950 m, 911 w, 882 w, 828 w, 666 m, 504 m, cm^{-1}. It may be also noted that the C-H peak expected at about 2900 cm^{-1} was very broad.

X-ray Crystal Structure Analysis. Crystals were obtained as described and mounted in a glass capillary. Data were measured on a PW1100/20 Phillips Four-Circle computer-controlled diffractometer. Mo Kα (λ = 0.71069 Å) radiation with a graphite crystal monochromator in the incident beam was used. The unit cell dimensions were obtained by a least-squares fit of 24 centered reflections in the range of $10° \leq \theta \leq 15°$. Intensity data were collected using the ω-2θ technique to a maximum 2θ of 50°. The scan width, $\Delta\omega$, for each reflection was 1.00 + 0.35 tan θ with a scan speed of 0.05 deg/min. Background measurements were made for a total of 20 s at both limits of each scan. Three standard reflections were monitored every 60 min. No systematic variations in intensities were found. Intensities were corrected for Lorentz and polarization effects. Absorption was corrected by using the Ψ-scan method. All non-hydrogen atoms were found by using the results of the SHELXS-86 direct method analysis.[16] After several cycles of refinements using a CYBER 855 computer, the positions of the hydrogen atoms were calculated and added with a constant isotropic temperature factor of 0.05 $Å^2$ to the refinement process. Refinement proceeded to a convergence by minimizing the function $\sum w(|F_o| - F_c|)^2$. A final difference Fourier synthesis map showed several peaks less than 1 e/$Å^3$ scattered about the unit cell without significant feature. The discrepancy indices $R = \sum||F_o| - |F_c||/\sum|F_o|$ and $R_w = [\sum w(|F_o| - |F_c|)^2/\sum wF_o^2]^{0.5}$ are presented with other pertinent crysallographic data in Table II.

Supplementary Material Available: Tables of positional and thermal parameters and bond lengths and bond angles (5 pages). Ordering information is given on any current masthead page.

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Mechanism of Reactions of Hydrogen Peroxide and Hydroperoxides with Iron(III) Porphyrins. Effects of Hydroperoxide Structure on Kinetics

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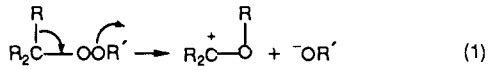
Abstract: The buffer-catalyzed and uncatalyzed reactions of various alkyl hydroperoxides and hydrogen peroxide with chelated protohemin chloride have been studied. The rates of the uncatalyzed reactions show the same dependence on structure as the catalyzed reactions. The rates of reactions of peracids and hydroperoxides show similar dependencies on leaving ion stability. These and other evidence indicate that these reactions proceed by heterolytic cleavage of the oxygen-oxygen bond under the conditions employed.

The cleavage of the oxygen-oxygen bond in peroxides takes two distinct pathways, heterolytic[1-3] or homolytic,[4,5] illustrated by eq 1 and 2 for organic peroxides. Reaction 1 is accelerated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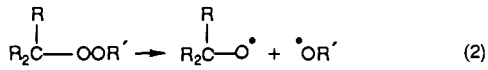
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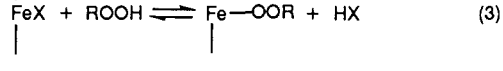
by increased electron density in R and decreased electron density in R′ and is catalyzed by acid in those cases where R′O⁻ is not self-sufficiently stable, i.e., R′ = alkyl or hydrogen.[2,3]

By contrast reaction 2 is accelerated by increased electron repulsion of the oxygen lone pairs and by resonance stabilization of R′O• and R_3CO•. Thus any reaction producing RO• will be sensitive to its stability. Electron-withdrawing groups as either R′ or R decrease the rate. Because RO• is a poor base, general or specific acid catalysis of reaction 2 is not to be expected and has not been observed.

Recent interests[6-12] in the metalloenzyme-catalyzed cleavage of peroxide bonds has prompted further investigation of these mechanisms in those cases where the peroxide contains a metal-oxygen bond. A similar dichotomy of mechanisms can be envisioned in the reactions of the biologically important iron(III) porphyrins (PFe^+) with hydroperoxides and peracids to presumably produce an iron(III)-hydroperoxide species (eq 3).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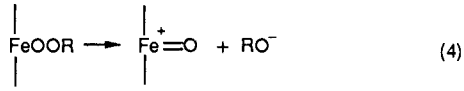
Heterolytic cleavage could occur with (eq 5) or without (eq 4) acid catalysis. It can reasonably be expected that either



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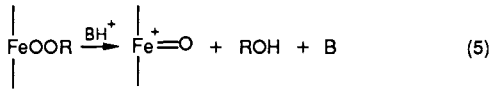

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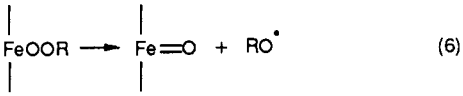
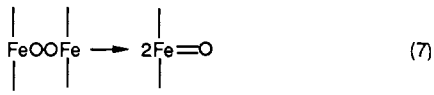
mechanism 5 or 6 occurs depending upon the conditions. Thus reaction 5 can be expected to dominate in the presence of sufficiently good proton donors, with extraordinary good leaving groups or both. By contrast, FeOOR in which RO^- is a very poor leaving group and in the absence of protic solvents is more likely to cleave by the homolysis reaction (6).[13] It would be of great interest to establish the conditions for the mechanism change.



(6)

In earlier investigations of the reactions of ROOH with iron(III) porphyrins[11,14] it was found that the reaction is accelerated by increased electron density at the iron, by increased stability of RO^-, and by increased concentration of collidine buffer. Reaction 5 has also been indicated in the work of Groves et al.[12] It has been demonstrated that peracids do not react with iron(III) porphyrins by homolytic cleavage in hydroxylic solvents.[11] The heterolytic cleavage of peracids in hydroxylic solvents with or without buffer catalysis are now well established.[11,14]

However, because the symmetrical peroxide in eq 7 cleaves very rapidly in a homolytic fashion,[13] it can be expected that reaction 6 might also be fast.[13b]



(7)

Recently both kinetic[14] and product analysis[15,16] studies have been interpreted in favor of reaction 6 for the reactions of alkyl hydroperoxides and hydrogen peroxide with iron(III) porphyrins in neutral aqueous or alcohol solvents in the absence of buffer catalysis.

In this paper we present data that indicates that reaction 6 at or near neutral pH values does not compete with heterolytic cleavage in the presence of methanol. This conclusion is extended to other hydroxylic solvents in a subsequent paper.

Experimental Section

Materials. Potassium iodide (reagent grade), potassium hydrogen phthalate (ACS alkimetric standard 99.9% assay), tetramethylammonium hydroxide (1.0 ± 0.1 M in CH_3OH), ferric chloride hexahydrate (Matheson, Coleman and Bell), sodium thiosulfate pentahydrate (100.4% assay), mercuric iodide (99.4% assay; J. T. Baker Chemical Co.), starch (soluble; Allied Chemical), sodium hydroxide volumetric solution (1.0 ± 0.005 N), hydrochloric acid volumetric solution (1.0 ± 0.005 N and AR reagent ~37%), sodium carbonate (anhydrous AR grade), barium hydroxide octahydrate (99.2% assay), sulfuric acid (95.98% assay), methanol (anhydrous reagent and Spectra AR grades), ethanol (95%), pentane (98%), chloroform (AR grade), benzene (AR grade), acetic acid (glacial AR 99.7%), formic acid (AR 88%), sodium acetate anhydrous (AR), potassium hydroxide (AR pellets), sodium chloride, potassium bromide (IR grade; Mallinckrodt), trimethylacetyl chloride (99%), triethylamine (99%), 1-(3-aminopropyl)imidazole (Aldrich Chemical Co.), 2,4,6-collidine (purified grade, 99.9%; Sigma), argon, and carbon monoxide (99.99%, HCL technical grade 99% minimum; Matheson Gas Products) were used as received except as noted. Deuterated solvents were from Stohler Isotope Chemicals. Tri-*tert*-butylphenol (Aldrich) was recrystallized three times from hot ethanol–water (9:1) solution before use. Collidine hydrochloride was prepared as previously described.[11a] Protohemin chloride (Calbiochem-Behring Corp. and Sigma) was used as received for synthesis. *tert*-Butyl hydroperoxide (90%) was obtained from Aldrich Chemical Co. and was vacuum distilled to yield a highly purified fraction [32 °C (13 Torr), 98 ± 1% assay]. Ethyl hydroperoxide (10–12%) was obtained from Polysciences, Inc., and was assayed to be 12.2 ± 0.2%. Hydrogen peroxide (30%) was obtained from Mallinckrodt and was assayed to be 26.4 ± 0.6%. Cumene hydroperoxide (80% minimum) was obtained from Pfaltz and Bauer, Inc., and was assayed to be 87.4 ± 0.7%. Trityl hydroperoxide (≥95%) was provided by Dr. W. A. Lee, and a single titration of this sample indicated ~95% purity. Phenyl peracetic acid was prepared as described in the literature[17] and was recrystallized three times from a benzene–pentane mixture to needlelike crystals (mp 64–67 °C,[18] 99 ± 1% assay). Determination of the purities of all oxidizing agents was performed by iodometric analysis as described below. All solutions used for acidimetric and iodometric titrations were prepared immediately before use with deionized water, which had been boiled and cooled under argon atmosphere, or with anhydrous reagent methanol, which had been refluxed and cooled under argon atmosphere.

Methods. Chromatography was performed on silica gel sheets (Eastman No. 13181) or on silica gel (Davidson Grade 62) columns. The eluent was 89% $CHCl_3$, 10% CH_3OH with either (a) 1% HCOOH or (b) 1% $(CH_3CH_2)_3N$ except where noted differently.

Visible spectra were recorded on a Kontron–Uvikon 810/820 spectrophotometer on which the wavelength had been calibrated with Holmium and Didymium filters. All visible spectra, extinction coefficients, and kinetic data collected were at 25 ± 1 °C. The temperature was maintained via a thermostated circulating water bath connected to the cell holder of the spectrophotometer. Visible spectra of NMR samples were obtained as previously described[19] on either the Uvikon 810/820 or a Cary 15 spectrophotometer.

Kinetic Data. The rates of intermediate formation by alkyl hydroperoxides and hydrogen peroxide were obtained by methods similar to those previously reported.[11] All kinetic runs were measured at 25 ± 1 °C on the Uvikon 810/820 instrument. The rate of oxidation of TBPH by H_2O_2 or alkyl hydroperoxide was monitored by the production of the tri-*tert*-butylphenoxy radical absorption at 400 nm (ϵ = 1800) or at 630 nm (ϵ = 335)[20-22] via both initial rate and pseudo-first-order methods. In the initial rate method, the ΔA vs time was monitored for the first 10% of the expected ΔA_∞ or until curvature in the line was observed. The second-order rate constants obtained by this method are $2k_2$ due to monitoring phenoxy radical production. At 630 nm, the second-order rate constant, k_2, was also obtained by pseudo-first-order rate methods. Simple linear regression of $-\ln (A_\infty - A_t)$ vs time from the manually digitalized spectral data yields k_{obsd} as the slope, and division by hemin concentration afforded the second-order rate constant, k_2. The rate of destruction of hemin was also monitored directly by the initial rate method in the absence of TBPH. The second-order rate constants obtained by all of the above methods were in good agreement with each other.

In all kinetic runs, visible spectra were used to determine the concentrations of the hemin derivative studied. Previous to every series of runs an injection of hemin–methanol solution was made into a known volume of 0.01 M HCl–methanol solution, and the visible spectrum of the hemin was obtained. The concentration of the hemin stock solution was then calculated from the previously determined mean extinction coefficients.

The kinetic runs performed at fixed pH were carried out in 2,4,6-collidine/2,4,6-collidine–HCl buffered methanol solutions usually at the pK_a of 2,4,6-collidine (~7.5).[23] In the kinetic runs in which the pH was

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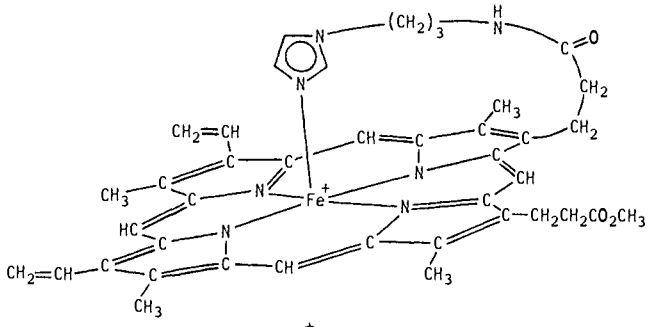
varied from the pK_a, the pH was calculated from the ratio of the free collidine to collidine–HCl.

Throughout the course of a large number of experiments, variables such as pH, general-base concentration, and the structure and concentration of hydroperoxide were systematically altered. In a typical experiment, a solution was prepared that was 0.100 M TBPH, buffered at pH 7.5 with 5.3×10^{-4} M 2,4,6-collidine and 5.3×10^{-4} M 2,4,6-collidine–HCl. Into an 8-in. 1-cm-path-length silica cuvette, 3 mL of the above solution was added, and the cuvette was septum sealed. An aliquot of 8 μL of 2.22×10^{-3} M methanol solution of 1^+Cl^- was injected into the cuvette, and the resulting 5.9×10^{-6} M 1^+Cl^- solution was deoxygenated by bubbling through a steady stream of solvent-saturated argon for 30 min. To this cuvette, 10 μL of a similarly deoxygenated 0.90 M H_2O_2–methanol solution was injected; the cuvette was vigorously shaken and quickly put into the spectrophotometer, and absorbance vs time data were collected. Triplicate samples were prepared and initial rate data collected at both 400 and 630 nm. Three additional samples were prepared exactly as above except that the concentration of 1^+Cl^- was increased to 1.05×10^{-4} M. Pseudo-first-order and initial-rate methods were used to analyze the absorbance vs time data collected from these samples at 630 nm. All of the second-order rate constants calculated from the individual kinetic runs described above were statistically compared to eliminate extraneous values,[24] and a mean and standard deviation was then calculated. This mean value is then reported as k_2 for that particular set of conditions.

Titration for Active Oxygen in Alkyl Hydroperoxides. An aliquot of alkyl hydroperoxide was placed into an Erlenmeyer flask and diluted to 5 mL with methanol. About 0.1 g of dry ice was added and the flask swirled briefly to sweep out oxygen. Prior to the complete disappearance of the dry ice, 1.0 mL of saturated aqueous potassium iodide and 15.0 mL of glacial acetic acid containing 1×10^{-4} M ferric chloride were added. The flask was quickly stoppered and placed in the dark in a 50 ± 1 °C water bath. A systematic investigation of the effect of incubation time for periods from 30 min to 12 h revealed that ~4 h resulted in the optimum reproducibility. Upon removal from the water bath and cooling the samples were unstoppered, diluted with 80 mL of deionized water, and titrated to a starch end point with standardized thiosulfate solution. The determinations of active oxygen were based upon the titrations of three to five samples of each of the alkyl hydroperoxides and of similarly prepared control samples that did not contain alkyl hydroperoxide. The control samples accounted for false readings of ≤1% in all cases.

Protohemin Mono-3-(1-imidazolyl)propylamide, Monomethyl Ester (1^+Cl^-). Model compound 1^+Cl^- was prepared by both the published procedure[19] and by the method described below, which is analogous to that of Almog et al.[25] for the preparation of mesohemin mono-3-(1-imidazolyl)propylamide, monomethyl ester. The protohemin mono-



1^+Cl^-

methyl ester chloride (0.5 g, 7.5×10^{-5} mol), in 250 mL dry pyridine, was treated with trimethylacetyl chloride (0.6 mL, 578 mg, 4.87 mmol) until conversion to the monomixed anhydride was complete as indicated by TLC of a methanol-quenched sample as above. 1-(3-Aminopropyl)-imidazole (0.3 mL, 288 mg, 2.3 mmol) was added to the reaction mixture, which was then stirred for 30 min. A TLC of the methanol-quenched mixture indicated >95% conversion to the desired product, R_f[a] = 0.44; R_f[b] = 0.59. Chromatography on silica gel and treatment with dilute aqueous HCl solution, as described above, afforded the pure protohemin chloride mono-3-(1-imidazolyl)propylamide, monomethyl ester (1^+Cl^-). The NMR of the reduced CO complex was identical with that previously described.[19] UV–vis: (0.01 M HCl in MeOH) 396 (140), 500 (7.6), 530 (5.7), 626 (3.1); (0.01 M NBu_4OH) 398.5 (83), 475 (9.9), 595 (7.2).

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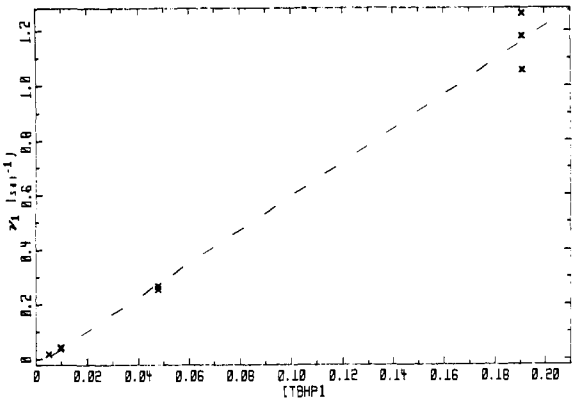

Figure 1. Rate of 2,4,6-tri-*tert*-butylphenoxy radical formation from the reaction of 1^+Cl^- with TBHP as a function of [TBHP] in unbuffered methanol at 25 °C. ν_i is the initial rate divided by $2[1^+Cl^-]$; slope = 6.2 ± 0.2 M^{-1} s^{-1}; intercept = −0.02 ± 0.02 s^{-1}; correlation coefficient (r) = 0.9959.

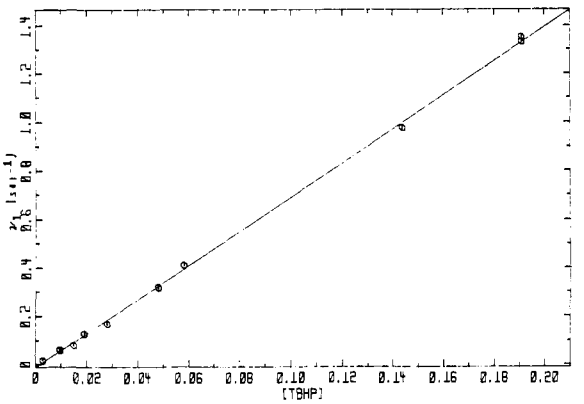

Figure 2. Rate of 2,4,6-tri-*tert*-butylphenoxy radical formation from the reaction of 1^+Cl^- with TBHP as a function of [TBHP] in collidine-buffered methanol at pH ~8.2, 25 °C. $[Collidine]_{free}$ = 0.01 M; $[collidine]_{free}/[collidine–HCl]$ = 5.0. ν_i is the initial rate divided by $2[1^+Cl^-]$; slope = 7.03 ± 0.04 M^{-1} s^{-1}; intercept = 0.009 ± 0.003 s^{-1}; r = 0.9997.

Results

The kinetic data reported in this study were obtained primarily by the initial rate method due to the slow reaction rates of intermediate formation that were generally observed. As in previous studies of this type[11,14] the rate of formation of the intermediate was determined by monitoring the production of the stable blue phenoxy radical from 2,4,6-tri-*tert*-butylphenol (TBPH).[20-22] Initial rate data was obtained at two of the λ_{max} of the TBPH phenoxy radical spectrum, 400 and 630 nm. The initial rate method requires that the molar absorptivity, ϵ(M), in units of M^{-1} cm^{-1}, for the phenoxy radical be known, in addition to the concentrations of the hemin catalyst and oxidant used.

Although most of the reported data were obtained by the initial rate method at 400 and 630 nm, the pseudo-first-order method was also employed at 630 nm. The pseudo-first-order results serve as a check upon the results obtained by initial rate methods. Since simple linear regression of $-\ln(A_\infty - A_i)$ vs time from the manually digitalized pseudo-first-order spectral data yields k_{obsd} as the slope, the second-order rate constant is then obtained without involving oxidant concentration or phenoxy radical molar absorptivities in the calculations.

A comparison of some k_2 values obtained by the initial rate method at 400 and 630 nm with those obtained by the pseudo-first-order method at 630 nm is made in Table I. The variation of the value of k_2 as a function of kinetic method and wavelength is shown to be small and random. In one case the spectral data obtained at 630 nm were analyzed by both initial and pseudo-first-order rate methods, resulting in only a ~3% difference between the k_2 values. The statistical mean of k_2 from all kinetic methods is given in Table I as the final value used in plots such

Table I. Variation in the Rate Constant Obtained for 2,4,6-Tri-*tert*-butylphenoxy Radical Production from H_2O_2 as Catalyzed by 1^+Cl^- as a Function of the Kinetic Method and Wavelength

[collidine][a] free, M	λ, nm	kinetic method[b]	no. of kinetic determinations	k_2 (mean ± σn),[c] M^{-1} s^{-1}
0.0005	400	initial rate	13	17.9 ± 0.5
	630	initial rate	4	18.0 ± 0.2
	630	pseudo first order	2	17.4 ± 0.2
		final value used		17.9 ± 0.5
0.0010	400	initial rate	3	26.8 ± 0.2
	630	initial rate	2	24.9 ± 0.3
	630	initial rate	1[d]	25.1
	630	pseudo first order	1[d]	24.4
		final value used		26 ± 1
0.0100	400	initial rate	2	185 ± 3
	630	initial rate	2	178 ± 1
	630	pseudo first order	1	191
		final value used		185 ± 5

[a] At 25 °C; pH = pK_a = 7.5 in methanol; [TBPH] = 0.1 M. [b] The ϵ(M) values of 1800 at 400 nm and 335 at 630 nm were used in the determination of initial rates. [c] k_2 is the initial rate divided by $2[1^+Cl^-][H_2O_2]$ and then statistically corrected for H_2O_2 symmetry. [d] This data set was analyzed by both initial rate and pseudo-first-order methods.

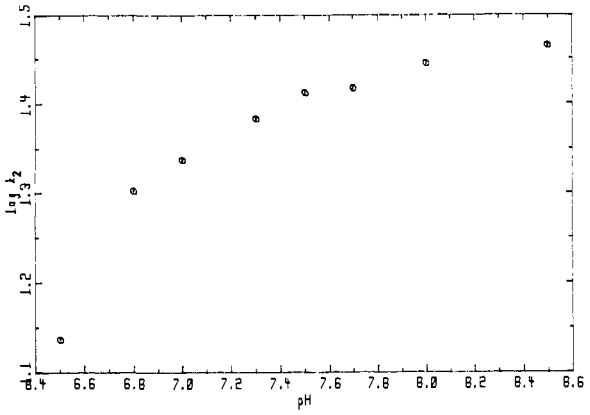

Figure 3. Rate of 2,4,6-tri-*tert*-butylphenoxy radical formation from the reaction of 1^+Cl^- with TBHP as a function of pH in methanol at 25 °C. $[Collidine]_{free}$ = 0.05 M; using pK_a collidine-H^+ in methanol ~7.5.

as that in Figure 1. The dependence of reaction rate on *tert*-butyl hydroperoxide is shown in Figure 1 in the absence of buffer and Figure 2 in buffer solution. The reaction has a first-order dependence upon hydroperoxide and upon the iron(III) porphyrin. The dependence of the rate upon pH is displayed in Figure 3.[26] Although somewhat accelerated by increasing pH from 6.5 to 7.5, the reaction shows little dependence upon pH in the range 7.5–8.5 where most of these studies are carried out. Similar results were reported for *m*-chloroperbenzoic acid. This is further illustrated in Figure 4 where the dependencies of rate on free collidine concentration at pH 7.5 and 8.5 are essentially identical. Similar independence of rate on pH in this range was also reported by Bruice et al.[14b] Further indication of general catalysis is indicated by the effect of a 1:1 acetate buffer (pH = 9.7)[11f] in the range of 0–0.06 M acetate concentration. The linear plot of Figure 5 indicates a lower slope (2300) than that for the collidine buffer and a 10-fold smaller slope/intercept value (see Table II).

The effect of alkyl hydroperoxide structure on the rate of intermediate formation of 1^+Cl^- as a function of collidine was investigated in methanol buffered at pH 7.5. The second-order rate constants obtained by the use of hydrogen peroxide (H_2O_2), ethyl hydroperoxide (EHP), trityl hydroperoxide (THP), cumene

(26) At low pH values the proximal base is removed by protonation, and at higher pH values hydroxy or μ-oxo forms of the hemin are produced. Therefore, we have not extended our work to these pH values in this study. See ref 14a–f for such studies.

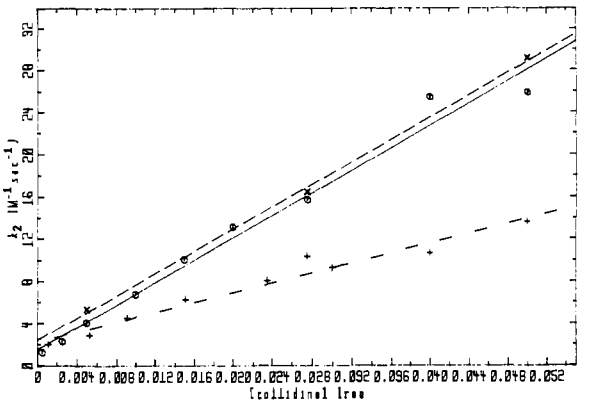

Figure 4. Plots of the rate constant for production of 2,4,6-tri-*tert*-butylphenoxy radical from the reaction of 1^+Cl^- with TBHP as a function of free collidine concentration in methanol at 25 °C: (+) (--) pH 6.5; (○) (—) pH 7.5; (×) (-·-) pH 8.5. Using pK_a (collidine-H^+) in methanol ~7.5, the second-order rate constant, k_2, is the initial rate divided by $2[1^+Cl^-][TBHP]$.

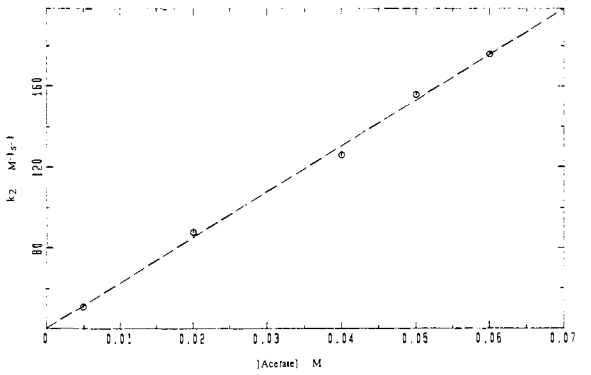

Figure 5. Plots of the rate constant for production of 2,4,6-tri-*tert*-butylphenoxy radical from the reaction of H_2O_2 with chelated protoheme (1^+Cl^-) in methanol as a function of acetate in a 1:1 acetic acid–acetate buffer at 25 °C. The second-order rate constant, k_2, is the initial rate divided by 2[hemin][HOOH].

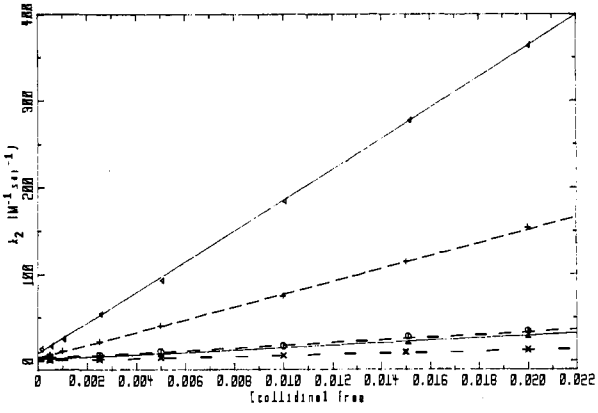

Figure 6. Plots of the rate constant for production of 2,4,6-tri-*tert*-butylphenoxy radical from the reaction of 1^+Cl^- with various hydroperoxides in methanol as a function of free collidine at pH 7.5, 25 °C: (▽) H_2O_2; (+) EHP; (○) THP; (△) CHP; (×) TBHP. Using pK_a (collidine-H^+) in methanol ~7.5, the second-order rate constant, k_2, is the initial rate divided by $2[1^+Cl^-][ROOH]$.

hydroperoxide (CHP), and *tert*-butyl hydroperoxide (TBPH) as oxidants are plotted against free collidine concentration in Figure 6. The rate of production of the high-valent intermediate of 1^+Cl^- with H_2O_2 is actually twice as large as represented in Figure 6. A statistical correction of all rates obtained with H_2O_2 has been made for the two equivalent oxygens so that a more meaningful comparison to alkyl hydroperoxides and peracids rates can be made. The results of simple linear regression analysis of the data presented in Figure 6 are listed in Table II.

Table II. Slope and Intercept Values Obtained from the Plots in Figure 6 for the Production of 2,4,6-Tri-*tert*-butylphenoxy Radical from Various Oxidants as Catalyzed by $\mathbf{1}^{+}Cl^{-}$ in Collidine-Buffered Methanol at 25 °C, pH 7.5[a]

ROOH: R =	slope, M^{-1} s^{-1}	intercept, M^{-1} s^{-1}	slope/intercept, M^{-1}	corr coeff
H	$(3.56 \pm 0.03) \times 10^4$	17.6 ± 0.8	2000 ± 90	0.9996
H[b]	$(2.7 \pm 0.2) \times 10^4$	16	1688	
H[c]	$(1.78 \pm 0.015) \times 10^4$	8.8 ± 0.4	2000 ± 90	0.9996
H[d]	$(2.3 \pm 0.085) \times 10^3$	40	57 ± 5	0.9980
CH_3CH_2	$(7.4 \pm 0.1) \times 10^3$	3.9 ± 0.2	1900 ± 100	0.9997
$(CH_3)_3C$	$(6.15 \pm 0.09) \times 10^2$	0.96 ± 0.04	640 ± 30	0.9992
cumyl	$(1.41 \pm 0.03) \times 10^3$	2.0 ± 0.1	710 ± 40	0.9999
trityl	$(1.5 \pm 0.1) \times 10^3$	3.5 ± 0.4	440 ± 60	0.9975
MCPBA[b,e]	$(2.8 \pm 0.1) \times 10^6$	$(6.4 \pm 0.3) \times 10^3$	440 ± 30	

[a] [TBPH] = 0.1 M; pH = pK_a = 7.5 in methanol at 25 °C. [b] From ref 11. [c] Statistically corrected for the symmetry of H_2O_2. [d] The buffer is 1:1 acetate–acetic acid. [e] *m*-Chloroperoxybenzoic acid.

The actual slope and intercept values as obtained in this study for H_2O_2 at pH 7.5 compare well with those in collidine-buffered methanol at pH 8.25 previously reported.[11] Slope and intercept values for MCPBA at pH 7.46 also reported in that study are included in Table II for comparison with those of the alkyl hydroperoxides and the statistically corrected values for H_2O_2. The relative standard deviations reported for the values of slope divided by intercept were calculated by the standard method of propagation of indeterminate errors.[27]

Similar plots of rate constants versus free collidine concentrations for protohemin dimethyl ester revealed smaller slopes, 3000, 1500, and 150, respectively, for hydrogen peroxide, ethyl hydroperoxide, and *tert*-butyl hydroperoxide as expected from the lower catalytic activity of this hemin compared to chelated protohemin. However, the ratios of these slopes are the same as those for chelated protohemin ($\mathbf{1}^{+}Cl^{-}$) shown in Table II. This demonstrates that the relative reactivities do not change with alterations in the hemin catalyst.

Discussion

We have employed chelated protohemin ($\mathbf{1}^{+}Cl^{-}$) in most of the studies reported here because the relevant heme proteins have a proximal base: phenolate in catalase,[28] imidazole in horseradish peroxidase and cytochrome *c* peroxidase,[29] and thiolate in cytochrome P-450.[30] However, since we find similar relative base-catalyzed reactivities of various hydroperoxides with and without the proximal imidazole, we suggest that our mechanistic conclusions might apply to simple hemins such as protohemin dimethyl ester as well.

In earlier work we[11] and Bruice et al.[14] were able to definitively exclude homolytic cleavage of peracids in protic solvents based upon the known lifetimes of acyloxy radicals. Bartlett and Hiatt[5] showed that the decomposition of *tert*-butyl phenylperacetate proceeds about 300 times faster than does *tert*-butyl peracetate and leads to complete cleavage to carbon dioxide and benzyl radicals. This and other evidence demonstrated that the phenylacetoxy radical has no lifetime and cleaves before cage diffusion.

$$PhCH_2C(=O)-OO^tBu \xrightarrow{\text{concerted}} [PhCH_2^{\bullet} + CO_2 + {}^{\bullet}O^tBu]_{cage} \longrightarrow \text{products} \quad (8)$$

The $PhCH_2CO_2^{\bullet}$ radical cannot be trapped. Any process producing this radical must produce carbon dioxide. Since we found none, we concluded that there is no (less than 0.5%) homolytic cleavage in the peracid reactions with iron(III) porphyrins under our conditions.

$$PhCH_2C(=O)OOH + Fe^{+} \longrightarrow PhCH_2C(=O)OH + Fe^{+}=O \quad (9)$$

Therefore there is no question concerning this reaction under conditions where solvent or buffer supplies protons for catalysis. Recently, Groves et al.[31] have used this same criterion to indicate homolysis under conditions where protic acid catalysis is minimized.

By contrast, the substitution of benzyl for methyl in the peroxide part of the perester does not lead to increased rates[32] and the $PhCH_2C(CH_3)_2O^{\bullet}$ can be trapped.[33]

$$PhCH_2C(CH_3)_2OOCR \longrightarrow PhCH_2C(CH_3)_2O^{\bullet} + RCO_2^{\bullet} \quad (10)$$

$$PhCH_2C(CH_3)_2O^{\bullet} + XH \longrightarrow PhCH_2C(CH_3)_2OH + X \quad (11)$$

From the extensive studies of tertiary alkoxy radicals by Walling,[34] Bartlett,[5] and others, several things are clear. None of the alkoxy radicals cleave fast enough to do so in the cage. For example *tert*-butoxy radical cleaves at a rate of about 10^5 s^{-1} at 40 °C and $PhCH_2CMe_2O^{\bullet}$ cleaves about 300 times faster.[33] Even this radical can be trapped. Thus, no alkoxy radical studied will decompose in the cage, which requires a rate constant for decomposition of 10^9 s^{-1}. Consequently, the criterion used for peracids cannot be used for hydroperoxides and any system studied to this date.

$$R_3CO^{\bullet} \xrightarrow{k < 10^7\ s^{-1}} R^{\bullet} + R_2CO \quad (12)$$

Since $RO^{\bullet}$ can be trapped, the absence of ketone is not an unequivocal indication of heterolytic cleavage. Similarly, because there are other sources of alkoxy radicals, the evidence for alkoxy radicals is not clearly indicative of homolytic cleavage of the FeOOR bond. For example, we have documented, by producing the oxene, $Fe^{+}=O$, separately with iodosylbenzene, that this oxene reacts with hydroperoxides to produce hydroperoxy and alkoxy radicals.[11d]

$$RIO + Fe^{+} \longrightarrow Fe^{+}=O + RI \quad (13)$$

$$Fe^{+}=O + ROOH \longrightarrow ROO^{\bullet} \quad (14)$$

$$2ROO^{\bullet} \longrightarrow RO_4R \quad (15)$$

$$RO_4R \longrightarrow [RO^{\bullet}O_2{}^{\bullet}OR]_{cage} \longrightarrow ROOR + O_2 \quad (16)$$

$$[RO^{\bullet}O_2{}^{\bullet}OR]_{cage} \longrightarrow 2RO^{\bullet} + O_2 \quad (17)$$

$$RO^{\bullet} + ROOH \longrightarrow ROH + ROO^{\bullet} \quad (18)$$

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(29) Poulos, T. L.; Kraut, J. *J. Biol. Chem.* **1980**, *255*, 8199.
(30) Poulos, T. L. In *Cytochrome P-450*; Ortiz de Montellano, P., Ed.; Plenum: New York, 1986; p 505.
(31) Groves, J. T.; Watanabe, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8443.
(32) Sheldon, R. A.; Kochi, J. *J. Am. Chem. Soc.* **1970**, *92*, 4120.
(33) (a) Kochi, J. *Free Radicals*; Wiley: New York, 1973; Vol. II, p 684. (b) Kochi, J. *Free Radicals*; Wiley: New York, 1973; Vol. II, p 697.
(34) Walling, C.; Padwa, A. *J. Am. Chem. Soc.* **1963**, *85*, 1593.

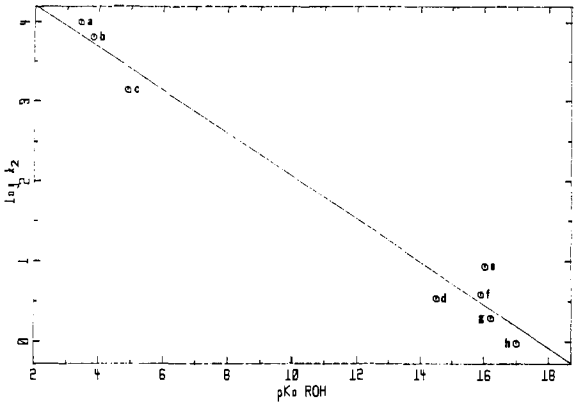


Figure 7. Plot of log k_2 versus pK_a of ROH for the reaction of various peroxy acids and hydroperoxides with 1^+Cl^- in methanol at 25 °C using collidine buffer at pH = pK_a = 7.5. The k_2 values used for the hydroperoxides are the intercepts listed in Table II at [collidine]$_{total}$ = 0 M. The k_2 values for the peroxy acids were obtained from the previous study[11] (Table II). The ROH pK_a values of the alcohols are from ref 38: (a) *p*-nitroperbenzoic acid (PNPBA); (b) *m*-chloroperbenzoic acid (MCPBA); (c) perlauric acid (PLA); (d) trityl hydroperoxide (THP); (e) hydrogen peroxide; (f) ethyl hydroperoxide (EHP); (g) cumene hydroperoxide (CHP); (h) *tert*-butyl hydroperoxide (TBHP). Slope = −0.27 ± 0.02; intercept = 4.7 ± 0.2; r = −0.9866; ψ = 0.19.

We[35] and others[4b] have shown that the only source of ROOR is cage collapse, which is accompanied by a 10-fold faster diffusion from the cage to produce free *tert*-butoxy radicals. Therefore, the production of each ROOR signals 20 RO• radicals from the chain reaction. We find ^{t}BuOO^{t}Bu produced in reactions of iron(III) porphyrins with ^{t}BuOOH. Other evidence for homolytic cleavage might be the presence of the Fe=O species. However, this species can also arise from the "catalase" reaction (14) or from comproportionation, well-documented for high-valent manganese porphyrins.[36,37]

$$\mathrm{Fe^{+}{=}O} + \mathrm{FeOH} \longrightarrow 2\mathrm{Fe{=}O} + \mathrm{H^+} \qquad (19)$$

These reactions make some of the evidence (RO• or Fe=O presence) equivocal, and other methods are needed. We therefore turned to the effects of medium, buffer, and structure on the rates of reaction.

Changes in structures of hemins, oxidants, solvent, or pH could affect either the preequilibrium reaction (3) or the rate-limiting bond cleavage of the heterolytic reaction (5) or the homolytic reaction (6). However, general catalysis, after correction for, in this case negligible, salt affects, applies only to the rate-limiting step. Nevertheless, these reactions do involve a preequilibrium followed by breaking of the O–O bond (for example, eq 20).

$$\mathrm{Fe^{+}} + \mathrm{ROOH} \underset{}{\overset{K_1}{\rightleftharpoons}} \mathrm{Fe^{+}{-}OOR} \overset{K_2}{\rightleftharpoons}$$

$$\mathrm{FeOOR} + \mathrm{H^+} \xrightarrow[k_c]{\mathrm{BH}} \mathrm{Fe^{+}{=}O} + \mathrm{ROH} + \mathrm{B^-} \qquad (20)$$

Therefore, the overall rate is a product of these constants. The rate law for any mechanism of cleavage can be written:

$$d[\mathrm{ROOH}]/dt = (\mathrm{Fe})(\mathrm{ROOH})K_1K_2k_c = (\mathrm{Fe})(\mathrm{ROOH})K_1K_2\Sigma k_{cat}(\mathrm{cat}) \qquad (21)$$

(The k_{cat} term includes the zero buffer term.) Because more basic hydroperoxides react at lower rates where the K_1K_2 product would be increased, we have concluded that k_c is much more sensitive to the nature of R than is either K_1 or K_1K_2.[11] We have found that the reaction increases with increasing RO^- stability in both peracids and hydroperoxides (Figure 7). Although we and Bruice et al. have considered plotting the log rate versus the pK_a of the leaving group for peracids and hydroperoxides on the same line, this is not necessarily valid. Peracids, which have been considered to use their internal hydrogen bond in epoxidation reactions, might respond differently from hydroperoxides to both leaving group structural changes and to general acid catalysis by buffers or hydroxylic solvents.

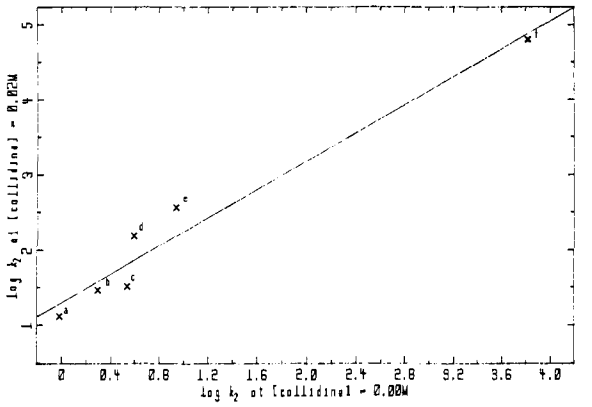


Figure 8. Plot of log k_2 values obtained at [collidine]$_{free}$ = 0.02 M and at [collidine]$_{total}$ = 0 M for the reaction of MCPBA and various hydroperoxides with 1^+Cl^- in collidine-buffered methanol at 25 °C, pH = pK_a = 7.5. The k_2 values at [collidine]$_{total}$ = 0 M are the intercepts of plots of k_2/[hemin] versus [collidine]$_{free}$: (a) TBPH, (b) CHP, (c) THP, (d) EHP, (e) H_2O_2, (f) MCPBA. Slope = 0.9 ± 0.1; intercept = 1.3 ± 0.2; r = 0.9791; ψ = 0.22.

Because these reactions are general base/acid catalyzed in methanol, additional terms are required.

$$d[\mathrm{ROOH}]/dt = (\mathrm{Fe^+})(\mathrm{ROOH})[k_{R'OH}(R'OH) + \Sigma k_{cat}(\mathrm{cat})] \qquad (22)$$

The catalysts can be base or acid. We have written the zero catalyst term to include R′OH as a general acid catalyst. Evidence for this is provided elsewhere.[11e]

Similarities in the response of rates to hydroperoxide structure can be taken as evidence for similar mechanisms. Figure 8 shows a plot of rate constants at zero buffer (k_{ROH}) for a series of hydroperoxides and a peracid against the rate constants for the buffer-catalyzed term taken at 0.02 M buffer concentration. The correlation is reasonably good and would certainly not be expected if mechanisms with and without buffer were different. We will therefore discuss these two cases, $k_{R'OH}$ and k_{cat}, interchangeably.

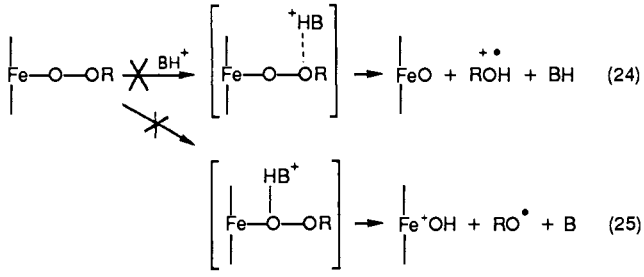
We first ask whether these data are consistent with homolytic cleavage. As Table II shows the rates increase as RO• stability decreases.[35] Judging by peroxide bond energies[33b] (H_2O_2, 51 kcal/M; ^{t}BuOOH, 44 kcal/M; ^{t}BuOO^{t}Bu, 37 kcal/M; ^{t}BuOOAc, 31 kcal/M) as well as other criteria, rates of formation or RO• are invariably in the order AcO• > ^{t}BuO• > HO•. This is exactly the reverse of what is found in reactions with iron(III) porphyrins. Assuming that both peracids and hydroperoxides are capable of homolytic decomposition,[31] a much greater acceleration of this process is expected for peracids than for, e.g., hydrogen peroxide, yet peracids show no homolysis in these solvents.

Although general catalysis of homolytic O–O bond cleavage is unprecedented, two possible general catalyses of this reaction can be examined.[39]

$$\mathrm{Fe^{+}{-}\overset{H}{O}OR} + \mathrm{B} \not\longrightarrow \left[\mathrm{Fe{-}\overset{H\cdots B}{O}{-}OR}\right]^{\ddagger} \longrightarrow \mathrm{FeO} + \mathrm{RO^{\bullet}} + \mathrm{BH^+} \qquad (23)$$

(35) (a) Hiatt, R.; Traylor, T. G. *J. Am. Chem. Soc.* **1965**, *87*, 3766. (b) Kiefer, H.; Traylor, T. G. *J. Am. Chem. Soc.* **1967**, *89*, 6667. (c) Kenley, R. A.; Traylor, T. G. *J. Am. Chem. Soc.* **1975**, *97*, 4700.
(36) Rosenberg, J. A. S. J.; Nolte, R. J. M.; Drenth, W. *J. Chem. Soc., Chem. Commun.* **1986**, *4*, 277.
(37) Groves, J. T.; Stern, M. K. *J. Am. Chem. Soc.* **1987**, *109*, 3813.
(38) Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 795.
(39) Suggestions made by reviewers.
(40) Xu, F., unpublished work.

Since Fe–OOR has been observed by Balch et al. at low temperature,[13] it has an activation energy for homolysis of at least 10 kcal/M. By contrast proton transfer from a positively charged species like $Fe^+(OH)OR$ must be on the order of 10^9–10^{10} M^{-1} s^{-1}. Thus concerted reaction is very unlikely. A second reaction involving general acid catalysis, protonating either species, is also very unlikely, both being very weak bases.

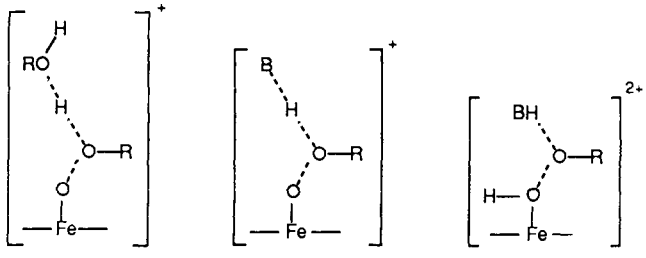


It is therefore difficult to incorporate general base or general acid catalysis into a homolytic reaction. We therefore conclude that the buffer-catalyzed reaction involves heterolysis of the O–O bond.

Comparison of the behavior of hydroperoxide reactions with the known heterolytic reactions of peracids is also instructive. Both the reactions of peracids and hydroperoxides are rather insensitive to pH in the collidine buffer range (7–8.5 in MeOH). Rates with both classes respond to stabilities of RO^-. Both peracids and hydroperoxides show external and internal general base catalysis, in methanol or methanol–water.[11a] The sensitivity of the reactions to buffer catalysis is best represented by the acceleration of rate, which is obtained from the buffer-catalyzed rate constant divided by the uncatalyzed rate constant, k_{cat}/k_{ROH} of eq 22, i.e., the slope/intercept values of Table II. These values range from 440 to 2000 and are thus rather similar. It is especially striking that *tert*-butyl hydroperoxide has a greater sensitivity to buffer (k_{slope}/k_{int} = 640) than does *m*-chloroperbenzoic acid (k_{slope}/k_{int} = 440). This is certainly not expected for a change from heterocyclic peracid reaction to homolytic ^{t}BuOOH cleavage.

By contrast, the protic solvent, general acid, or general base catalyzed reaction of a hydroperoxide is expected to display exactly the properties we have reported if heterolytic cleavage is involved. Its reaction rate should be and is accelerated by (1) proximal bases,[11a] (2) hydrogen bonding to the proximal base,[11c] (3) more stable leaving anions,[11a] (4) more aqueous solvents,[11a] (5) general acids and/or bases,[11a] (6) internal general acids and/or bases.[11a] Furthermore, the hydroperoxides share all these effects with peracids, the latter known to cleave heterolytically.

These studies provide evidence for catalyzed heterolytic cleavage of peracids, hydroperoxides, and hydrogen peroxides in protic solvents. We extend this conclusion to less protic solvents elsewhere.[11d,40] A general mechanism for hydroperoxide reactions, which we and others have previously suggested, might be represented by the following transition states for solvent, base, and acid catalyzed reactions (eq 26).



$$\frac{-d[ROOH]}{dt} = (ROOH)\left(\left|\begin{matrix}\\ Fe^+\end{matrix}\right)\left[k_{R'OH}(ROH) + k_B(B) + k_{BH^+}(BH^+)\right] \quad (26)$$

(41) We calculate pK_a values of 10.7 and 12.8, respectively, using the method of Ballinger and Long[38] compared to the values of 9.1 and 11.1 calculated by Bruice and Lee.[14a]

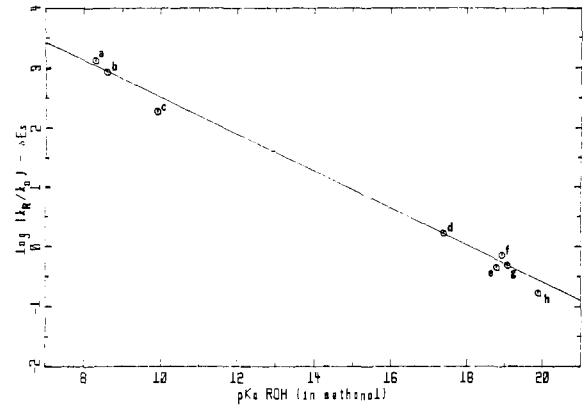


Figure 9. Plot of log $(k_R/k_0) - \delta(E_S)$ vs pK_a values for ROH (in MeOH) for the rate data in Figure 7. The k_0 is the second-order rate constant for H_2O_2, and k_R, the rate constant of the other oxidants, all at zero buffer concentration. The value of δ = 0.13 was obtained from multiple regression analysis. Data are slope = −0.31 ± 0.01; intercept = 5.6 ± 0.2; r = −0.9963; $\psi \leq 0.10$.

A plot of the observed reaction rates against the pK_a^{ROH} of the leaving group alcohol is shown in Figure 7. The rate constants are the intercept values listed in Table II. Similar plots are expected for k_B judging from the correlation in Figure 8. These data could be interpreted as involving different slopes for peracids and hydroperoxides although a slope cannot be established for the hydroperoxides.

The plot in Figure 7 is greatly improved by inclusion of the steric parameter E_S for the substituents in R, as shown in Figure 9.[11f] This suggests a considerable steric effect in the reaction. We have also observed steric effects in iodosylbenzene reactions with ortho-substituted tetraphenylhemins.

In summary, all of our data are consistent with the heterolytic cleavage reaction (5) for all the peracids and hydroperoxides.

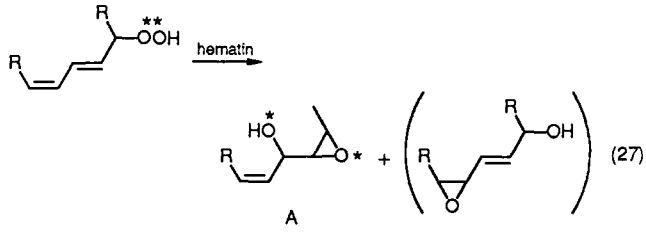
These conclusions necessitate some discussion of observations, which have been suggested as indicating homolytic cleavage. Mansuy et al.[15] suggested that the free-radical-derived products obtained from the attempted epoxidation of cyclohexene with cumene hydroperoxide and a hemin chloride indicated that cumyloxy radicals were produced. These could arise from homolytic cleavage (reaction 6) or from the catalase process (reactions 15–18). Addition of imidazole brought about epoxidation. This was attributed to a change to heterolytic cleavage upon addition of a proximal imidazole as would be the case with our chelated hemin. However, we find the sensitivities to GBC to be similar with and without proximal base. Furthermore, we have been able to obtain high-yield epoxidation of norbornene (with iron(III) tetrakis(2,6-dichlorophenyl)porphine chloride) using ^{t}BuOOH in the absence of proximal imidazole by avoiding reactions 14–18 at low ^{t}BuOOH concentration. Additionally, the exo/endo ratio of epoxides is approximately the same using ^{t}BuOOH and iodosylbenzenes and very different from that in norbornene epoxidation with *tert*-butylperoxy radicals.[42] It would seem likely that imidazole is somehow inhibiting the chain decomposition of hydroperoxides. This chain decomposition is very ineffective with peracids, and for this reason catalase type reactions do not usually interfere with peracid–hemin reactions.[35c]

Several other reports of the production of alkoxy radicals and their cleavage products have appeared, sometimes as evidence for the homolysis process 6. However, the catalase type reaction (15) produces peroxy and subsequently alkoxy radicals, and this process has not been eliminated. Indeed major production of acetone from *tert*-butoxy radicals has been reported in some studies.[14f] This is good evidence for extremely poor radical trapping since *tert*-butoxy radicals are easily trapped no matter how they are formed. Thus, in the presence of a reasonably active hydrogen atom donor, acetone should not be produced even if the FeOO^{t}Bu cleaved

(42) Traylor, T. G.; Fann, W.-P.; Bandyopadhyay, D., submitted for publication in *J. Am. Chem. Soc.*

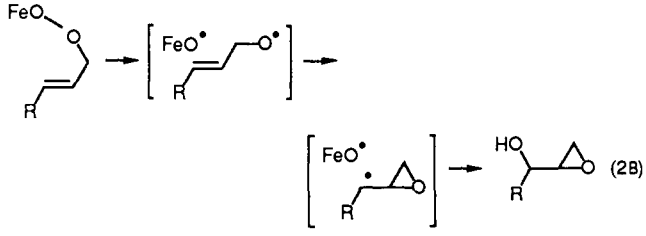
homolytically. We do not find acetone in appreciable amounts in our studies in alcohols. As the concentration of ^{t}BuOOH approaches zero and thus abstraction from this hydroperoxide becomes negligible, some acetone might appear in inert solvents. The cleavage products from alkoxy radicals in the reported studies have not been demonstrated to be products of reaction 6.

Dix and Marnett[16] have demonstrated in an elegant ^{18}O labeling study that diene hydroperoxides are converted to two epoxides, in which A retains both oxygens from the same hydroperoxide.



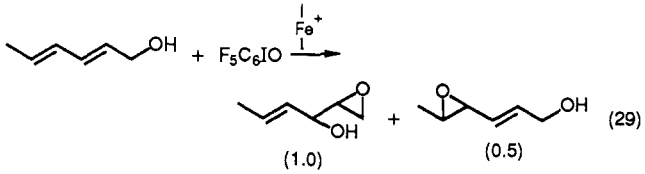
(27)

They proposed the logical sequence in which homolysis leads to a radical that rearranges and collapses.



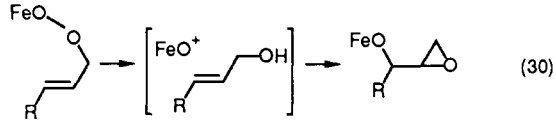
(28)

We have epoxidized 1-hydroxy-2,4-*trans*,*trans*-hexadiene with the hemin–iodosylbenzene system to a similar mixture of epoxides.[40]



(29)

This suggests an alternative possibility for the hydroperoxide rearrangement in which either a concerted or an "oxene rebound" (eq 30) mechanism could give the results mentioned above.



(30)

There are two things that speak against this being the major pathway. First, this would not explain their finding that some oxygen from O_2 gets incorporated. Second, the oxene rebound requires a reaction of oxene with the alkene which is faster than can reasonably be expected. Therefore, the radical process seems to be more likely. Possibly the reaction in the micellar suspension with a simple heme does not experience efficient acid catalysis. This work seems to suggest homolysis under some conditions.

Our conclusions agree with those of Mansuy[15] and Marnett et al.[16d] that five-coordinated hemins such as chelated protohemin ($\mathbf{1}^+Cl^-$) react with hydroperoxides by heterolysis. We and others also have provided strong evidence[16d] that electronegatively substituted iron(III) porphyrin chlorides such as iron(III) tetrakis-(2,6-dichlorophenyl)porphyrin react with hydroperoxides as well as peracids by heterolytic cleavage of the O–O bond. Evidence for homolytic cleavage has been presented for iron(III) porphyrin chlorides that are not electronegative, such as hematin or tetraphenylhemin. But it is clear that accurate biomimetic models of peroxidases such as $\mathbf{1}^+Cl^-$ react by heterolytic cleavage. Thus, peroxidase, being like $\mathbf{1}^+Cl^-$ plus buffer, surely reacts by heterolysis.

In our earlier work we plotted log k_{ROOH} versus pK_a^{ROH} for peracids, hydrogen peroxide, and *tert*-butyl hydroperoxides on a single line with a slope of −0.24. Bruice and Lee[14a] extended this study to several other hydroperoxides including $Ph_2C(CN)OOH$ and $Ph_2C(CO_2Me)OOH$. Calculating pK_a values of 9 and 11 for the corresponding alcohols,[41] these authors found a break in a similar plot at about $pK_a = 11$ and proposed homolytic cleavage for hydroperoxides leading to alcohols with pK_a values above 11. Generally, these authors have reported the same rates for *tert*-butyl hydroperoxide, trityl hydroperoxide, and hydrogen peroxide, in stark contrast to the results we report here.[43] In our system, we do not find a clear break in slopes, especially when the steric effects of these large hydroperoxides are taken into account as in Figure 9. Therefore, while these data do not definitively exclude homolysis of alkyl hydroperoxides, they cannot be taken as evidence for a change in mechanism from the heterolytic reaction demonstrated for peracids.[44]

The close similarity of reactions of peracids and hydroperoxides discussed above provides strong evidence for a consistent mechanism that would then have to be heterolysis. Our studies have been carried out at room temperature, usually in alcohol solvents. Under these conditions, for example, in nonpolar solvents at low temperature and in the absence of proton donors, homolysis appears to occur, at least in some cases. Further studies will be required to determine the conditions for these mechanism changes. We conclude that the reaction of chelated protohemin with hydrogen peroxide constitutes a biomimetic model for peroxidases and leads directly to the same intermediate $PFe^+{=}O$ (compound I), as do peroxidases and catalase.

Acknowledgment. We are grateful to the National Science Foundation (Grant CHE 84-20612) for support and to the National Institutes of Health (Grant RR 02652).

(43) Interestingly, the raw data of Figure 7 for the least sterically hindered hydroperoxides ^{t}BuOOH and EtOOH show the $\Delta\log k/\Delta pK_a$ value is 0.57, compared to 0.6 for *m*-chloroperbenzoic acid and perlauric acid. The effect of leaving group on rate is just as large for hydroperoxides as for peracids! This implies that the plots of log *k* vs pK_a^{ROH} might have similar but displaced slopes for peracids and hydroperoxides. Further studies of unhindered hydroperoxides are needed.

(44) The oxidation of the tri-*tert*-butylphenol by ^{t}BuOOH with the Fe^{III}(TPP)Cl catalyst produces a very low yield of the phenoxyl radical (in contrast to H_2O_2 or RCO_3H reactions), and initial rate versus pseudo-first-order rate methods give very different values of the second-order rate constants in contrast to Table I. Therefore, data for hydroperoxides are difficult to obtain with this catalyst. Although we find in at least six different catalyst and several different solvent systems that H_2O_2 always reacts faster than ^{t}BuOOH, we invariably encounter difficulty in obtaining accurate data for ^{t}BuOOH due to side reactions. This problem is not as great for the catalyst $\mathbf{1}^+Cl^-$, which reacts faster than does Fe^{III}(TPP).