more closely with the third entry, which is calculated on the assumption that no acetic anhydride is formed. We do not wish to stress the good agreement between these two values as much as the lack of agreement in the other case. This disagreement implies that acetate ions can catalyse the hydrolysis of *p*-nitrophenyl acetate by a process other than the mechanism

$$\mathrm{ROAc} + \mathrm{OAc}^- \rightleftharpoons \mathrm{Ac_2O} + \mathrm{OR}^- \qquad (3)$$

$$\mathrm{Ac_2O} + \mathrm{H_2O} \longrightarrow 2\mathrm{AcOH} \qquad (4)$$

Although this mechanism must be unimportant in the present case it may still contribute to a minor extent. There are probably conditions under which it could be shown to be significant and our results do not disprove Bender and Neveu's conclusion that the analogous mechanism (with intermediate formation of acetic benzoic anhydride) applies to the acetate-catalysed hydrolysis of 2,4-dinitrophenyl benzoate.[2b] The general situation is probably similar to that applying for hydrolysis of acid anhydrides. Here certain carboxylate-catalysed reactions proceed by way of a more reactive anhydride which is formed by a carboxylate exchange in the original anhydride.[4] Examples of this behaviour are the formate-catalysed hydrolysis of acetic anhydride[11] and the chloroacetate-catalysed hydrolysis of acetic chloroacetic anhydride.[5] Other carboxylate-catalysed reactions do not involve this prior substitution and require a different mechanism. The acetate-[7,11] and the chloroacetate-catalysed[5] hydrolysis of acetic anhydride exemplify this second type. It seems probable that the second mechanism is the more general and that the carboxylate-substitution contributes to the catalysis only under the special condition when this substitution (i) is sufficiently fast to compete with the ordinary catalysis and (ii) produces a more easily hydrolysed compound. The results for the chloroacetate-catalysed hydrolysis of acetic anhydride show that the second of these conditions by itself is insufficient. Although acetic chloroacetic anhydride is considerably more easily hydrolysed than acetic anhydride, it is not an intermediate in the reaction,[5] evidently because the substitution of chloroacetate ions for acetate ions is not sufficiently faster than the hydrolysis of acetic anhydride (catalysed by chloroacetate ion by a different mechanism). In the acetate-catalysed hydrolysis of *p*-nitrophenyl acetate reaction (3) may similarly not be sufficiently fast for the formation of acetic anhydride to be important, although such a mechanism may apply in different circumstances.

The ratio of the catalytic coefficient of acetate ion to the spontaneous rate has the value 8·2 l. mole^{-1} (Jencks and Carriuolo's results[8] lead to a ratio of 15·4 l. mole^{-1}). This agrees quite well with the corresponding ratios for some ethyl esters which, on more indirect evidence, are thought not to involve an anhydride intermediate:[9] ethyl difluoroacetate, 11; ethyl dichloroacetate, 10; ethyl chloroacetate, 7; ethyl trichloroacetate (in 40% alcohol), 8. However, it is not yet certain to what extent this similarity could be relied on as an indication of mechanism. In the hydrolysis of acetic anhydride[7] the ratio $k_{\mathrm{OAc^-}}/k_0$ lies around 1·8 or 1·5 (according to whether the electrolyte effect is or is not allowed for), and for formate catalysis the value is around 30. Here acetate- and formate-catalysis represent two different catalytic mechanisms. Both these values differ from the ratio for esters and it seems certain that the value can be considered only in relation to a certain class of compound.

We have previously represented the acetate-catalysed hydrolysis of acetic anhydride as general base-catalysis with a composite mechanism.[7] As a working hypothesis the same mechanism can be applied to the acetate-catalysed hydrolysis of *p*-nitrophenyl acetate as shown (HX represents a general Brønsted acid). The case HX = $\mathrm{H_3O^+}$ constitutes the "spontaneous" reaction, and HX = $\mathrm{CH_3{\cdot}CO_2H}$ implies acetate-catalysis.

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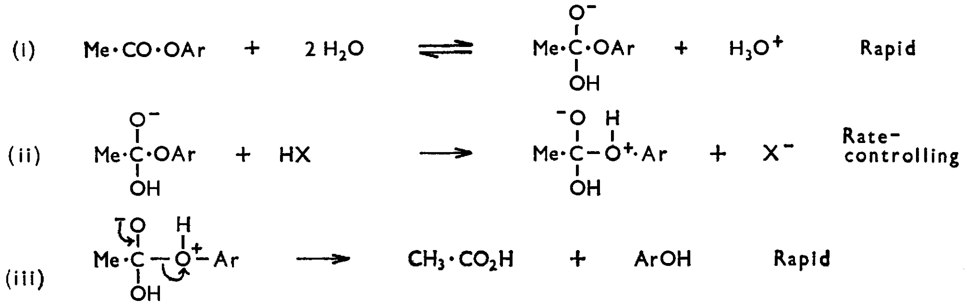
[11] Kilpatrick, *J. Amer. Chem. Soc.*, 1928, **50**, 2891.

The Brønsted exponent α in step (ii) ($k_{\text{ii}} = GK^{\alpha}_{\text{HX}}$), calculated as described in ref. 7, has the value 0·22 (compared with 0·43 in the hydrolysis of acetic anhydride,[7] and 0·49 in the hydrolysis of trimethylacetic anhydride [12]). This mechanism suggests that general base-catalysis occurs in all hydrolyses (involving acyl fission) of esters and similar compounds in which there is an appreciable " genuine " spontaneous rate. (We use the term " genuine " to exclude hydrolyses of compounds such as half-esters for which a pH-independent contribution to the reaction arises from an acid-catalysed hydrolysis of the conjugate base of the half-ester.) Our procedure now gives a general test for distinguishing this base-catalysis from nucleophilic catalysis.



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[12] Butler and Gold, *J.*, 1962, 976.