Steric and pH Effects on the Rate of Dakin Oxidation of Acylphenols†

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The rates of hydrogen peroxide oxidation of a series of *o*- and *p*-acylphenols with a variety of aliphatic substituents on the carbonyl carbon [*o*- or *p*-OHC_6H_4COR, where R = H, CH_3, CH_2CH_3, $CH(CH_3)_2$, and $C(CH_3)_3$] have been measured over a range of alkaline pH conditions. *p*-Hydroxypivalophenone was here synthesized for the first time, to complete this series. Relative rates of Dakin oxidation appear to be more strongly affected by the bulk of the aliphatic carbonyl substituent than those found for parallel alkaline ester hydrolyses and somewhat less strongly than those for perbenzoic acid oxidations. Correlations of oxidation rate with pH show a double maximum and a high rate throughout the pH range 9.5–13.5 for *o*-hydroxyacetophenone and a single maximum of about half the ortho rates over the narrower pH range of 11.5–13.5 for *p*-hydroxyacetophenone. Unimolecular involvement of undissociated hydrogen peroxide in the rate-determining step of the lower pH maximum for *o*-hydroxyacetophenone and of hydroperoxide anion in the high-pH maximum for both *o*- and *p*-hydroxyacetophenone is one explanation consistent with the observed results.

Dakin oxidation has been surveyed on a product basis,[1] and from this evidence and by analogy with Baeyer–Villiger reaction[2] a pathway has been proposed to relate these various elements (Scheme I). We have previously demonstrated preparative means for improving the rate[4] and, on the basis of considerations prompted by inconsistencies present in the current picture of the Dakin pathway, have examined the kinetics of the process.[5] This work clearly established the tacitly accepted first-order dependence of rate on acyl compound concentration and also demonstrated significantly faster oxidation of *o*- than of *p*-hydroxyacetophenone (Ib). While the ultraviolet analytical method used for this earlier work did give reliable results, a great deal of experimental time was required for each run, and it did not lend itself to detection or realization of other subtleties of the process.

An ^1H NMR based method was tested with oxidations of *p*-hydroxyacetophenone, which permitted the detection of *p*-hydroxyphenyl acetate, thus providing experimental evidence for the formation of this previously only postulated Dakin intermediate, and supported details of development of its elusive isolation.[6] By providing a more convenient and rapid rate-analysis tool than ultraviolet spectroscopy, ^1H NMR with frequency locking also provided the experimental capability to examine the kinetics of many more variables of this process.

This paper reports the pattern of rate constants obtained for the Dakin oxidation of a series of *o*- and *p*-acylphenols, Ia–e, selected to study the effect of bulk of the R group on the rate and the course of Dakin oxidation. *p*-Hydroxypivalophenone, which was required to complete this series of experiments, was successfully synthesized here for the first time by using lithium cuprate intermediates. More detailed rate studies were also conducted with *o*- and *p*-hydroxyacetophenones over a range of buffered pH's to assist in explaining the details of hydrogen peroxide involvement in the process.

Experimental Section

o- and *p*-hydroxybenzaldehydes, -acetophenones, and -propiophenones were purchased and used in the pure state obtained (by NMR) except for *o*-hydroxyacetophenone, which was vacuum distilled, and *p*-hydroxyacetophenone, which was crystallized from ethanol and then sublimed [160 °C (0.5 mm)] to yield pure material, mp 109–110 °C (lit.[7] mp 109 °C). The isobutyrophenones and *p*-hydroxypivalophenone were prepared as described below. Elemental analysis was by A. B. Gygli, Toronto, Ontario, Canada.

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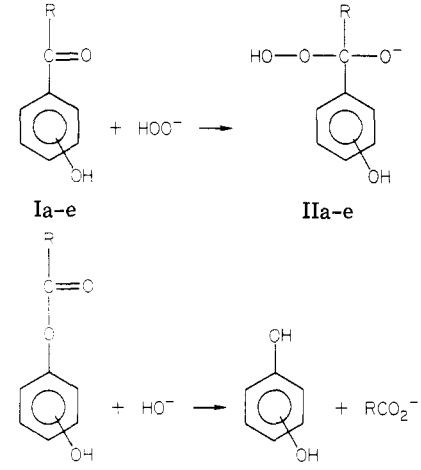
Scheme I.[a] Currently Accepted Dakin Pathway[3]



[a] a, R = H; b, R = CH_3; c, R = CH_2CH_3; d, R = $CH(CH_3)_2$; e, R = $C(CH_3)_3$.

***o*- and *p*-Hydroxyisobutyrophenones.** A method previously described for the synthesis of *o*- and *p*-hydroxypropiophenones[8] was used to rearrange phenyl isobutyrate (200 g, 1.22 mol) in carbon disulfide (200 mL) with aluminum chloride (185.5 g, 1.4 mol). The 160 g of crude extract was vacuum distilled up a short column to give *o*-hydroxyisobutyrophenone as a colorless oil: 34.2 g; bp 130 °C (16 mm) [lit.[9] bp 121–123 °C (21 mm)]. The para isomer [a pale yellow oil; 30.1 g; bp 200 °C (17 mm) [lit.[9] bp 196–198° (21 mm)]] crystallized spontaneously on cooling overnight at 0 °C. It was recrystallized twice from hexane; mp 58–59 °C (not previously reported crystalline).

***p*-Hydroxypivalophenone (IV).** Unsaturate-free pentane was dried and distilled from sodium and then with freshly predried 4A molecular sieves [180 °C (0.5 mm), 12 h]. Tetrahydrofuran (THF) was freed of peroxides and distilled from lithium aluminum

(1) Dakin, H. D. *Am. Chem. J.* **1909**, *42*, 477. Hudlicky, M. *Chem. Listy* **1952**, *46*, 567. Pliml, J. *Chemie (Prague)* **1958**, *10*, 647.
(2) House, H. O. "Modern Synthetic Reactions"; W. A. Benjamin: New York, 1965; p 123.
(3) Bunton, C. A. In "Peroxide Reaction Mechanisms", Edwards, J. O., Ed.; Interscience: New York, 1962; p 14. Lee, J. B.; Uff, B. C. *Q. Rev., Chem. Soc.* **1967**, *21*, 429. Chin, L. J. "Selection of Oxidants in Synthesis"; Marcel Dekker: New York, 1971. Whiting, D. A. In "Comprehensive Organic Chemistry"; Barton, D., Ollis, W. D., Ed.; Pergamon Press: Toronto, 1979; Vol. 1, p 720.
(4) Hocking, M. B. *Can. J. Chem.* **1973**, *51*, 2384.
(5) Hocking, M. B.; Ong, J. H. *Can. J. Chem.* **1977**, *55*, 102.
(6) Hocking, M. B.; Ko, M.; Smyth, T. A. *Can. J. Chem.* **1978**, *56*, 2646.
(7) "Dictionary of Organic Compounds", 4th ed.; Eyre and Spottiswoode: London, 1965; Vol. 3, p 1639.
(8) Blatt, A. H., Ed. "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. II, 543.
(9) Ogata, Y.; Sawaki, Y. *J. Org. Chem.* **1972**, *37*, 2953.

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Table I. Comparison of ^{13}C NMR Shifts[a] of Model Compounds with Those for 4-Hydroxypivalophenone (I, R = $C(CH_3)_3$)

carbon	4-methoxy-pivalophenone[29]	found for 4-hydroxy-pivalophenone [I, R = $C(CH_3)_3$]	estimated by using shift additivities: 4-hydroxy-pivalophenone[29]	estimated by using shift additivities: 4-hydroxy alkylphenol[30]
C-4	161.3	159.5	157.3	157.3
C-3	112.7	115.1	115.0	114.9
C-2	130.3	131.3	129.4	129.0
C-1	129.2	129.6	130.2	130.8
C=O	203.8	208.3	207.2	
CCH_3	43.1	44.0	43.8	
CH_3	28.0	28.5	28.2	

[a] Shifts are given in parts per million from internal tetramethylsilane.

hydride onto 4A molecular sieves. High-purity argon (<5 ppm moisture, <3 ppm oxygen) was used for inert gas blanketing, and all air-sensitive solution additions were via syringes or cannulas. Glassware was assembled hot after prebaking (120 °C for 24 h) and cooled in a slow stream of argon.

p-Acetoxybenzoic acid was prepared from *p*-hydroxybenzoic acid and recrystallized from water and then benzene to yield colorless crystals, mp 188–194 °C (lit. mp 186 °C,[10] 192–194 °C[11]).

p-Acetoxybenzoyl chloride was obtained by treating *p*-acetoxybenzoic with 2 molar equiv of thionyl chloride in the presence of a trace of aluminum chloride. *p*-Acetoxybenzoyl chloride was recovered by distillation: bp 146–148 °C (12 mm) [lit.[10] bp 145–146 °C (12 mm)]; IR (neat) λ_{max} 1780, 1760 cm^{-1} (RCOCl, RCO_2R).

tert-Butyl chloride, from *tert*-butyl alcohol and concentrated hydrochloric acid, was reacted with lithium[12] in pentane to prepare *tert*-butyllithium. The concentrations of both *n*-butyl- and *tert*-butyllithium obtained were determined via a dibromoethane modification[13] of a double-titration technique.[14]

To a stirred solution of dry *tert*-butyl alcohol (4.32 g, 58 mmol) in THF (30 mL) cooled to 0 °C in an argon atmosphere[15] was added a solution of *n*-butyllithium in pentane (37 mL; 58 mmol) precooled to 0 °C, and stirring was continued for 20 min at this temperature. The solution was then warmed to 20 °C by using a water bath to act as a thermal ballast, and a further 75 mL of THF plus the preplaced cuprous iodide (11.8 g, 58 mmol) were added via a rotatable, L-shaped addition arm.[16] The mixture was then rapidly stirred for 30 min, by which time the solid phase was well dispersed. It was then cooled to −78 °C with stirring and the *tert*-butyllithium in pentane (31 mL, 57 mmol) prechilled to −20 °C was added over 2–3 min, followed by a solution of *p*-acetoxybenzoyl chloride (10 g, 50 mmol) in 50 mL of THF prechilled to −78 °C. The mixture was stirred at this temperature for 20 min and then quenched by the addition of 30 mL of dry methanol.

The quenched mixture was poured into 200 mL of saturated aqueous ammonium chloride, stirred well, and filtered, and the filtrate was extracted with ether (3 × 100 mL). The combined extracts were washed with 1% aqueous sodium thiosulfate (3 × 150 mL) and dried (Na_2SO_4), and the solvent was evaporated to yield a pale yellow oil (9.21 g) which crystallized on standing. Distillation gave pure *p*-hydroxypivalophenone: 7.14 g (80%); bp 170–174 °C (5 mm). An analytical sample purified by several recrystallizations (cyclohexane, heptane) with charcoal gave colorless elongated prisms: mp 88–89 °C (from heptane); MS, *m/e* (relative intensity) 178 (M^+, 3.9), 122 (8.3), 121 (100), 93 (9.3), 71.5 (M*), 65 (9.8), 57 (5.8), 41 (6.9), 39 (9.0), 37.1 (M*), 29 (5.1); IR (Nujol) λ_{max} 3480, 3380, 1656–1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.80 (d, 2 H), 6.85 (d, 2 H, J = 9.02 Hz), 6.13 (s, 1 H), 1.38 (s, 9 H); ^{13}C NMR ($CDCl_3$, fully decoupled), see Table I. Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.85; H, 7.92.

Negative *p*-Hydroxypivalophenone Preparations. Aluminum chloride[17,18] or *p*-toluenesulfonic acid[19] with phenyl pivaloate in 1:1 to 2:1 mole ratios and at temperatures from ambient to 100 °C, with or without solvent, gave significant isobutylene and carbon monoxide evolution plus varying proportions of phenol, *p*-tert-butylphenol, pivalic acid, and unchanged phenyl pivaloate. Phosphorus oxychloride[20] with phenyl pivaloate (0.25:1 to 1.3:1 mole ratio) neat or in benzene nearly quantitatively returned the initial ester, even after boiling for as long as 8 h.

Methods employing prior complexation of phenol and pivaloyl chloride, acid, or anhydride with either aluminum chloride[21] or zinc chloride[22] gave significant carbon monoxide evolution and some *p-tert*-butylphenol but mostly recovered starting materials. A trace of the desired product, 5, was obtained from one experiment in which aluminum chloride complexed phenol was combined with pivaloyl chloride in carbon disulfide.

Steric Effect Rate Measurements. Reaction rates were followed by using a Perkin-Elmer R-32 90-MHz NMR instrument, operated in the ^1H-locked mode onto solvent water. The probe temperature was controlled at 37.0 ± 0.5 °C via the Joule–Thompson effect attachment of the instrument and was calibrated by using the shift difference of the proton NMR of methanol in a sealed tube. The scanning rate, sensitivity, and filter adjustments were selected so as to give a linear peak height response with concentration for the absorptions of interest, by prior test with known concentrations. Oxidations of salicylaldehyde and *p*-hydroxybenzaldehyde (Ia) were followed by the loss in intensity of the aldehydic proton absorption and those of the corresponding acetophenones by the acyl methyl singlet.[6] Propiophenone oxidation rates were followed by the loss in intensity of the ketone methylene quartet, the center of which lay 0.65 ppm upfield of the methylene quartet for propionate anion. The isobutyrophenone methyl doublet which overlapped with that of isobutyrate anion (0.033 ppm upfield) could nevertheless be clearly differentiated on 300-Hz sweep-width scans. The singlet of the methyls of the *tert*-butyl group of *p*-hydroxypivalophenone appeared at δ 1.39, 0.23 ppm downfield of pivaloate anion and clearly differentiable on a 10-ppm sweep width.

A solution of an exactly weighed amount of aqueous base (usually 15–25 mL) was placed in a thermostated bath at 37 °C at the same time as a stock quantity of nominal 30% hydrogen peroxide of known concentration determined iodometrically,[4] the latter in a new polyethylene bottle previously conditioned in hydrogen peroxide for 24 h. As the solutions came to bath temperature, a sample of the solution of the acyl compound was placed

(10) Schoenenberger, H.; Holzheu-Eckardt, J.; Bamann, E. Arzneimittel-Forsch **1964**, *14*, 324; *Chem. Abstr.* **1964**, *61*, 9430*b*.
(11) Kunitake, T.; Shinkai, S.; Aso, C. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1111.
(12) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Vol. 1, Wiley: New York, 1964; Vol. 1, pp 96, 97, and references cited therein.
(13) Whitesides, G. M.; Casey, C. P., Krieger, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1379.
(14) Gilman, H.; Haubein, A. H. *J. Am. Chem. Soc.* **1944**, *66*, 1515.
(15) Owens, F. H.; Fellmann, R. P.; Zimmerman, F. P. *J. Org. Chem.* **1960**, *25*, 1808.
(16) Posner, G. H.; Whitten, C. E.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 7788.
(17) Suzuki, H.; Wada, H.; Maruyama, K.; Goto, R. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1201. Weiss, P.; Niederl, J. B. *J. Am. Chem. Soc.* **1949**, *21*, 2647. Nightingale, D. V.; Sublett, R. L.; Carpenter, R. A.; Radford, H. D. *J. Org. Chem.* **1951**, *16*, 655. Briggs, T. I.; Dutton, G. G. S.; Merler, E. *Can. J. Chem.* **1956**, *34*, 851.
(18) Ralston, A. W.; McCorkle, M. R.; Bauer, S. T. *J. Org. Chem.* **1940**, *5*, 657.
(19) Knowles, M. B. (Eastman Kodak, Co.) U.S. Patent 2763691, 1956; *Chem. Abstr.* **1957**, *51*, 879*e*.
(20) Weygand, C. "Organic Preparations"; Interscience: New York, 1945; pp 484–486.
(21) Witt, O. N.; Braun, O. *Ber.* **1914**, *47*, 3216.
(22) Spruit, C. P. J. *Recl. Trav. Chim. Pays-Bas* **1947**, *66*, 655. *Chem. Abstr.* **1948**, *42*, 1921*i*.

Table II. Peak Height vs. Time Data for the Dakin Oxidation of *p*-Hydroxypropiophenone in 0.60 M Aqueous Sodium Hydroxide at 37 °C[a]

time, min	ketone quartet peak height,[b] mm	reacted [ketone], M	$\frac{1}{a-b} \times \ln \frac{b(a-x)}{a(b-x)}$, L mol^{-1}
0.0	112	0.00	0.00
4.0	108	0.01353[c]	0.08115[c]
7.0	105	0.02368	0.14571
10.0	100.5	0.03892	0.24912
15.0	97.2	0.05922	0.40084
20.0	89.7	0.08121	0.58615
23.0	85.9	0.08967	0.66414
27.0	86.0	0.10152	0.78046
30.0	74.5	0.12351	1.02179
40.0	64.0	0.13535	1.16763

[a] Initial ketone concentration = 0.40 M; initial hydrogen peroxide concentration = 0.48 M (and "*b*" in second-order rate calculation). [b] Normalized to constant total peak height, ketone quartet plus propionate anion quartet. [c] Number of significant figures quoted correspond to those carried through subsequent kinetic calculations and are not intended to convey experimentally significant figures.

in an NMR tube to obtain a zero reaction reading and then returned to the stock solution. To start a run, we added the appropriate quantity (e.g., 32.5 μL) of hydrogen peroxide to the solution of acyl compound via a polytipped microliter pipet, the solution thoroughly mixed, and a zero-time measurement recorded. Then an aliquot was withdrawn into a new NMR tube of the same dimensions as the zero-reading tube, by prior matching, and appropriate peak heights were recorded at intervals, the time being noted as the pen traced the center of the scanned peak or multiplet. In this way it was possible to obtain a concentration reading in about 2 min after mixing and about every 90 s thereafter for faster reactions, or at longer intervals (usually conducted at weekends) for slower runs (see Table II). The rates obtained (Tables III and IV) were determined from the slopes of the least-squares fits of plots of the form $[1/(a-b)] \ln b(a-x)/a(b-x)$ vs. time. A minimum of six points giving a correlation coefficient, *r*, of 0.99 or better was taken as the criterion of a successful run. Rate reproducibility of duplicate runs was normally within 15% and at the worst, within 25%.

pH Effect Rate Measurements. Buffers were made up according to procedures of standard reference sources,[23-25] with in each case the combined solutions specified made up to 100-mL volumes with distilled water: pH 8, 46.80 mL of 0.10 M NaOH + 50 mL of 0.10 M KH_2PO_4;[23] pH 9, 21.3 mL of 0.10 M NaOH + 50 mL of 0.10 M H_3PO_3 + 0.10 M KCl;[23] pH 10, 43.90 mL of 0.10 M NaOH + 50 mL of 0.10 M H_3BO_3 + 0.10 M KCl);[23] pH 11, 4.1 mL of 0.10 M NaOH + 50 mL of 0.05 M Na_2HPO_4;[24] pH 12, 26.9 mL of 0.10 M NaOH + 50 mL 0.05 M Na_2HPO_4;[24] pH 13, 66 mL of 0.20 M NaOH + 25 mL of 0.20 M KCl.[25]

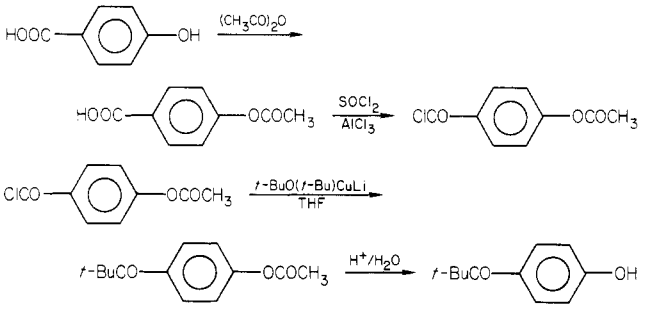
The pH susceptibility runs were only carried out with the *o*- and *p*-hydroxyacetophenones but otherwise were operated as described for steric effect determination (Table VII). Rates were determined on points obtained early in the run to ensure as little change in pH as possible. Rate reproducibility of duplicate runs was usually within 10%, with occasional variations being as much as 15%.

Results and Observations

Even though Fries rearrangement readily afforded the *o*- and *p*-hydroxyisobutyrophenones, it failed to yield *o*- and *p*-hydroxypivalophenones from phenyl pivaloate, even when using variations of the unsuccessful procedures of others.[26] From the isobutylene obtained from some of these experiments and the carbon monoxide loss, it is probable that the migrating acylium ion (pivaloyl carbocation) simply has inadequate stability to survive migration.

p-Hydroxypivalophenone (IV), however, was obtained in 75% yield (38% from *p*-hydroxybenzoic acid) by applying the lithium cuprate method[16] (Scheme II). All precautions[12] were necessary for success, lithiations only being successful with lithium which had been first mechanically[27] and then melt-alloyed with sodium.[27] Along with analytical and other physical data the ^{13}C NMR shifts

Scheme II. Preparative Sequence Used for *p*-Hydroxypivalophenone



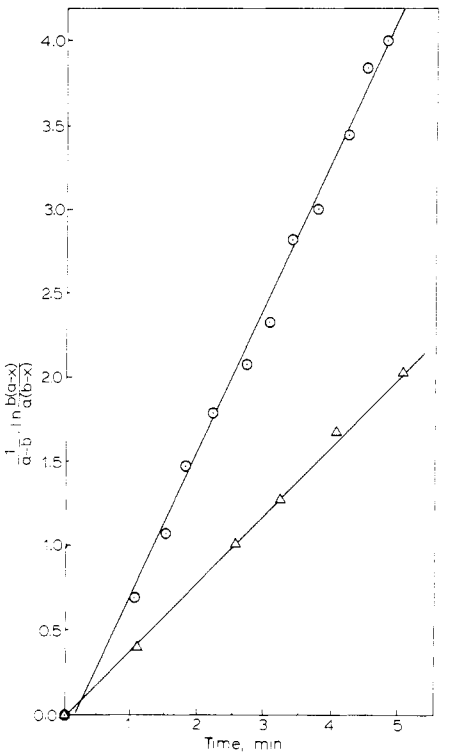


Figure 1. Dakin oxidations in 1.0 M aqueous sodium hydroxide at 37 °C: *p*-hydroxybenzaldehyde (0.191 M) with 0.50 M hydrogen peroxide, ⊙; *o*-hydroxypropiophenone (0.383 M) with 0.26 M hydrogen peroxide, △.

(23) Lange, N. A., Ed. "Lange's Handbook of Chemistry", 10th ed.; McGraw-Hill: Toronto, 1961; p 972.
(24) Perrin, D. D.; Dempsey, B. "Buffers for pH and Metal Ion Control"; Chapman and Hall: London, 1974.
(25) Weast, R. C., Ed. "Handbook of Chemistry and Physics"; 56th ed.; Chemical Rubber Publishing Co.: Cleveland, OH, 1976; p D-134.
(26) Rothstein, E.; Saville, R. W. *J. Chem. Soc.* **1949**, 1946. Yamase, Y. *Bull. Chem. Soc. Jpn.* **1961**, *34*, 484.
(27) Mumford, C. *Chem. Br.* **1978**, *14*, 170.
(28) Stiles, M.; Mayer, R. P. *J. Am. Chem. Soc.* **1959**, *81*, 1501.
(29) Stothers, J. B. "Carbon-13 NMR Spectroscopy"; Academic Press: New York, 1972; p 287.
(30) Levy, G. C.; Nelson, G. L. "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists"; Wiley-Interscience: Toronto, 1972; p 81.

Table III. Second Order Rate Constants for the Oxidation of *o*-Acylphenols, HOC_6H_4COR, in Aqueous Alkaline Hydrogen Peroxide[a] at 37 °C

	R = H			R = CH_3			R = CH_2CH_3			R = $CH(CH_3)_2$		
[NaOH], M	[aldeh], M	[H_2O_2], M	k_2, L mol^{-1} min^{-1}	[ketone], M	[H_2O_2], M	k_2, L mol^{-1} min^{-1}	[ketone], M	[H_2O_2], M	k_2, L mol^{-1} min^{-1}	[ketone], M	[H_2O_2], M	k_2, L mol^{-1} min^{-1}
0.60				0.049	0.12	8.8×10^{-3}						
				0.052	0.29	0.12[b]						
				0.053	0.18	0.016				0.094	0.26	0.024
	0.182	0.19	1.5	0.186	0.55	1.9	0.190	0.35	0.56[c]			
	0.182	0.37	4.5									
				0.386	0.29	1.1						
1.0	0.193	0.26	0.82				0.192	0.24	0.075	0.194	0.55	2.6×10^{-3}[d]
				0.379	0.46	0.31	0.383	0.26	0.39			
							0.388	0.18	0.20			
2.0	0.367	0.50	0.80	0.350	1.04	0.14	0.372	0.50	0.036	0.372	1.04	2.6×10^{-3}[e]
	0.367	0.50	0.76				0.379	0.46	5.5×10^{-3}[b]			

[a] Data are ranked first according to sodium hydroxide concentration in the reaction solution and within a particular base concentration in order of increasing substrate concentration. Coefficients of correlation were 0.99 or better, except where otherwise footnoted. Additional data for R = CH_3 is given in Table VIII. [b-e] Coefficients of correlation were 0.98, 0.97, 0.96, and 0.93, respectively.

Table IV. Second-Order Rate Constants for the Oxidation of *p*-Acylphenols, HOC_6H_4COR, in Aqueous Alkaline Hydrogen Peroxide at 37 °C

	R = H			R = CH_3			R = CH_2CH_3			R = $CH(CH_3)_2$		
[NaOH], M	[aldeh], M	[H_2O_2], M	k_2, L mol^{-1} min^{-1}	[ketone], M	[H_2O_2], M	k_2, L mol^{-1} min^{-1}	[ketone], M	[H_2O_2], M	k_2, L mol^{-1} min^{-1}	[ketone], M	[H_2O_2], M	k_2, L mol^{-1} min^{-1}
0.60				0.0343	0.24	0.22						
	0.188	0.37	1.35	0.187	0.55	0.49				0.096	0.26	0.010
	0.197	0.19	0.84	0.379	0.46	0.095	0.379	0.46	0.031			
1.0	0.191	0.26	0.27									
	0.191	0.50	0.87	0.379	0.46	0.038[a]	0.379	0.46	5.5×10^{-4}	0.185	0.55	1.4×10^{-4}
2.0	0.350	1.04	0.46	0.350	1.04	2.2×10^{-3}	0.379	0.46	2.6×10^{-4}	0.350	1.04	$<1 \times 10^{-5}$

[a] Coefficients of correlation were 0.99 or better throughout, except for *p*-hydroxyacetophenone in 1.0 M base, where it was 0.98. Additional data for R = CH_3 is given in Table VIII. [b] No reaction was observed with 0.112 M *p*-hydroxypivalophenone (R = $C(CH_3)_3$) in 0.60 M sodium hydroxide with 0.37 M hydrogen peroxide over a period of 6 days, and at most 2% was observed over a period of 6 months even with a further addition of hydrogen peroxide. This corresponds to a rate constant of not more than 2.1×10^{-7} L mol^{-1} min^{-1}, or approximately 5 orders of magnitude slower than the corresponding isobutyrophenone (R = $CH(CH_3)_2$; see text).

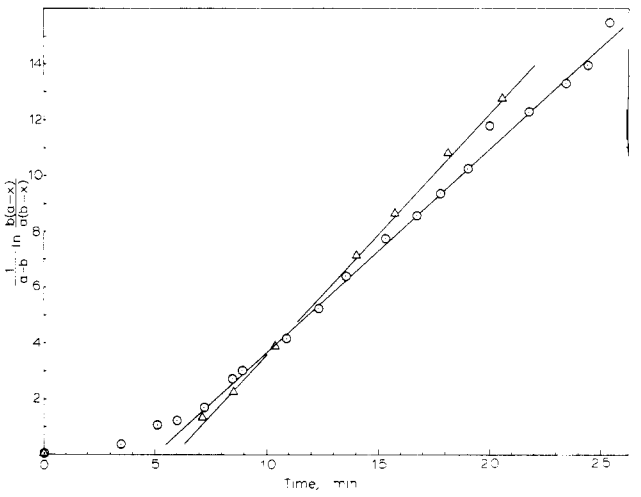


Figure 2. Dakin oxidations at 37 °C: *p*-hydroxybenzaldehyde (0.350 M) with 1.04 M hydrogen peroxide in 2.0 M aqueous sodium hydroxide, △ (time axis is ×0.2, i.e., 10 min ≡ 2 min; *y* axis is ×0.1, i.e., 2 ≡ 0.2); *o*-hydroxyacetophenone (0.053 M) with 0.24 M hydrogen peroxide in 0.60 M aqueous sodium hydroxide 37 °C, ⊙ (for experimental data, see Table VIII).

for the *p*-hydroxypivalophenone corresponded very closely to calculated estimates from model compounds (Table I).

Aldehyde and ketone oxidations gave smooth concentration vs. time curves (e.g., data of Table II) and, in the majority of cases, a good straight-line fit to second-order kinetics (Figure 1). Detailed reaction conditions and slopes for this series of experiments are given in Tables III and IV. Coefficients of correlation to second-order coordinates for experimental data obtained in this way were predominantly 0.99 or better, from which the rate data reported are estimated to be accurate to ±10%. For a few runs, as noted in the tables, coefficients of correlation dropped to 0.93–0.98 despite experimental repetitions, and for these the rate data are less reliable.

The poorer fits of data to kinetic plots on second-order coordinates were obtained from a very few special sets of circumstances such as for substrates which reproducibly demonstrated an induction period. This was a feature, in particular, of *p*-hydroxybenzaldehyde reactions, but only in 2 M sodium hydroxide (e.g., Figure 2), and of *o*-hydroxyacetophenone oxidations both under slow and fast reaction conditions at pH 12 and in 0.60, 1, and 2 M aqueous sodium hydroxide (e.g., Figure 2). An induction period was also shown by *p*-hydroxyacetophenone, but only in 2 M sodium hydroxide. These induction periods could have been caused by a contribution to the primary substrate-consuming process by some other simultaneous reaction of the same or different order, which was a possibility tested earlier and shown to be unlikely.[5] They could also be the consequence of a primary or secondary product of the oxidation having an inhibiting or promoting effect on the primary process under observation (e.g., ref 31). In either case, for the purposes of the rates recorded here, these are taken from the straight line obtained on the kinetic plot after the initial slow rate-induction period (Tables III and IV).

Rate measurements were not possible at uniform substrate or oxidant concentrations across the whole range of substitutions tested. Even though the NMR method used could conveniently follow quite rapid reactions, very fast reactions had to be moderated by decreasing the concentration of the acyl compound or the oxidant, or both, to maintain isothermal conditions.

Table V. Calculated[a] Composite Second-Order Rate Constants for Oxidation of *o*-Acylphenols, HOC_6H_4COR, in Aqueous Alkaline Hydrogen Peroxide

[NaOH], M	(second-order rate constant) × 0.50 M/$[H_2O_2]$ × 10^3 for: R = H	R = CH_3	R = CH_2CH_3	R = $CH(CH_3)_2$
0.60	3910	36.7		
	6050	207		
		44		
		1730		46
		1900	800	
1.0	1560		156	2.4
		340	750	
			555	
2.0	800	67	36	0.96
	760		6	

[a] Calculated to put all rate constant data on a common 0.50 M hydrogen peroxide concentration basis, for purposes of comparison; units = mol L^{-1} min^{-1}.

Slower reactions required higher concentrations of substrate and (or) oxidant to obtain conveniently observable rates. But this was not always possible to the extent desired because of the solubility limits imposed by other variables. Another prospective method of comparison, use of large enough excesses of hydrogen peroxide to enable determination of the pseudo-first-order rate constants for the oxidation of the whole series of acyl phenols, again was not feasible since low enough substrate concentrations under these conditions became too dilute to allow accurate determination of ketone concentrations by the NMR method.

It was possible, however, to remove much of the effect of the different concentrations of hydrogen peroxide actually present[32] and make semiquantitative rate comparisons of the second-order rate constants obtained under a wide variety of conditions by recalculating these data on the basis of an arbitrary constant hydrogen peroxide concentration throughout. Thus, rate = k_2[acyl phenol][H_2O_2] = k_{cp}[acyl phenol], where k_{cp} = k_2(arbitrary [H_2O_2]/actual [H_2O_2]). In this expression the arbitrary [H_2O_2] was taken as 0.50 M, for convenience, which allowed determination of the new composite second-order rate constants, k_{cp}; thus k_{cp} = k_2[0.50 M]/[H_2O_2], where the concentration of hydrogen peroxide employed in each experiment was applied to the denominator of the adjustment. The rate constants obtained in this way allowed a more straightforward comparison of the relative reactivities of substrates by decreasing the rate dependence on concentration and solvent effects (Tables V and VI).

The composite second-order rate constants, k_{cp}, determined in this way for the *o*-acylphenols in 0.60 M sodium hydroxide gave a substrate relative rate ranking of (Ia, R = H) = 2–40 × (Ib, R = CH_3) = 0.25–2 × (Ic, R = CH_2CH_3) = 17 × (Id, R = $CH(CH_3)_2$) (Table V). In all cases the aldehyde clearly reacted about 30 times faster than the *o*-hydroxyisobutyrophenone. Raising the base concentration to 1.0 and 2.0 M in sodium hydroxide *lowered* the composite second-order rate constants by a factor of 2 for each base concentration increase for the aldehyde and, in general, even more sharply lower for all the ketones. This aspect is commented on later.

(31) Hamilton, G. A.; Friedman, J. P. *J. Am. Chem. Soc.* **1963**, *85*, 1008.
(32) Jones, D. D.; Johnson, D. C. *J. Org. Chem.* **1967**, *32*, 1402.
(33) Ingold, C. K. "Structure and Mechanism in Organic Chemistry"; G. Bell and Sons: London, 1953; p 758.
(34) DeTar, D. F. *J. Org. Chem.* **1980**, *45*, 5166.
(35) Wiberg, K. B. *J. Am. Chem. Soc.* **1955**, *77*, 2519.

Table VI. Calculated[a] Composite Second-Order Rate Constants for Oxidation of *p*-Acylphenols, HOC_6H_4COR, in Aqueous Alkaline Hydrogen Peroxide

	(second-order rate constant) × 0.50 M/[H_2O_2] × 10^3 for:				
[NaOH], M	R = H	R = CH_3	R = CH_2CH_3	R = $CH(CH_3)_2$	R = $C(CH_3)_3$
0.60		460			
	1820	450		19	~0[b]
	2210	100	33		
1.0	520				
	870			0.13	
		41	0.60		
2.0	220	1.1	0.28	$<5 \times 10^{-3}$	

[a] Calculated to put all rate constant data on a common 0.50 M hydrogen peroxide concentration basis, for purposes of comparison; units = mol L^{-1} min^{-1}. [b] See text and Table IV.

Table VII. Comparison of Relative Rates with Substituent Effects for Dakin Oxidation vs. Ester Hydrolyses and Baeyer-Villiger Oxidation

	rate[g]			
substrate and medium	R = H	R = CH_3	R = CH_2CH_3	R = $C(CH_3)_3$
o-OHC_6H_4COR				
0.60 M NaOH[a]	108	17	17	
2.0 M NaOH (Dakin oxidn)	780	67	21	
p-OHC_6H_4COR				
0.60 M NaOH[b]	106	18	2	~0
2.0 M NaOH (Dakin oxidn)	44 000	220	56	
CH_3CO_2R, aqueous base[c] (ester hydrol)		7	4	0.06
$RCO_2C_2H_5$				
aqueous NaOH[d]		2	2	0.07[d]
88% ethanol[c] (ester hydrol)		10	4.7	0.11 (1.02)[e]
o-OHC_6H_4COR, 40% ethanol[f] (Baeyer-Villiger)	350	9	7	
p-OHC_6H_4COR, 40% ethanol[f] (Baeyer-Villiger)	340	3	2	

[a] Determined from Table V via simple averages. Values in 0.60 M NaOH must be multiplied by 48.0 to obtain correct rates relative to those given for 2.0 M NaOH. Ortho oxidation rates in 0.60 M NaOH relative to para oxidation in 0.60 M NaOH may be obtained by multiplying the former by 2.42. [b] Determined from Table VI via simple averages. Values in 0.60 M NaOH must be multiplied by 3800 to obtain correct rates relative to those given for 2.0 M NaOH. [c] Data from ref 31. [d] Data from ref 32. The value for R = $C(CH_3)_3$ was obtained in 40% aqueous dioxane. [e] Parenthesized value is relative rate on the same scale for $RCO_2C_2H_5$ where R = C_6H_5. [f] Data from ref 33 for Baeyer-Villiger oxidations using perbenzoic acid. [g] Rates given are calculated to give a uniform rate of 1 for R = $CH(CH_3)_2$ for all cases to enable a common basis for comparison between reaction types.

The rates of oxidation of the *p*-acylphenols were all slower than for the corresponding *o*-acylphenols, ranging from about $^1/_2$ to $^1/_3$ the rate for the aldehydes Ia (R = H) to 2–3 orders of magnitude slower for the more substituted examples (Tables VI and VII). With the *p*-acylphenols in 0.60 sodium hydroxide the composite second-order rate constants, k_{cp}, were more regular and quite similar to those of the ortho examples: (Ia, R = H) = 4–20 × (Ib, R = CH_3) = 3–15 × (Ic, R = CH_2CH_3) = 2 × (Id, R = $CH(CH_3)_2$). No reaction was observed over 6 days and at most 2% reaction over a period of 6 months for R = $C(CH_3)_3$, even in 0.60 M sodium hydroxide, chosen for this substrate because it was the medium giving the highest oxidation rates with all other substrates tested. This would correspond to a second-order rate constant of not more than 2.1×10^{-7} or to a k_{cp} of 2.9×10^{-4} L mol^{-1} min^{-1}.

As with the *o*-acylphenols a clear rate *decrease* was noted for reactions of *p*-acylphenols conducted in solutions containing base concentrations higher than 0.60 M. Increasing the sodium hydroxide concentration successively to 1.0 and 2.0 M slowed the rate for *p*-hydroxybenzaldehyde by a factor of 2 or 3, an effect which became more evident from the retardation factors in the 10–40 range noted for all the *p*-hydroxyketones (Table VI).

In 0.60 M aqueous sodium hydroxide, nearly ideal Dakin oxidation conditions, the effect of substituent on rate was found to lie between the generally smaller influence found in ester hydrolyses and the more pronounced effect under Baeyer–Villiger (BV) oxidation conditions (Table VII). That the effect on the rate of Dakin oxidations should be less, at least for I (R=H), than the effect on BV oxidations is not surprising considering the greater bulk of the perbenzoate anion than the hydroperoxide anion. It is not clear why the steric differentation for hydroperoxide anion should be greater than for hydroxide with the demonstrated greater nucleophilicity of the former.[36]

o- and *p*-hydroxyacetophenone were selected as substrates to provide a sensitive measure of the effect of pH on rate in a more extensive study since rate retardation with increased pH was greater with ketones than with aldehydes of both series tested. The numerical results of this study are given in Table VIII and the comparison of the pH's at which low and high rates were observed is presented on a more uniform basis in Figure 3. The generally slower rate of oxidation of *p*-hydroxyacetophenone is again apparent. But the difference in the pH range showing high oxidation rates for each substrate is markedly different, from pH ~9.5–13.5 for the ortho to only ~11.5–13.5 for the para. Also the substantial rate decline observed at very high pH's was unexpected.

Discussion

Any pathway proposed for Dakin oxidation has to account for a first-order dependence on acyl phenol and hydrogen peroxide concentrations when [H_2O_2] ≃ [acyl

(36) Ogata, Y.; Sawaki, Y. *J. Org. Chem.* **1972**, *37*, 2953.

Table VIII. Effect of pH on Second-Order Rate Constants of Dakin Oxidation at 37 °C

	o-hydroxyacetophenone			p-hydroxyacetophenone		
aqueous soln	[ketone], M	$[H_2O_2]$, M	rate × 10^3, L mol^{-1} min^{-1}	[ketone], M	$[H_2O_2]$, M	rate × 10^3, L mol^{-1} min^{-1}
buffer, pH 8	0.016	0.24	3.9	0.034	0.24	5.3
buffer, pH 9	0.016	0.24	6.2	0.034	0.24	12.9
buffer, pH 10	0.016	0.24	277	0.034	0.24	13.3
buffer, pH 11	0.016	0.24	274, 240[a]	0.034	0.24	74.5
buffer, pH 12	0.016	0.24	257, 232[a]	0.034	0.24	364
buffer, pH 13	0.016	0.24	329, 307[a]	0.034	0.24	314
0.60 M NaOH[b]	0.053	0.24	705	0.034	0.24	222, 170[a]
1.0 M NaOH[b]	0.40	0.48	180	0.38	0.46	38
2.0 M NaOH[b]	0.35	1.04	140	0.35	1.04	2

[a] Results of duplicate runs. [b] Measured pH's were determined by using a Metrohm EA 107-UX high-pH electrode standardized in pH 12 buffer and corrected for alkali error from a calibration curve and are as follows: 0.60 M, 13.7; 1.0 M, 13.8; 2 M, 13.9.

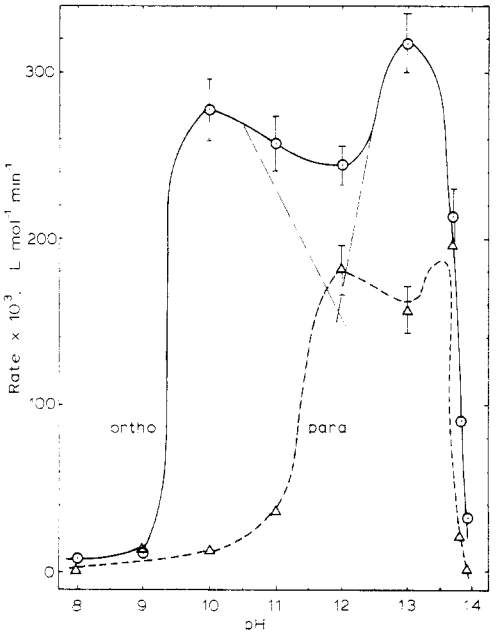


Figure 3. Plot of k_{cp}'s vs. pH for the rate of oxidation of *o*- and *p*-hydroxyacetophenone (effectively 0.016 M) with 0.24 M hydrogen peroxide (for the effective concentration, see the text) at 37 °C.

Table IX

	primary reacting species		approx oxidation rate	
pH	phenol	H_2O_2	ortho	para
low, <9	AH	H_2O_2	0	0
low, ~10	AH	H_2O_2	fast	0
mid, 10–11	AH, A^-	H_2O_2, HO_2^-	fast	0 to very slow
high, 11–13.5	A^-	HO_2^-	fast, ~2× para	moderately fast

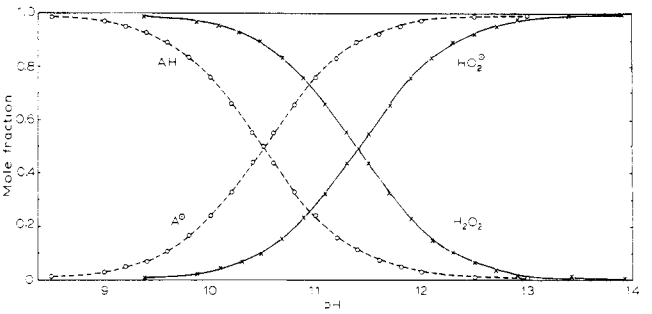


Figure 4. Plot of calculated mole fractions of aqueous *o*-hydroxyacetophenone and hydrogen peroxide vs. pH.

phenol], as used here, and a first-order dependence on acyl phenol and ~1.4-order dependence on hydrogen peroxide concentrations when $[H_2O_2] \gg$ [acyl phenol], conditions used in our earlier work.[5] It also has to accommodate the rate vs. pH profile determined here for *o*- and *p*-hydroxyacetophenones (Figure 3, pK_a's in 40% ethanol at 25 °C: ortho, 10.50;[36] para, 8.71,[36] 8.05 (in H_2O)[37]). In considering the rate profile, it should be noted that similar rate profiles, though occurring over a broader and lower pH range (6–12) were recorded by Ogata and Sawaki[36] for alkaline BV oxidations of *o*- and *p*-hydroxyacetophenones. These too were generally faster and had a broader high-rate region for the ortho ketone than for the para, but the profiles for both substrates roughly centered on the pH corresponding to the pK_a of the phenol substrate. In a related study with (*p*-methoxyphenyl)-2-propanone in 0.10 M hydrogen peroxide using alkaline BV conditions, Jones and Johnson[32] obtained maximum oxidation rates at 0.10 M sodium hydroxide concentrations.

As a first step in development of a pathway it is useful to consider the dominant species present at the experimental pH's used (see Table IX). By use of this information in consideration of the increase in oxidation rate of *p*-hydroxyacetophenone with pH, it was found that the rate increase coincided very closely to the increase in hydroperoxide anion concentration alone (Figure 3). The observed rate increase began at about pH 10, when the phenol would already be 95+% ionized; hence the onset of the high-rate pH range only requires dependence on the 11.4 pK_a value (at 37 °C)[38] of hydrogen peroxide and not a concerted dependence on the pK_a's of both substrates. The detailed oxidation pathway of *p*-hydroxyacetophenone as given in Scheme IIIa is based on this premise.

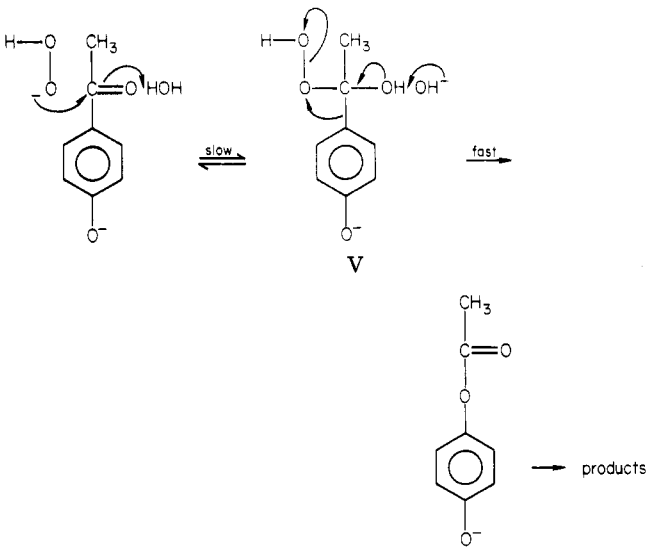
When the increase in oxidation rate of *o*-acylphenols with pH was considered in a like manner (Figure 4) to require phenolate anion and hydroperoxide anion for high oxidation rates, it would be predicted that a slower resultant increase in rate with pH (i.e., a 4–5-fold increase to maximum rate, over 2 full pH units) should be observed and that this should occur over the pH range 10–12, not between 9 and 10 as observed (Figure 3). However, high oxidation rates at pH 10 could be accommodated by invoking participation of undissociated hydrogen peroxide in the oxidation. This suggestion, to be plausible, requires that the carbonyl carbon of undissociated (at these pH's)

(37) Bordwell, F. G.; Cooper, G. D. *J. Am. Chem. Soc.* **1952**, *74*, 1058.

(38) Evans, M. G.; Uri, N. *Trans. Faraday Soc.* **1949**, *45*, 224. See also: Kolczynski, J. R.; Roth, E. M.; Shanley, E. S. *J. Am. Chem. Soc.* **1957**, *79*, 531.

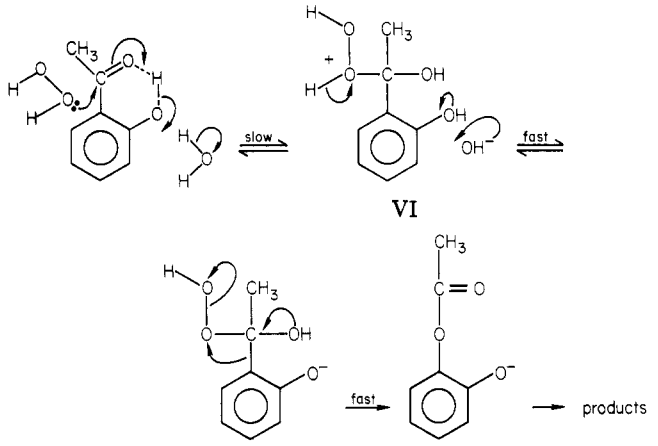
Scheme III

(a) Oxidation Pathway for *p*-Hydroxyacetophenone at pH 11–13.5



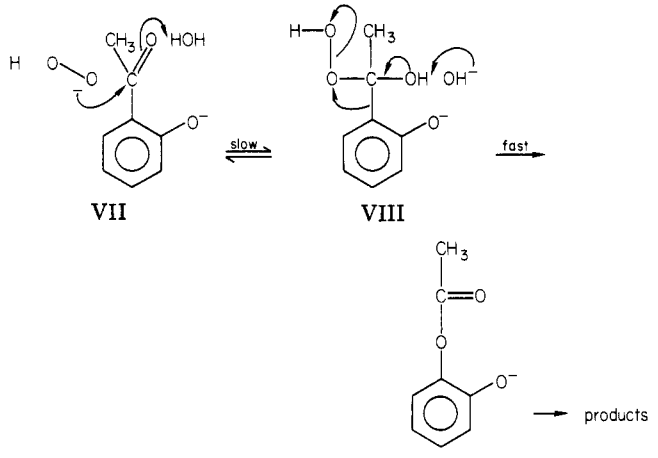
V

(b) Oxidation Pathway for *o*-Hydroxyacetophenone at pH 9.5–11.5



VI

(c) Oxidation Pathway for *o*-Hydroxyacetophenone at pH 10.5–13.5



VII VIII

o-hydroxyacetophenone be more electrophilic, an "autoprotic catalysis", than the carbonyl carbon of *p*-hydroxyacetophenone. From the pK_a of ~10.5 for the ortho compound (vs. ~8.5 for the para) and from the nearly 3 orders of magnitude acceleration of ester hydrolysis in an analogous system,[39] this appears to be qualitatively true. Intermediate VI is reversibly formed in this manner (Scheme IIIb).

Once addition to the carbonyl occurs to form VI, hydrogen bonding of the phenolic hydroxyl to the carbonyl oxygen is no longer possible. In this manner the pK_a of VI is decreased from that of the starting acyl phenol, estimated from the rate plot to be about 9.5. Below a pH of about 8.5, where ionization of VI cannot occur, the adduct may form but can only redissociate since it does not possess a sufficiently electron-rich ring (i.e., phenolate anion) for migration to occur. However, at a high enough pH for ionization of VI, rapid phenolate migration occurs, and the whole process becomes hydrogen peroxide attack rate limited. In this way, Scheme IIIb explains the pathway prevailing for the first observed (lower pH) maximum in Figure 3.

For *o*-hydroxyacetophenone oxidation at and above pH 10.5, the concentration of hydroperoxide anion, a much better nucleophile, begins to become significant. At the same time the concentration of undissociated phenol decreases, in favor of an increase in the concentration of phenolate anion VII, which provides a poorer nucleophilic center for hydroperoxide anion attack than that provided by the undissociated phenol. This reduced reactivity effectively moderates the rate increase anticipated from the higher concentration of hydroperoxide anion at these pH's. As soon as adduct VIII forms, rearrangement occurs since the phenol is already ionized at the time of hydroperoxide addition (Scheme IIIc). This pathway, which parallels the sole pathway for *p*-acylphenol oxidation, is the explanation for the second ortho ketone rate maximum observed (Figure 3). Ortho oxidations at intervening pH's proceed via a combination of processes b and c in Scheme III.

The precipitous drop in oxidation rates observed for both *o*- and *p*-acylphenols at pH's above 13.5 could be due to any of a combination of factors. Among the possibilities are an effective decrease in hydrogen peroxide anion activities from associations and the potential formation of peroxide dianion[40] or from ionization of the second peroxidic hydrogen in adducts V, VI, or VIII. It may also be caused by the increase in ionic strength alone. A hint of the same or similar processes operating may be the 1.4 dependence on hydrogen peroxide concentrations as noted earlier.[5] Unfortunately, at the moment not enough is known about the behavior of aqueous peroxide at these high basicities[41] to enable more than these speculative comments regarding this rate-attenuation behavior.

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Registry No. *o*-Ia, 90-02-8; *p*-Ia, 123-08-0; *o*-Ib, 118-93-4; *p*-Ib, 99-93-4; *o*-Ic, 610-99-1; *p*-Ic, 70-70-2; *o*-Id, 6640-69-3; *p*-Id, 34917-91-4; IV, 72569-10-9; phenyl isobutyrate, 20279-29-2; *p*-acetoxybenzoic acid, 2345-34-8; *p*-acetoxybenzoyl chloride, 27914-73-4; *tert*-butyllithium, 594-19-4.

(39) Hansen, B. *Acta Chem. Scand.* **1963**, *17*, 1375.
(40) Ardon, M. "Oxygen: Elementary Forms and Hydrogen Peroxide"; W. A. Benjamin: New York, 1965; p 88.
(41) "Gmelins Handbuch der Anorganischen Chemie"; Verlag Chemie: Weinheim, 1966; Sauerstoff, Lieferung 7, System-Nummer 3, p 2272.