

Nucleophilic Reactivity

Part VIII. Kinetics of Reactions of Acetic Anhydride with Nucleophiles in Water

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Rate constants of the reactions of acetic anhydride with the nucleophiles OH^- , PhO^- , 4-MePhO^- , 4-ClPhO^- , $4\text{-NO}_2\text{PhO}^-$, PO_4^{3-} , CO_3^{2-} , HPO_4^{2-} , H_2PO_4^- , and H_2O were measured in aqueous solutions at different temperatures. A linear free energy relationship between the logarithm of the rate constant and the $\text{p}K_a$ values of the conjugate acid of the nucleophile was found for a restricted group of reactions. When the leaving group of the substrate was weakly basic (e.g. acetic anhydride and 2,4-dinitrophenyl acetate) the values of the slope of the linear free energy relationship of the reactions of phenyl acetate and nitrosubstituted phenyl acetates with similar nucleophiles were found to be constant, about 0.44, whereas a slope of about 0.56 was obtained when the substrate involved a relatively more strongly basic leaving group (phenyl and 4-nitrophenyl acetates). The experimental second-order rate constant was found to be equal to the rate constant of the formation of the addition intermediate for reactions connected with relatively low values of the slope (0.44). For the steeper slope values (0.56), the experimental rate constant is equal to the product of the rate constant of the formation of the addition intermediate and the ratio of the rate constants of decomposition of the intermediate to products or to starting materials.

EXPERIMENTAL

Reaction of acetic anhydride with hydrogen phosphate ion. Reaction rates were measured with a recording spectrophotometer Beckman DK-2 at 240 nm. Acetic anhydride was added to a 1 cm cell containing a 1:1 molar ratio mixture of potassium dihydrogen phosphate and disodium hydrogen phosphate at constant temperature. The concentration of acetic anhydride was initially about 0.05 M and the total phosphate salt concentrations were varied between 0.01 M and 0.1 M. First-order rate constants were calculated using the Guggenheim method.¹ The second-order rate constants of the reaction between acetic anhydride and hydrogen phosphate ion were obtained from the slope of the plot of the first-order rate constants against the hydrogen phosphate ion concentration. These values are shown in the Table 1. Alkaline hydrolysis and the reaction with dihydrogen phosphate ion are negligible.

This reaction was also studied with a Radiometer TTT1e pH-stat. Acetic anhydride was added at constant temperature to a reaction mixture containing an approximately 10:1 molar ratio mixture of disodium hydrogen phosphate and potassium dihydrogen phosphate. The concentration of anhydride was initially about 0.01 M and the total phosphate salt concentrations were varied from zero to about 0.2 M. The reaction mixture was automatically titrated at constant pH with 0.1 M potassium phosphate solution.

The pH-meter was calibrated at each temperature with three standard buffer solutions,² 0.05 M potassium hydrogen phthalate, 0.025 M potassium hydrogen phosphate and disodium hydrogen phosphate, and 0.01 M borax solutions.

The second-order rate constant k_{HPO_4} is equal to the slope of the straight line obtained by plotting the first-order rate constants against the hydrogen phosphate ion concentrations. The values of the rate constants are shown in Tables 1 and 2, as are the rate constants k_{OH^-} of the alkaline hydrolysis of acetic anhydride obtained by extrapolating the rate constants to zero phosphate concentration. The rate constants k_{HPO_4} obtained by the two different methods differ somewhat because of experimental errors. Kirsch and Jencks³ have reported a value of $k_{\text{HPO}_4} = 148 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$ at 25°C.

Reaction of acetic anhydride with dihydrogen phosphate ion. The sum of the first-order rate constants of the hydrolysis of acetic anhydride and its reaction with dihydrogen phosphate ion were obtained by the photometric method in solutions containing a large excess of potassium dihydrogen phosphate which was varied between 0.1 M and 1 M. The ratio of the two rate constants was calculated from the analysis of the reaction products of acetic anhydride with water and dihydrogen phosphate ion by hydrolysing the acetyl phosphate produced in the reaction. Values of both rate constants $k_{\text{H}_2\text{PO}_4}$ and $k_{\text{H}_2\text{O}}$ could be obtained separately and are shown in Table 1. The value of $k_{\text{H}_2\text{PO}_4}$ is rather inaccurate because a maximum of about one percent of anhydride reacted with dihydrogen phosphate ion. The increase in the total rate observed when increasing the hydrogen phosphate ion concentration is mainly due to a positive salt effect of the hydrolysis reaction of acetic anhydride.

Table 1. Second-order rate constants k_2 of reactions of acetic anhydride with nucleophiles N in water at different temperatures.

N	5°C	$10^3 k_2/\text{M}^{-1}\text{s}^{-1}$		25°C	Method
		10°C	15°C		
OH ⁻	270 000		505 000	895 000	pH-stat, phosphate
OH ⁻	360 000			1110 000	pH-stat, carbonate
PhO ⁻		432 000			pH-stat
4-MePhO ⁻		862 000			pH-stat
4-ClPhO ⁻		419 000			pH-stat
4-NO ₂ PhO ⁻		14 300			pH-stat
PO ₄ ³⁻	370		1 780		product analysis
PO ₄ ³⁻	580		1 190	2 810	pH-stat
CO ₃ ²⁻	640		1 550	2 500	pH-stat
HPO ₄ ²⁻	25		52	99	photom.
HPO ₄ ²⁻	24.3		57.3	144	pH-stat
H ₂ PO ₄ ⁻			0.16		product analysis
H ₂ O	0.0126		0.0260	0.472	photom.

Reaction of acetic anhydride with phosphate and hydroxide ions. The first-order rate constants of acetic anhydride in reaction mixtures containing potassium phosphate and disodium hydrogen phosphate at constant pH were obtained by the pH-stat method. Four simultaneous reactions should be considered:

$$k = k_{\text{H}_2\text{O}} + k_{\text{OH}} c_{\text{OH}} + k_{\text{HPO}_4} c_{\text{HPO}_4} + k_{\text{PO}_4} c_{\text{PO}_4} \quad (1)$$

This equation can be rearranged to:

$$(k - k_{\text{H}_2\text{O}} - k_{\text{HPO}_4} c_{\text{HPO}_4}) f_{\text{OH}} = k_{\text{OH}} K_w / a_{\text{H}} + k_{\text{PO}_4} c_{\text{PO}_4} f_{\text{OH}} \quad (2)$$

when c_{OH} is replaced by $K_w / a_{\text{H}} f_{\text{OH}}$. a_{H} is constant at constant pH. The activity coefficient f_{OH} was calculated using the following equation:

$$\log f = -A z_1^2 \left(\frac{I^{\frac{1}{2}}}{1 + I^{\frac{1}{2}}} - bI \right) \quad (3)$$

A value of $b = 0.25$ was used.^{4,5} Values of $k_{\text{H}_2\text{O}}$, k_{HPO_4} , c_{HPO_4} , and c_{PO_4} are known individually. The rate constant k_{PO_4} was obtained from the slope of a plot of the left side of eqn. 2 against values of $c_{\text{PO}_4} f_{\text{OH}}$. Values of k_{OH} were calculated using the reported⁶ values of K_w . The results are shown in Tables 1 and 2. The values of k_{PO_4} are inaccurate because of the experimental difficulties in measuring fast reactions by the pH-stat method and in calculating activity coefficients at high ionic strength.

Table 2. First-order rate constants k_1 and second-order rate constants k_{HPO_4} obtained as intercept and slope, respectively, when plotting the observed first-order rate constants against the disodium hydrogen phosphate concentrations. Values of k_{PO_4} were obtained from slopes when plotting $(k_{\text{obs}} - k_{\text{H}_2\text{O}} - k_{\text{HPO}_4} c_{\text{HPO}_4}) f_{\text{OH}}$ against $c_{\text{PO}_4} f_{\text{OH}}$.

$T^\circ\text{C}$	pH	$10^3 k_1 / \text{s}^{-1}$	$10^3 k_{\text{PO}_4} / \text{s}^{-1} \text{M}^{-1}$	$10^3 k_{\text{HPO}_4} / \text{s}^{-1} \text{M}^{-1}$	$k_{\text{OH}} / \text{s}^{-1} \text{M}^{-1}$
5	7.81	0.74		24.3	
5	9.99	6.54 ^a	710		258
5	10.53	20.5 ^a	450		285
15	7.62	1.50		57.5	
15	9.68	11.0 ^a	580		508
15	10.20	35.8 ^a	1800		498
25	7.47	2.80		144	
25	9.45	25.6 ^a	2810		895

$$^a k_1 = k_{\text{OH}} K_w / a_{\text{H}}$$

Values of k_{PO_4} were also obtained by measuring the ratio of the amounts of products formed in a simultaneous hydrolysis reaction and the reaction of phosphate ion with acetic anhydride. An aqueous solution of acetic anhydride was rapidly mixed with a solution containing disodium hydrogen phosphate and potassium phosphate of about 20:1 molar ratio and the consumption of phosphate at the end of the reaction was analysed by titrating with a hydrochloric acid solution. The hydroxide ion and phosphate ion concentrations in the reaction mixture were calculated using the values⁶ of the base constant of phosphate ion $K_b = 0.0053$ and $0.0110 \text{ mol dm}^{-3}$ at 5°C and 15°C , respectively, and the values of activity coefficients obtained using eqn. 3. Because phosphate ions were present in excess compared to anhydride, the ratio $c_{\text{OH}} / c_{\text{PO}_4}$ remains approximately constant during the reaction and k_{PO_4} can be calculated.

$$k_{\text{PO}_4} = k_{\text{OH}} \frac{c_{\text{OH}}}{c_{\text{PO}_4}} \frac{n_{\text{OH}}}{n_{\text{PO}_4}} - k_{\text{HPO}_4} \frac{c_{\text{HPO}_4}}{c_{\text{PO}_4}} \quad (4)$$

The values of k_{PO_4} were calculated from the amount of anhydride which reacted with hydroxide ions n_{OH} and with phosphate ions n_{PO_4} and the known values of the rate constants k_{HPO_4} . These values shown in Table 1 are rather inaccurate due to experimental difficulties and errors in calculating activity coefficients in solutions of high ionic

strength. The error limits are expected to be about 50 %.

Reaction of acetic anhydride with carbonate ion. The first-order rate constant k of acetic anhydride when reacting in reaction mixtures containing sodium carbonate and sodium hydrogen carbonate was determined by pH-stat method. The reaction mixture initially contained about 0.01 M acetic anhydride. The concentration of sodium hydrogen carbonate was varied from zero to about 0.5 M and the concentration of sodium carbonate from zero to about 0.005 M. The reaction mixture was titrated with 0.1 M sodium carbonate solution. The second-order rate constants k_{CO_3} and k_{OH} were calculated according to the equation:

$$\left(k - k_{\text{H}_2\text{O}}\right) f_{\text{OH}} = k_{\text{OH}} \frac{K_w}{a_{\text{H}}} + \left(k_{\text{CO}_3} + k_{\text{HCO}_3} \frac{c_{\text{HCO}_3}}{c_{\text{CO}_3}}\right) c_{\text{CO}_3} f_{\text{OH}} \quad (5)$$

The values of the slope of the linear plot of the left side of eqn. 5 against $c_{\text{CO}_3} f_{\text{OH}}$ are equal to $k_{\text{CO}_3} + k_{\text{HCO}_3}(c_{\text{HCO}_3}/c_{\text{CO}_3})$. Values of $k_{\text{HCO}_3}(c_{\text{HCO}_3}/c_{\text{CO}_3})$ were found to be negligible in our experiments. Values of k_{CO_3} and k_{OH} are shown in Tables 1 and 3. Measurements at low pH are necessary in order to obtain values of k_{HCO_3} , but complications due to the slow reaction $\text{CO}_2 + \text{H}_2\text{O} = \text{H}_2\text{CO}_3$ and the volatility of carbon dioxide make it difficult to obtain reliable data.

Table 3. First-order rate constants $k_1 = k_{\text{OH}}K_w/a_{\text{H}}$ and second-order rate constants k_{CO_3} obtained as intercept and slope, respectively, by plotting $(k_{\text{obs}} - k_{\text{H}_2\text{O}}) f_{\text{OH}}$ against $c_{\text{CO}_3} f_{\text{OH}}$.

$T/^\circ\text{C}$	pH	$10^3 k_1/\text{s}^{-1}$	$10^3 k_{\text{CO}_3}/\text{M}^{-1}\text{s}^{-1}$	$k_{\text{OH}}/\text{M}^{-1}\text{s}^{-1}$
5	9.13	1.00	660	316
5	9.67	4.20	530	386
5	10.21	14.4	730	380
25	8.48	3.80	2880	1250
25	8.98	13.6	2180	1075
25	9.48	32.8	2370	1150

The values of k_{OH} obtained from experiments in, respectively, phosphate and carbonate buffer solutions differ somewhat. The results obtained in carbonate buffer solutions are possibly less reliable because of the simultaneous reactions of carbon dioxide. Kirsch and Jencks³ have reported a value of $k_{\text{OH}} = 967 \text{ M}^{-1} \text{ s}^{-1}$ at 25°C and Bunton and Fendler⁷ a value of $k_{\text{OH}} = 158 \text{ M}^{-1} \text{ s}^{-1}$ at 0°C . Previously reported⁶ values of k_{OH} obtained by a flow method are about 20 times larger than the present values and must be considered to be in error. The previously reported⁹ value of $k_{\text{OH}}/k_{\text{PhO}} = 1.36$ at 25°C obtained from product analysis can be combined with the value of $k_{\text{PhO}} = 432 \text{ M}^{-1} \text{ s}^{-1}$ at 10°C from Table 1. A value of $k_{\text{OH}} = 588 \text{ M}^{-1} \text{ s}^{-1}$ at 10°C is obtained which is within the range of k_{OH} values obtained by the other methods.

Reactions of acetic anhydride with phenoxide ions. The first-order rate constants were calculated by the Guggenheim method¹ from measurements by the pH-stat method in reaction mixtures containing initially about 10^{-4} M anhydride and about 0.01 M phenol by titrating with 0.002 M sodium carbonate solution at constant pH and temperature, 10°C . The respective concentrations of phenoxide ion and substituted phenoxide ions in the reaction mixtures were calculated using values of $\text{p}K_a = 10.12, 10.48, 9.63,$ and 7.33 at 10°C which in turn were calculated using values¹⁰ of $\text{p}K_a = 9.90, 10.26, 9.40,$ and 7.15 at 25°C and values¹¹ of the enthalpies of ionization of $\Delta H = 5.65, 5.65, 5.80,$ and 4.70 kcal mol^{-1} for phenol, *p*-cresol, *p*-chlorophenol, and *p*-nitrophenol, respectively. Mean values of the second-order rate constants k_{PhO} obtained from kinetic measurements at different initial phenol concentrations and different pH values are collected in Table 1.

DISCUSSION

A linear free energy relationship is obtained for the reactions of acetic anhydride with basic oxygen-containing nucleophiles when the logarithms of the rate constants k are plotted against the pK_a values, Table 4, of the conjugate acids of the nucleophiles; Fig. 1.

$$\log k = (0.45 \pm 0.01) pK_a - 4.95 \pm 0.01 \quad (6)$$

Table 4. Parameters of the Arrhenius equation for the reactions of acetic anhydride with nucleophiles in water.

N	$\log A$	$E/kJ \text{ mol}^{-1}$	$3 + \log k$ 5°C	pK_a 5°C
OH ⁻	12.01	40.5	5.431	16.475
4-MePhO ⁻			5.936 ^a	10.48 ^a
PhO ⁻			5.636 ^a	10.12 ^a
4-ClPhO ⁻			5.622 ^a	9.63 ^a
4-NO ₂ PhO ⁻			4.156 ^a	7.53 ^a
PO ₄ ³⁻	10.21	54.5	2.76	12.46
CO ₃ ²⁻	8.56	46.7	2.806	10.553
HPO ₄ ²⁻	8.77	55.3	1.393	7.281
H ₂ PO ₄ ⁻			-1.1	2.073
H ₂ O			-1.900	-1.745

^a at 10°C.

The rate constants of the hydrolysis reaction and the reactions of phosphate and phenoxide ions with anhydride deviate from this linear free energy relationship. The rate constants of various hydrolysis reactions commonly deviate from linear free energy relationships when water is used as solvent. The deviation of the rate constant of the phosphate ion reaction from eqn. 6 is unexpected but could at least partly be due to the relatively large experimental error anticipated for this reaction. Positive deviations of eqn. 6 are observed for the reactions of different phenoxide ions with anhydride, Fig. 1. The value of the ratio $k_{\text{OH}}/k_{\text{PhO}} = 1.0$ at 5°C, however, is not very different from the values 1.04, 1.28, and 1.26 obtained previously¹² for the ratio of the rate constants of the reactions of methyl benzenesulphonate at 25°C, methyl nitrate at 90°C, and methyl perchlorate at 0°C, respectively. Linear free energy relationships similar to eqn. 6 were also obtained¹² for these three reactions. The slope of the linear free energy relationship is 0.24 for all three. The rate constants of the reactions with hydroxide ion deviate from the straight line¹² but those of reactions with phenoxide ion do not.¹² Hydroxide and phenoxide ions involving a σ -type bond between oxygen and carbon show a different kind of reactivity compared with the reactions of nucleophiles containing oxygen bonded to carbon, nitrogen, phosphorus, *etc.* by π -type bonds with carbon atoms involving only σ -type bonds (*e.g.* the methyl group) or with carbon atoms involving also π -type bonds (*e.g.* the carbonyl group of acetic anhydride).

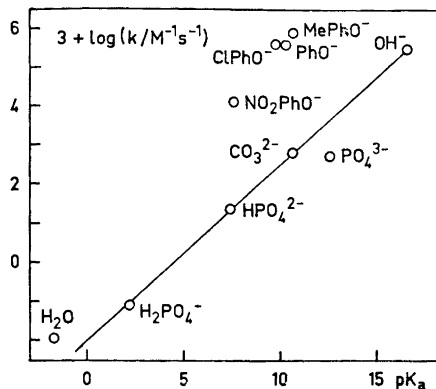


Fig. 1. Logarithms of the second-order rate constants of the reactions of acetic anhydride with nucleophiles in water at 5°C plotted against the pK_a values of the conjugate acids of the nucleophiles in water at 25°C.

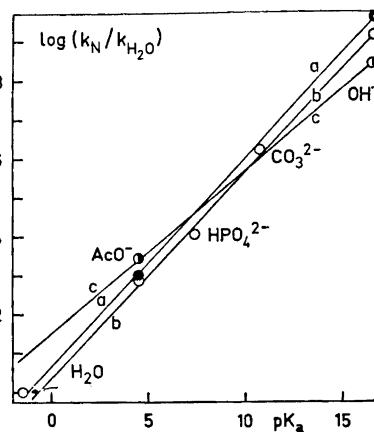
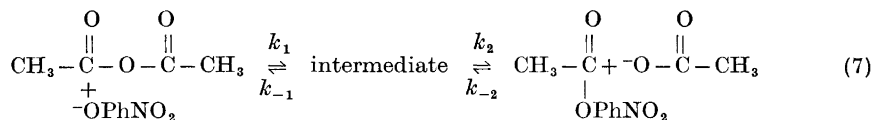


Fig. 2. Logarithms of the ratios of the second-order rate constants of the reactions of phenyl acetate (a), 4-nitrophenyl acetate (b), and 2,4-dinitrophenyl acetate (c) with nucleophiles and water, respectively, in water at 25°C plotted against the pK_a values of the conjugate acids of the nucleophiles in water at 25°C.

A linear free energy relationship similar to eqn. 6 is also obtained^{13,14} for reactions of 4-nitrophenyl acetate with basic oxygen-containing nucleophiles, Fig. 2. The slope is, however, different, about 0.54 ± 0.02 . It is useful to compare the rates of reactions of 4-nitrophenyl acetate with acetate ions and the rates of reactions of acetic anhydride with 4-nitrophenoxide ions because in both cases the same addition intermediate is expected:



By steady state treatment eqn. 8 is obtained for the experimental rate constants for the overall reactions from left to right, k_{PhO} , and from right to left, k_{AcO} .

$$k_{\text{PhO}} = k_1/(1 + k_{-1}/k_2) \quad \text{and} \quad k_{\text{AcO}} = k_{-2}/(1 + k_2/k_{-1}) \quad (8)$$

If it is assumed that $k_2 \ll k_{-1}$ then¹³ $k_{\text{AcO}} = k_{-2} = 5.0 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ at 25°C and $(k_{-1}/k_2)k_{\text{PhO}} = (k_{-1}/k_2)50 \gg 50 \text{ M}^{-1} \text{ s}^{-1}$ at 25°C. k_{PhO} is estimated from the value obtained at 10°C. It is, however, unlikely that the addition of 4-nitrophenoxide ion to the carbonyl group of acetic anhydride would be more than 10^5 times faster than the addition of acetate ion to the carbonyl group of 4-nitrophenyl acetate because the basicities of acetate ion ($pK_a = 4.76$) and 4-nitrophenoxide ion ($pK_a = 7.15$) are not very different. It is therefore more likely that $k_2 \gg k_{-1}$, as one would expect because acetate ion is a better leaving

group than 4-nitrophenoxide ion. In this case $k_{\text{phO}} = k_1 = 50 \text{ M}^{-1} \text{ s}^{-1}$ and $k_2 \gg 5.0 \cdot 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$.

The value of the slope 0.45, obtained for reactions of acetic anhydride with nucleophiles, is a measure of the sensitivity of k_1 of the addition reaction to changes in the basicity of the nucleophile when attacking the carbonyl carbon of acetic anhydride. On the other hand the value of the slope 0.54 is a measure of the sensitivity of $k_{-2} k_{-1}/k_2$ to changes in the basicity of the nucleophile in reactions with 4-nitrophenyl acetate. If the sensitivities of addition reactions of nucleophiles to the carbonyl group of acetic anhydride and 4-nitrophenyl acetate are about equal, then the difference in the values of the slopes $0.54 - 0.45 = 0.09$ would approximately represent the sensitivity of the ratio k_{-1}/k_2 to changes in basicity of the nucleophile when it adds to 4-nitrophenyl acetate. As expected, the value is positive, because an increase in the basicity of the nucleophile would decrease the reverse reaction of the intermediate to the starting materials.

A value of 0.43 is obtained for the slope of the linear free energy relationship for the reactions of 2,4-dinitrophenyl acetate with the nucleophiles¹⁵ OH^- , AcO^- at 25°C . This is close to the value of the slope (0.45) obtained for acetic anhydride, as would be expected for substrates with a good leaving group (AcO^- , $\text{p}K_{\text{a}} = 4.74$ and 2,4-dinitrophenoxide ion, $\text{p}K_{\text{a}} = 4.08$). For the reactions¹⁵ of phenyl acetate with the nucleophiles OH^- and AcO^- , a value of 0.54 is obtained for the slope, which is close to the value (0.54) obtained for the reactions of 4-nitrophenyl acetate with the nucleophiles. In these cases the substrate does not have a good leaving group (phenoxide ion, $\text{p}K_{\text{a}} = 9.90$ and 4-nitrophenoxide ion, $\text{p}K_{\text{a}} = 7.15$). Values of the slope A of eqn. 6 could perhaps serve as a guide when studying the mechanism of nucleophilic reactions at carbonyl carbon for choosing between the two possibilities $k_{-1} \gg k_2$ or $k_{-1} \ll k_2$.

Acknowledgements. The authors wish to record their indebtedness to Miss Aili Hökkä for performing some of the experiments, and to the *Finnish Academy* for financial aid.

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Received May 15, 1973.

Acta Chem. Scand. **27** (1973) No. 9