terium in the acetyl group by NMR.

p-$NO_2C_6H_4O_2CCL_2NHCbz$ (L = H, D). $HO_2CCD_2NH_3Cl$ was obtained by refluxing diethyl acetamidomalonate (Aldrich) overnight in 20% DCl/D_2O (Sigma). Treatment in 1 M $NaHCO_3$ with benzyl chloroformate produced $CbzNHCD_2COOH$, which was coupled to p-nitrophenol with dicyclohexylcarbodiimide in ethyl acetate (30 m, 40 °C; 90 m, 25 °C). The labeled substrate (L = D) was recrystallized twice from absolute ethanol containing 0.1% acetic acid [white crystals, mp 124 °C; lit. mp (L = H) 128 °C (ref 26), 124-125 °C (ref 27)]. Incorporation of deuterium was >95% by NMR. The protiated substrate was prepared similarly except that H_2O was appropriately used in place of D_2O.

Kinetic Procedures. Rates were obtained by automated spectrophotometry as described before.[11] Runs with isotopic substrates were conducted in alternation and with use of the same stock solutions.

Registry No. p-$NO_2C_6H_4O_2CCH_2NHCbz$, 1738-86-9; p-$NO_2C_6H_4O_2CCD_2NHCbz$, 84712-45-8; p-$NO_2C_6H_4O_2CCH_3$, 830-03-5; p-$NO_2C_6H_4O_2CCD_3$, 81408-98-2.

(26) Yamazaki, N.; Yamaguchi, M.; Higashi, F.; Kakinoki, H. *Synthesis* **1979**, 355-356. Yamazaki, N.; Higashi, F. *Tetrahedron* **1974**, *30*, 1323. Yamazaki, N.; Higashi, F.; Kazaryan, S. A. *Synthesis* **1974**, 436-437.

(27) Iselin, B.; Rittel, W.; Sieber, P.; Schwyzer, R. *Helv. Chim. Acta* **1957**, *40*, 373.

Monooxygen Donation Potential of 4a-Hydroperoxyflavins As Compared with Those of a Percarboxylic Acid and Other Hydroperoxides. Monooxygen Donation to Olefin, Tertiary Amine, Alkyl Sulfide, and Iodide Ion

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Abstract: The reaction of the hydroperoxides diphenylhydroperoxyacetonitrile (**4**), methyl diphenylhydroperoxyacetate (**5**), and 5',6',7',8'-tetrahydro-4a'-hydroperoxy-3'-methylspiro[cyclohexane-1,2'-(4a'*H*)quinazoline]-4'(3'*H*)-one (**6**) with I^-, thioxane, and *N*,*N*-dimethylbenzylamine (DMBA) are first order in both hydroperoxide and substrate. For both **5** and **6**, I_3^- is produced in 100% yield. Product analysis for the reaction of **4**, **5**, and **6** with thioxane and DMBA established that the hydroperoxides are converted to the corresponding alcohols and that thioxane sulfoxide and *N*,*N*-dimethylbenzylamine *N*-oxide are formed. The reactions are quantitative. The reaction of **4** with I^- proved to be complicated. The alcohol generated from **4** is the cyanohydrin of benzophenone. The dissociation of the benzophenone cyanohydrin product is competitive with I_3^- formation so that CN^- produced in the dissociation reacts with I_3^- to yield ICN. Kinetic and thermodynamic analyses have provided the pertinent rate and equilibrium constants associated with the overall time course for reaction of **4** with I^-. The second-order rate constant for the reaction of *m*-chloroperbenzoic acid (**1**) with I^- has been determined and the second-order rate constant for reaction of **1** with thioxane was obtained from experiments in which thioxane and I^- were employed as competitive substrates. The second-order rate constants for reaction of **1**, **4**, **5**, and **6** with I^-, thioxane, and DMBA were compared with like constants for the reactions of 4a-hydroperoxy-5-ethyl-3-methyllumiflavin (**2**), 1-carba-1-deaza-4a-hydroperoxy-5-ethyl-3-methyllumiflavin (**3**), *t*-BuOOH (**7**), and H_2O_2 (**8**). A log-log plot of the rate constants for monooxygen transfer from hydroperoxides to thioxane (k_S) and to DMBA (k_N) was found to be linear and of slope 1.0. The best line for the plot of log k_S vs. the log of the rate constants for reactions with I^- (k_I) was of slope 1.1. The points for *m*-chloroperbenzoic acid were found to fit the log k_S vs. log k_I plot. These results show that the second-order rate constants for reactions of I^-, thioxane, and DMBA are of like dependence on the electronic and steric characteristics of the hydroperoxides and percarboxylic acid **1**. A linear free energy plot correlates the log of the second-order rate constants vs. pK_a of YOH for oxygen transfer from YOOH = **1**, **2**, **4**, **5**, **7** and **8** ($\beta_{lg} = -0.6$). In these reactions the 4a-hydroperoxyflavin **2** is the most efficient monooxygen donor of the hydroperoxides investigated, being 10^3-10^6 more reactive than *t*-BuOOH and $\sim 10^3$ less reactive than the peracid **1**. The kinetics of epoxidation of 2,3-dimethyl-2-butene by the hydroperoxides **2**-**6** were investigated by following both hydroperoxide disappearance and product formation. The results of these investigations, which include further reaction of epoxide with hydroperoxide to provide pinacol and 2,3-dimethyl-1-buten-3-ol, are discussed. Evidence for epoxidation of 2,3-dimethyl-2-butene by **2** or its 1-carba-1-deaza analogue **3** could not be obtained. The order of monooxygen donation to I^-, :S< and :N< by the hydroperoxides, for which **2** and **3** were most reactive, does not apply to the epoxidation reaction. The flavin hydroperoxides are decomposed in $CHCl_3$ by a free radical reaction. Hydroperoxide **2** exhibits a chemiluminescent oxidation of *p*-tolualdehyde, whereas hydroperoxides **4**-**6** do not.

4a-Hydroperoxyflavins are important intermediates in oxygen activation in biochemistry. Both enzyme bound[1] and free,[2] these substances oxidize I^-, sulfides, and secondary and tertiary amines at rates exceeding those for alkyl hydroperoxides by many orders of magnitude. Our present interest is in the comparative reactivities of 4a-hydroperoxyflavins and other electron-deficient hydroperoxides and percarboxylic acids.

Brill and Indicator[3] showed that low yields of stereospecifically derived epoxides are obtained when olefin and *t*-BuOOH are reacted neat and that the reaction is catalyzed by certain metal ions. In the hands of Sharpless and co-workers, the employment

(1) Masters, B. S. S.; Ziegler, D. M. *Arch. Biochem. Biophys.* **1971**, *145*, 358. Kadlubar, F. F.; McKee, E. M.; Ziegler, D. M. *Ibid.* **1973**, *156*, 46.
(2) (a) Ball, S.; Bruice, T. C. *J. Am. Chem. Soc.* **1980**, *102*, 6498. (b) Kemal, C.; Chan, T. W.; Bruice, T. C. *J. Am. Chem. Soc.* **1977**, *99*, 7064.

(3) Brill, W. F.; Indicator, N. *J. Org. Chem.* **1964**, *29*, 710. Brill, W. F. *J. Am. Chem. Soc.* **1963**, *85*, 141. Indicator, W.; Brill, W. F. *J. Org. Chem.* **1965**, *30*, 2074.

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of metal ion catalysis has resulted in the development of useful synthetic methodology for the epoxidation of alkenes by such alkyl hydroperoxides as *tert*-butyl hydroperoxide.[4] Rebek[5] has shown, however, that the placement of the hydroperoxy group upon a tert carbon carrying an electron-withdrawing substituent leads, in cases, to synthetically useful epoxidizing agents which do not require added metal ion. It has been pointed out by Rebek that both the 4a-hydroperoxyflavins and several peroxides developed in his laboratory for alkene epoxidation share in common the substitution of the hydroperoxy group upon a tert carbon containing a carbonyl function α to the hydroperoxy moiety.

The objectives of this investigation have been (i) to determine if the second-order rate constants for the reaction of *m*-chloroperbenzoic acid and a series of hydroperoxides with such diverse nucleophiles as I^-, amines, and alkyl sulfides follow a single linear free energy relationship, (ii) to determine if the ability to epoxidize alkenes follows the same relationship and if 4a-hydroperoxyflavins epoxidize alkenes, and (iii) to ascertain if chemiluminescence accompanies the oxidation of aldehydes by hydroperoxides other than 4a-hydroperoxyflavins.

Experimental Section

Materials. *tert*-Butyl alcohol was refluxed over calcium hydride, distilled under an atmosphere of dry nitrogen, and subjected to several cycles of freeze–vacuum–thaw to remove final traces of oxygen. Dimethyl formamide was dried over activated 4A molecular sieves and vacuum distilled by using a dry nitrogen bleed. Chloroform was washed with water, dried over $CaCl_2$, and distilled from P_2O_5 under an N_2 atmosphere. *M*-Chloroperbenzoic acid (**1**) was obtained from Aldrich Chemical Co. and stored under an inert atmosphere. The samples used assayed at 85% percarboxylic acid by iodometric titration. 4a-Hydroperoxy-5-ethyl-3-methyllumiflavin (**2**) and the 1-carba-1-deaza analogue (**3**) were synthesized as described previously.[6,2a] **2** was assayed at 89% pure by iodometric titration. 5′,6′,7′,8′-Tetrahydro-4a′-hydroperoxy-3′-methylspiro[cyclohexane-1,2′(4a′*H*)-quinazoline]-4′(3′*H*)-one (**6**) was obtained by the procedures of Zigeuner and Gübitz,[7] mp 169–171 °C (lit.[7] mp 169–171 °C), and assayed at 97% pure by iodometric titration. The IR spectrum of solid **6** in Nujol Mull showed absorption bands at 1660 cm^{-1} (substituted imine) and 1685 cm^{-1} (C=O of amide). The NMR spectrum (δ scale) in Me_2SO-d_6 showed OOH 5.7 ppm (exchanges on adding D_2O), NCH_3 3.6 ppm, CH_2/8′ 2.1 ppm, and 8 CH_2 1.5 ppm. Anal. Calcd for $C_{14}H_{22}O_3N_2$: C, 63.16; H, 8.27; N, 10.53. Found: C, 63.23; H, 8.5; N, 10.36. Diphenylhydroperoxyacetonitrile (**4**) was synthesized by the method of Selekson and Watt,[8] mp 87–88 °C (lit.[9] mp 85–86 °C). The IR spectrum of solid **4** in Nujol Mull showed absorption bands at 2270 cm^{-1} (C≡N) and 3300 cm^{-1} (OOH). The NMR spectrum (δ scale) in $CDCl_3$ showed OOH 9.0 ppm (exchanges on adding D_2O) and Ar 7.4 ppm. Anal. Calcd for $C_{14}H_{11}O_2N$: C, 74.66; H, 4.88; N, 6.22; O, 14.22. Found: C, 74.53; H, 4.84; N, 6.33; O, 14.06. Methyl diphenylhydroperoxyacetate (**5**) was synthesized by the method of Avramoff and Sprinzak,[10] m.p. 66–68 °C (lit.[10] mp 69.5–70.5 °C), and assayed at 97% pure by iodometric assay. IR spectrum of solid **5** in Nujol Mull showed absorption bands at 1720 cm^{-1} (C=O) and 3450 cm^{-1} (OOH). NMR spectrum (δ scale) in $CDCl_3$ shows OOH 9.4 ppm (exchanges on adding D_2O); CH_3 3.8 ppm; Ar 7.3 ppm. Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.77; H, 5.43; O, 24.81. Found: C, 69.96; H, 5.55; O, 24.16. A mixture of 2,3-dimethyl-1-butene 3-hydroperoxide (A) and 2,3-dimethyl-2-butene 1-hydroperoxide (B) was obtained by a literature method,[11] bp 50–54 °C [lit. bp 51–54 °C (9 mmHg)]. 2,3-Dimethyl-1-buten-3-ol was prepared by literature methods,[12] bp 115 °C (lit. bp 118 °C). Pinacol was obtained from Aldrich Chemical Co. Tetramethylethylene oxide was synthesized by literature methods,[13] bp 90–92 °C (lit. bp 90–90.5 °C). 2,3-Dimethyl-2-butene was obtained from Aldrich Chemical Co. and fractionally distilled 3× under nitrogen from powdered sodium hydroxide in order to remove traces of epoxide. *N*,*N*-Dimethylbenzylamine was distilled under dry nitrogen and purged with oxygen-free argon for at least 2 h. *N*,*N*-Dimethylbenzylamine *N*-oxide was prepared by the reaction of excess 30% H_2O_2 with *N*,*N*-dimethylbenzylamine in methanol as described by Cope.[14] The *N*-oxide was isolated and stored as the hydrochloride salt. Regeneration of *N*-oxide was carried out in *tert*-butyl alcohol by reaction with a stoichiometric quantity of potassium *tert*-butoxide. Thioxane was distilled over the blue anion radical of benzophenone and subsequently subjected to several cycles of freeze–vacuum–thaw. Thioxane oxide was synthesized by literature methods,[15] bp 140–148 °C (14 mmHg) [lit. bp 147 °C (15 mmHg)]. *p*-Tolualdehyde was obtained from Aldrich Chemical Co., distilled under an atmosphere of dry nitrogen, and subjected to several cycles of freeze–vacuum–thaw to remove final traces of oxygen.

Kinetics and Product Analysis. In those experiments which are stated to be anaerobic, we have attempted to avoid trace metal catalysis. In such instances, glassware was soaked in aqua regia, washed in doubly distilled water, soaked in EDTA solution, washed with doubly distilled water, and vacuum-oven dried. Solvent and reagents were stored under oxygen-free nitrogen, and all weighings, preparations of solutions, and kinetic studies were carried out under the same nitrogen atmosphere.

Reactions of hydroperoxides with *N*,*N*-dimethylbenzylamine, thioxane, and 2,3-dimethyl-2-butene were followed by determining the decrease in hydroperoxide with time via an iodometric assay (vide infra). In the case of 2,3-dimethyl-2-butene as the substrate, the appearance of epoxide and other products as pinacol and 2,3-dimethyl-1-buten-3-ol were also followed with time. The time courses for appearance of epoxide, pinacol, 2,3-dimethyl-1-buten-3-ol, and thioxane oxide were established by GC employing standard curves constructed by use of authentic samples. 2,3-Dimethyl-1-buten-3-ol and pinacol formed by reaction of **5** with tetramethylethylene oxide were identified by GC–MS and by conversion of the latter to pinacolone with acid. The yield of *N*,*N*-dimethylbenzylamine *N*-oxide was determined by a modification[2a] of the method of Ziegler and Pettit.[16] Unreacted hydroperoxides were determined by withdrawing 0.01–0.2 mL of the kinetic solutions, at given time intervals, and introducing these aliquots into 3 mL of 95% ethanol containing sodium acetate (2×10^{-2} M), acetic acid (2×10^{-3} M), and sodium iodide (0.1 M).[17] The concentration of unreacted hydroperoxide was determined from the concentration of I_3^- (358 nm) produced. The rate constants for I_3^- production are characteristic of the hydroperoxide and serve as a fingerprint for hydroperoxide identification. This feature was of use in alkene epoxidation studies wherein the starting hydroperoxide concentration could be determined as well as allylic hydroperoxide generated from oxidation of alkene. The apparent rate constants for the reaction of the allylic hydroperoxides **A** and **B** with I^- were determined by following the formation of I_3^- in solutions varying in [NaI] from 2.5×10^{-2} to 1.0×10^{-1} M (four dilutions). Under the experimental conditions of $[I^-] \gg [A] + [B] \simeq 2 \times 10^{-5}$ M, the appearance of I_3^- was found to be biphasic, each phase being pseudo first order. In turn, the pseudo-first-order rate constants were found to be dependent upon the first power of $[I^-]$ (plots not shown). The two rate constants k_A' and k_B', determined from the linear plots (not shown) of k_{obs1} and k_{obs2} (eq 1) vs.

$$\frac{d[I_3^-]}{dt} = k_{obsd_2}[A] + k_{obsd_2}[B] \qquad (1)$$

$$k_{obsd_1} = k_A'[I^-] \qquad k_{obsd_2} = k_B'[I^-]$$

$[I^-]$, are 1.08×10^{-2} M^{-1} s^{-1} and 9.9×10^{-4} M^{-1} s^{-1}. The determination of the concentrations of A and B as products was easily accomplished by the addition of aliquots of the reaction solutions (at t_∞) to the standard buffered ethanolic solution of NaI and following the rate of I_3^- formation. In these product assays, it was noted the I_3^- formation was biphasic and that the values of k_{obsd_1} and k_{obsd_2} when corrected for $[I^-]$ were equal to the rate constants determined independently for A and B. From product analyses, k_A' and k_B' were found to be 1.09×10^{-2}–1.26×10^{-2} M^{-1} s^{-1} and 1.12×10^{-3}–1.22×10^{-3} M^{-1} s^{-1}. Thus, though A and B cannot be differentiated, they most certainly are both formed in epoxidation of 2,3-dimethyl-2-butene and can be quantitatively assayed. The reaction of *m*-chloroperbenzoic acid with I^- was followed by stopped-flow spec-

(4) Sharpless, K. B.; Verhove, T. R. *Aldrichimica Acta* **1979**, *12*, 63.
(5) Rebek, J., Jr. *Heterocycles* **1981**, *15*, 517.
(6) Kemal, C.; Bruice, T. C. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 995.
(7) Zigeuner, G.; Gubitz, G. *Monatsh. Chem.* **1970**, *101*, 1556.
(8) Selekson, J. J.; Watt, D. S. *J. Org. Chem.* **1975**, *40*, 267.
(9) McCready, R. Ph.D. Thesis, University of Pittsburgh, 1980.
(10) Avramoff, M.; Sprinzak, Y. *J. Am. Chem. Soc.* **1958**, *80*, 5433. *Ibid.* **1963**, *85*, 1655.
(11) Foote, C. S.; Wexler, S.; Ando, W.; Higgins, R. *J. Am. Chem. Soc.* **1968**, *90*, 975.
(12) Schenck, G. O.; Schulte-Elte, K.-H. *Justus Liebigs Ann. Chem.* **1958**, *618*, 185. Foote, C. S.; Wexler, S.; Ando, W.; Higgins, R. *J. Am. Chem. Soc.* **1968**, *90*, 975.
(13) Eliel, E. L.; Rerick, M. N. *J. Am. Chem. Soc.* **1960**, *82*, 1365.
(14) Cope, A. C.; Towle, P. H. *J. Am. Chem. Soc.* **1949**, *71*, 3423.
(15) Dankleff, M. A. P.; Curci, R.; Edwards, J. O.; Pyun, H. Y. *J. Am. Chem. Soc.* **1968**, *90*, 3209.
(16) Ziegler, D. M.; Pettit, F. H. *Biochem. Biophys. Res. Commun.* **1964**, *15*, 188.
(17) In a previous study (see ref 2a) iodide formation was followed by employing 95% ethanol contalning acetic acid and 0.1 M sodium iodide. The rate constants for the reaction of hydroperoxides with I^- are not changed on employing an acetate buffer (as used in this study), but the stability of the I_3^- product is greatly enhanced.

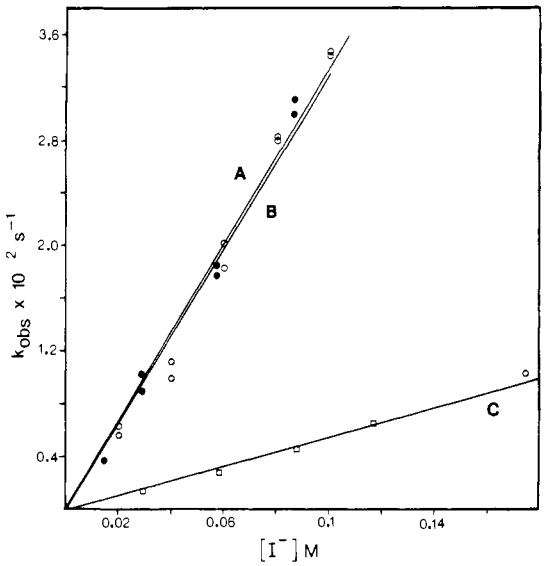


Figure 1. Plots of k_{obsd} for the reaction of I^- with hydroperoxides vs. iodide concentrations. Plots A and B pertain to hydroperoxides **4** and **5**, respectively (95% EtOH, 30 °C anaerobic). For the kinetic methodology used in obtaining the pseudo-first-order rate constants for reaction of **4** with I^-, see the text. Plot C pertains to the hydroperoxide **6** (same solvent as for **4** and **5** but with 5% DMF).

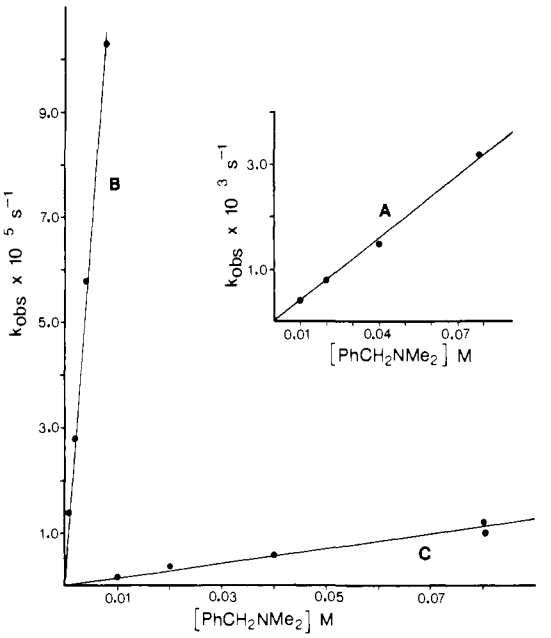


Figure 2. Plots of k_{obsd} for the reactions of *N,N*-dimethylbenzylamine with hydroperoxides in *t*-BuOH (30 °C) vs. *N,N*-dimethylbenzylamine concentrations. Plot A is for **4**, plot B for **5**, and plot C for **6**. Initial concentrations of hydroperoxides at 3.2×10^{-4} M.

trophotometry. The reaction of thioxane with *m*-chloroperbenzoic acid was studied as a competition with I^- oxidation (see Results).

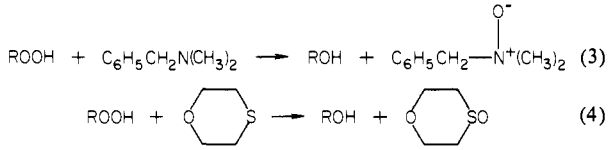
Analysis. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN. NMR's were carried out on a Varian T-60 NMR spectrometer. IR's were carried out on a Perkin-Elmer sodium chloride spectrophotometer. GC's were carried out on a Varian 3700 series gas chromatograph (5% OV-17 on Chromosorb 80–100 W-HP 6-ft column) by using a Varian CDS 101 electronic integrator for peak area determinations. (The retention time for tetramethyl ethylene oxide was approximately 8 min at 50 °C.) Iodometric analyses were carried out on a Cary Model 16K spectrophotometer. Kinetic studies involving the observations of absorbance changes with time employed a Cary 118C or Durham-Gibson stopped-flow spectrophotometer. Photon counting studies were carried out on a P.A.R. photon counter, Model 1140A.

Results

The reactions of the hydroperoxides 4, 5, and 6 with I^-, *N,N*-dimethylbenzylamine, and thioxane were studied under the pseudo-first-order conditions (30 °C) of [substrate] ≫ [hydroperoxide]. Strict anaerobic conditions (unless stated otherwise) were employed. The formation of I_3^- on oxidation of I^- was followed spectrophotometrically (358 nm) while N-oxidation of *N,N*-dimethylbenzylamine and S-oxidation of thioxane were followed by iodometric determination of the remaining **4**, **5**, and **6** at chosen times (see Experimental Section). All reactions followed the first-order rate law and plots of the pseudo-first-order rate constants (k_{obsd}) vs. substrate concentration were found to be linear. The plots of k_{obsd} vs. $[I^-]$ for oxidation of I^- (95% ethanol, 30 °C) by **5** and **6** are presented in Figure 1, while plots of k_{obsd} vs. the concentrations of *N,N*-dimethylbenzylamine and thioxane (absolute *tert*-butanol, 30 °C) for reactions of **4**, **5**, and **6** are presented in Figures 2 and 3, respectively. The linearity of the various plots establish that the reactions of **5** and **6** with I^- and **4**, **5**, and **6** with tert amine and sulfide are first order in the hydroperoxides, as well as first order in substrate (eq 2–4). The second-order rate

$$ROOH + I^- \xrightarrow{slow} ROH + IO^- \qquad (2)$$

$$IO^- + 2I^- \xrightarrow{2H^+} I_3^- + H_2O$$



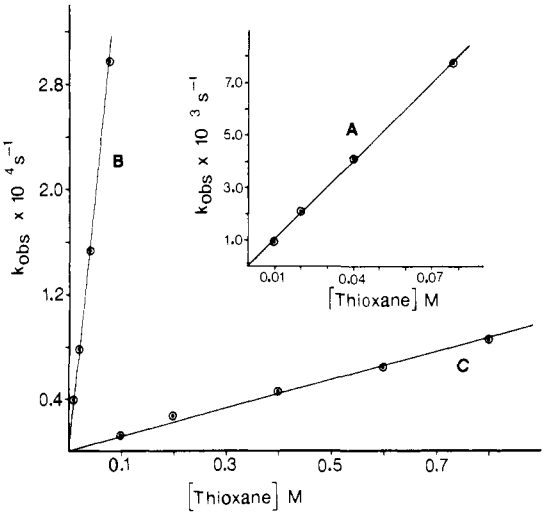


Figure 3. Plots of k_{obsd} for the reaction of thioxane with hydroperoxides (*t*-BuOH, 30 °C) vs. thioxane concentration. Plot A is for **4**, plot B for **5**, and plot C for **6**. Initial concentrations of hydroperoxides at 3.2×10^{-4} M.

constants calculated from the slopes of Figures 1–3 are presented in Table I. Product yields, calculated from the [**4**] employed, were 105% sulfoxide (from thioxane) and 99.7% *N*-oxide (from *N,N*-dimethylbenzylamine). In the instance of **5**, the percent yield of *N*-oxide was 98%.

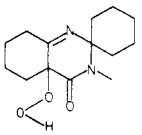
Representative plots of the time dependence of the absorbance of I_3^- formed on reaction of **4** with I^- are shown in Figure 4. The curves of Figure 4 were fitted by the equation for two consecutive first-order (k_Ψ and k_Ψ') reactions. The appearance and disappearance of I_3^- are explained via reactions 5a–c.

$$(C_6H_5)_2C(OOH)CN + 3I^- + 2H^+ \xrightarrow{k_1' = 3.56 \times 10^{-1}\ M^{-1}\ s^{-1}} (C_6H_5)_2C(OH)CN + H_2O + I_3^- \qquad (5a)$$

$$(C_6H_5)_2C(OH)CN \xrightarrow{k_2 = 5.63 \times 10^{-2}\ s^{-1}} (C_6H_5)C{=}O + HCN \qquad (5b)$$

$$CN^- + I_3^- \underset{}{\overset{K_c = 68\ M}{\rightleftharpoons}} ICN + 2I^- \qquad (5c)$$

Table I. Second-Order Rate Constants for the Reaction of Hydroperoxides with I^-, Thioxane, *N,N*-Dimethylbenzylamine, and 2,3-Dimethyl-2-butene (Anaerobic 30 °C)

ROOH	substrate	solvent	k_2 (M^{-1} s^{-1})
m-$ClC_6H_4CO_3H$ (1)	NaI	95% EtOH[b]-2% DMF	4.6×10^3
1	NaI	95% *t*-BuOH[b]-2% DMF	1.1×10^4
$(C_6H_5)_2C(OOH)CN$ (4)	NaI	95% EtOH[b]	3.4×10^{-1}
$(C_6H_5)_2C(OOH)CO_2Me$ (5)	NaI	95% EtOH-DMF[b] [3:0.4 (v/v)]	3.3×10^{-1}
 (6)	NaI	95% EtOH-DMF[b] [3:0.4 (v/v)]	5.4×10^{-2}
1	thioxane	95% EtOH[a,b]-5% $CHCl_3$	5.3×10^1
1	thioxane	95% *t*-BuOH[a,b]-5% $CHCl_3$	9.3×10^1
4	thioxane	absolute *t*-BuOH[b]	1.0×10^{-1}
5	thioxane	absolute *t*-BuOH	3.8×10^{-3}
6	thioxane	absolute *t*-BuOH	1.1×10^{-4}
4	$C_6H_5CH_2N(CH_3)_2$	absolute *t*-BuOH[b]	4.0×10^{-2}
5	$C_6H_5CH_2N(CH_3)_2$	absolute *t*-BuOH	1.3×10^{-3}
6	$C_6H_5CH_2N(CH_3)_2$	absolute *t*-BuOH	1.4×10^{-5}
4	$(CH_3)_2C{=}C(CH_3)_2$	absolute *t*-BuOH	5.6×10^{-5}
5	$(CH_3)_2C{=}C(CH_3)_2$	absolute *t*-BuOH	7.5×10^{-6}
5	$(CH_3)_2C{=}C(CH_3)_2$	absolute *t*-BuOH	1.0×10^{-4} (60 °C)
5	$(CH_3)_2C{=}C(CH_3)_2$	absolute $CHCl_3$	4.5×10^{-5}

[a] CH_3CO_2Na, 3.33×10^{-4} M; CH_3COOH, 3.33×10^{-5} M; NaI, 1.15×10^{-3} M. [b] Aerobic.

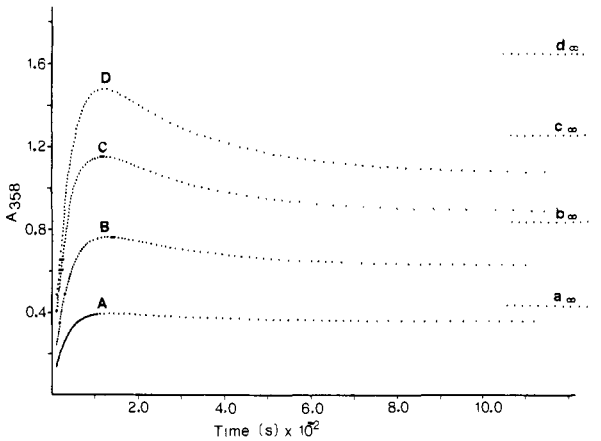


Figure 4. Plots of I_3^- absorbance (358 nm) for reactions of **4** with I^- (8×10^{-2} M NaI, 1.6×10^{-2} M CH_3CO_2Na, 1.6×10^{-3} M CH_3CO_2H) at 30 °C vs. time. For the various plots the initial concentrations of **4** are (A) 1.67×10^{-5} M, (B) 3.33×10^{-5} M, (C) 5.00×10^{-5} M, and (D) 6.67×10^{-5} M. a_∞, b_∞, c_∞, and d_∞ are the concentrations of I_3^- that would have been formed at completion of the reaction of eq 5a had not the reactions of eq 5b,c interceded.

The rate constant for appearance of I_3^- (k_Ψ) was found to show a first-order dependence on $[I^-]$ as anticipated for the reaction of hydroperoxide with I^- (eq 5a). Under the pseudo-first-order conditions of constant $[I^-] = 0.08$ M $\gg [(C_6H_5)_2C(OOH)CN]$, a variation in hydroperoxide concentration (4.2×10^{-6}–8.3×10^{-5} M) did not bring about a change in either the rate constants for the appearance of I_3^- or those for its disappearance. This is as anticipated from eq 5. Thus, under the pseudo-first-order conditions employed, the bimolecular rate expression of eq 5a becomes eq 6b, wherein k_Ψ is the product of the constant value of $[I^-]$ and

$$\frac{d[I_3^-]}{dt} = k_1'[I^-][ROOH] \quad (6a)$$

$$\frac{d[I_3^-]}{dt} = k_\Psi[ROOH] \quad (6b)$$

the constant k_1'. The value of k_1' was determined as the slope of a plot of k_Ψ vs. $[I^-]$. A change in $[(C_6H_5)_2C(OOH)CN]$ does not alter k_Ψ', in accord with eq 5b where the peroxide is not present as a reactant. In the disappearance of I_3^-, reaction 5b is rate determining. The equilibrium constant K_e (eq 5c) was determined from the final absorbance of I_3^- in the reaction of **4** with I^- and independently from the reaction of cyanide with I_3^- (where $[CN^-]_T = [HCN] + [CN^-] = [HCN]$ in 95% ethanol with 2×10^{-2} M CH_3CO_2Na plus 2×10^{-3} M CH_3COOH) (eq 7). In Figure 4,

$$K_e = \frac{[ICN][I^-]^2}{[I_3^-][CN^-]_T} \quad (7)$$

the plots A–D are from representative kinetic runs wherein the concentration of hydroperoxide is increased on going from A to D. In this figure marked a_∞, b_∞, c_∞, and d_∞ are the concentrations of I_3^- that would have been formed at completion of the reaction of eq 5a had not the reactions of eq 5b,c interceded. The difference in $[I_3^-]$ between the experimentally determined infinity and the hypothetical infinity ($A_\infty - a_\infty$, $B_\infty - b_\infty$, etc.) when divided by the ϵ for I_3^- equals [ICN] at the completion of reaction. The values of $[HCN] = [I_3^-] = a_\infty$, b_∞, etc. Knowing the concentration of I^- employed ($[I^-] \gg [HCN]$, $[I_3^-]$, and [ICN]) allowed the calculation of K_e' for each kinetic determination. The values of K_e' determined from the kinetic studies and by the mixing of solutions of NaCN with solutions of I^- containing I_3^- proved to be identical (Table II).

Table II. Apparent Equilibrium Constants for the Reaction of Cyanide with I_3^- Determined from the Reaction of 4 with I^- (95% Ethanol, 1.6×10^{-2} M $CH_3CO_2^-Na^+$, 1.6×10^{-3} M CH_3CO_2H, 30 °C) and from the Reaction of Cyanide with I_3^- (95% Ethanol, 2×10^{-2} M $CH_3CO_2^-Na^+$, 2×10^{-3} M CH_3CO_2H, 30 °C)

concentrations of reactants (M)				
4	I^-	NaCN	I_3^-	K_e
8.33×10^{-6}	8×10^{-2}			55
1.67×10^{-5}	8×10^{-2}			52
3.33×10^{-5}	8×10^{-2}			75
5.00×10^{-5}	8×10^{-2}			66
6.67×10^{-5}	8×10^{-2}			79
8.33×10^{-5}	8×10^{-2}			85
				av: 68 ± 11
	1×10^{-1}	1.07×10^{-5}	2.13×10^{-5}	66
	1×10^{-1}	2.13×10^{-5}	2.13×10^{-5}	62
	1×10^{-1}	2.13×10^{-5}	2.13×10^{-5}	64
	1×10^{-1}	3.2×10^{-5}	2.13×10^{-5}	72
	1×10^{-1}	4.27×10^{-5}	2.13×10^{-5}	75
	1×10^{-1}	5.33×10^{-5}	2.13×10^{-5}	71
				av: 68 ± 4

The reaction of *m*-chloroperbenzoic acid with I^- occurs in the stopped-flow time range, and because of this feature, the reaction could be studied under aerobic conditions without concern for O_2

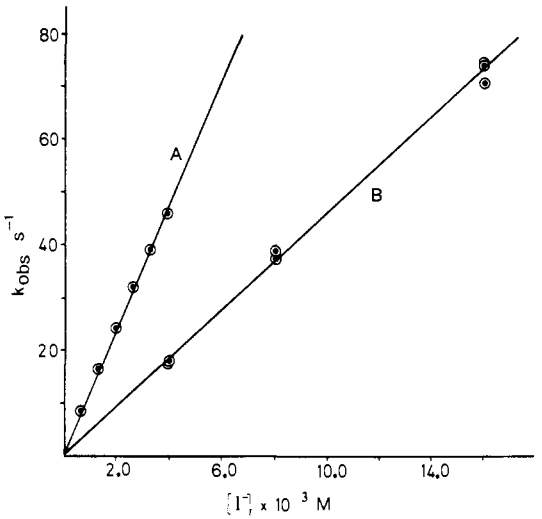
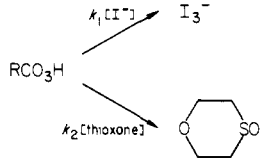


Figure 5. Plots of k_{obsd} for the reaction of *m*-chloroperbenzoic acid (1.77×10^{-5} M) with NaI in 95% *t*-BuOH–DMF (CH_3CO_2Na, 3.33×10^{-4} M; CH_3CO_2H, 3.33×10^{-5} M) at 30 °C (A) and the reaction of *m*-chloroperbenzoic acid (2×10^{-5} M) with NaI in 95% EtOH–DMF (CH_3CO_2Na, 1.66×10^{-4} M; CH_3CO_2H, 1.66×10^{-5} M) at 30 °C (B) vs. concentrations of NaI.

oxidation of I^-. Formation of I_3^- under the conditions of $[I^-] \gg$ [peracid] was found to be pseudo first order in 95% ethanol–2% DMF and 95% *tert*-butyl alcohol–2% DMF (both solvents being 3.33×10^{-4} M in $CH_3CO^-Na^+$ and 3.33×10^{-5} M in CH_3CO_2H). Plots of k_{obsd} vs. $[I^-]$ are presented in Figure 5 and the apparent second-order rate constants for oxidation of I^- by peracid were calculated as the slopes (Table I).

The oxidation of thioxane by *m*-chloroperbenzoic acid cannot be followed spectrally due to lack of significant spectral changes accompanying the reaction. Also, iodometric titration of remaining peracid at given times is not possible due to the large rate constants for peracid disappearance in the presence of thioxane. A suitable means for the determination of the second-order rate constant for reaction of thioxane with peracid was found in the study of the competitive reactions of I^- and thioxane with peracid (eq 8) where



(8)

the rate of I_3^- formation could be followed. Under the conditions of [thioxane] $\gg$ [*m*-$ClC_6H_4CO_3H$] $\ll$ $[I^-]$, the disappearance of peracid and appearance of I_3^- follow the same first-order rate law. The individual rate constants (eq 8) are related as shown in eq 9. The value of k_1 is known (Table I) as are the initial con-

$$\frac{[I_3^-]}{[\text{sulfoxide}]} = \frac{k_1[I^-]}{k_2[\text{thioxane}]} \quad (9a)$$

$$k_2 = \frac{k_1[I^-][\text{sulfoxide}]}{[\text{thioxane}][I_3^-]} \quad (9b)$$

centrations of I^- and thioxane. The product ratio was determined by simply determining the decrease in $[I_3^-]$ formed at various concentrations of thioxane and equating this to [sulfoxide]. Sulfoxide does not react with I^- under the conditions and timing of these experiments. In practice, $[I^-] = 1.15 \times 10^{-3}$ and [thioxane] was varied between 7.5×10^{-3} and 2.50×10^{-2} M. In the solvent 95% ethanol containing 5% $CHCl_3$, a second-order rate constant of $(5.3 \pm 0.4) \times 10^1$ M^{-1} s^{-1} was obtained while in 95% *tert*-butanol containing 5% $CHCl_3$, the second-order rate constant was determined as $(9.3 \pm 0.2) \times 10^1$ M^{-1} s^{-1}. No attempt to determine the second-order rate constant for the reaction of *N,N*-dimethylbenzylamine with *m*-chloroperbenzoic acid was made. It was felt that the possibility of salt formation between these two reagents could not be assured against.

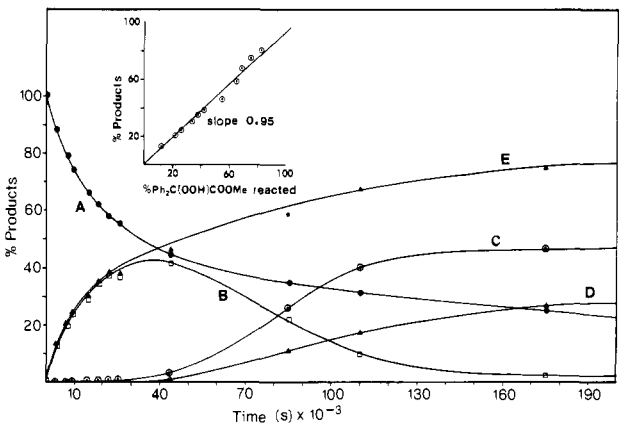
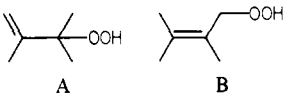


Figure 6. Time course for the reaction of the hydroperoxide **5** (3.33×10^{-1} M) with 2,3-dimethyl-2-butene (3.33×10^{-1} M) under aerobic conditions, 30 °C. Plot A represents the concentration of **5** as a function of time. The time dependence for the formation and disappearance of tetramethyl ethylene oxide is shown in plot B. Plots C and D represent the time dependence of formation of 2,3-dimethyl-1-buten-3-ol and pinacol, respectively. Plot E is the sum of (B) + (C) + (D) vs. time. The inset to the figure is a plot of the percent **5** reacted at times *t* vs. the sum of the percent yields of the products (pinacol plus allyl alcohol plus epoxide) at time *t*.

Epoxidation of 2,3-dimethyl-2-butene by hydroperoxides 4–6 was studied under aerobic and anaerobic conditions by employing a number of solvents. Results of aerobic epoxidation experiments will be discussed first.

Though **6** is unstable when warmed in $CHCl_3$, it could be determined that epoxide was formed (48% yield based on remaining alkene) upon warming (60 °C, 24 h) a solution containing 1:1 (3.33×10^{-1} M) of **6** and 2,3-dimethyl-2-butene (referred to as alkene) in $CHCl_3$. Employing the solvent DMF at 60 °C under *aerobic* conditions, **6** (6.4×10^{-3} M) was allowed the opportunity to react with increasing concentrations of alkene (0.1–0.8 M). Though the rate of epoxide appearance increased with increase in the concentration of alkene, the percent yield of epoxide, based on initial [**6**], increased to over 100% (at 0.8 M alkene, a 200% yield was obtained after 24 h). The percent yields of allyl hydroperoxides, based on initial [olefin], were found to be relatively constant (0.6%, 0.5%, 0.3%, and 0.2%) and independent of the presence or absence of **6**. Radical initiated autoxidation of 2,3-dimethyl-2-butene by O_2 is known to yield the allyl hydroperoxides A and B and the corresponding allyl alcohols as well as epoxide,



A B

pinacol, acetone, and resin (for example, see ref 18). In *tert*-butanol at 60 °C under aerobic conditions when employing 1:1 of **6** and alkene (at the maximum concentrations allowed by solubility, 1×10^{-2} M), the disappearance of **6** followed a sigmoidal time course. After 8 days, [**6**] had decreased to 50% and there was formed but a 2% yield of epoxide.

When **5** and alkene were allowed to react under aerobic conditions (1:1 at 0.333 M) in $CHCl_3$ at 60 °C for 24 h, epoxide was formed in over 90% yield. Analogue fitting of the time dependence of the concentrations of **5**, olefin, and epoxide provided the second-order rate constant of 6.3×10^{-4} M^{-1} s^{-1}. Allyl hydroperoxides A and B were found to be formed in 0.5% yield based on the initial [**5**]. No pinacol or allyl alcohols could be detected. The reaction of **5** with olefin under anaerobic conditions was also examined (**5**:olefin = 1:1, 3.33×10^{-1} M, 60 °C) by employing *t*-BuOH as the solvent. The results are provided in Figure 6. Examination

(18) Van Sickel, D. E.; Mayo, F. R.; Arluck, R. M.; Syz, M. G. *J. Am. Chem. Soc.* **1967**, *89*, 967.

Scheme I

initiation

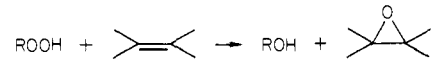
$$n\,ROOH \longrightarrow RO\cdot + HO\cdot + (n-1)ROOH$$

$$n\,ROOH + O_2 \longrightarrow ROO\cdot + HO_2\cdot + (n-1)ROOH$$

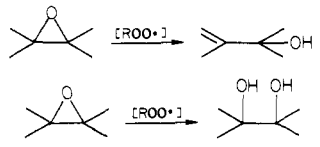
$$ROOH + HO_2\cdot \longrightarrow ROO\cdot + H_2O_2$$

$$RO\cdot/HO\cdot + ROOH \longrightarrow ROO\cdot + ROH/HOH$$

epoxidation



product formation and chain continuation



of Figure 6 reveals that the decrease in [**5**] is accompanied by an increase in epoxide concentration to a maximum of ~40% yield and that the epoxide then decreased in concentration with accompanying formation of the two final products, 2,3-dimethyl-1-buten-3-ol and pinacol. Also present at the completion of the reaction (95 h) was 0.02% yield of the allyl hydroperoxides A and B (based on the initial [**5**] = [olefin]). If one plots (inset to Figure 6) the concentration of **5** which has disappeared from solution at time t vs. the combined concentrations of epoxide, pinacol, allyl alcohols, and allyl peroxides formed at time t, there is obtained a linear plot of slope 0.95. This result shows that the yield of oxidation products at any time t is always equal to the hydroperoxide consumed. In the absence of **5** (absolute t-BuOH, 60 °C), there is *no formation* (after 13 days) of pinacol and allyl alcohol from authentic epoxide in the presence or absence of O_2. The epoxide was found to be completely stable. In experiments in which **5** (0.33 M) was allowed to react with epoxide (0.33 M, 60 °C, t-BuOH) under both anaerobic and aerobic conditions, there was obtained both pinacol and the allyl alcohol as products. Very little **5** was consumed and the lag phase was dependent upon the presence (~4×10^4 s) or absence (~2×10^5 s) of O_2. It was also found in kinetic runs in the presence of O_2 and **5** (0.33 M as in all these experiments) that the lag phase for formation of pinacol and allyl alcohols was identical (60 °C, t-BuOH) regardless of whether epoxide or olefin was employed. The ratios of allyl alcohol to pinacol, however, were found to be different when epoxide rather than olefin was the substrate. When olefin was employed, the ratio of allyl alcohol (47.7% yield): pinacol (35.5% yield) = 1.4:1. When epoxide was employed as substrate, the ratio of allyl alcohol (83.3% yield):pinacol (19.2% yield) = 4.2:1. In these experiments, the [**5**] remained almost constant during the course of the run with epoxide but was, of course, consumed in the run with olefin. An observation of mechanistic significance was the finding that, if epoxide was employed at the usual concentration of 0.33 M, but under the pseudo-first-order condition of [epoxide] ≫ [**5**], formation of allyl alcohol and pinacol from epoxide did not occur. In other words, conversion of epoxide to pinacol and allyl alcohol must be dependent on greater than first order in [**5**]. Since epoxide is converted to pinacol and allyl alcohol with far less than a stoichiometric consumption of **5**, this reaction must represent an autocatalysis with **5** involved in the initiation step. Further, since the length of the lag phase is dependent upon the presence or absence of O_2, the formation of the autocatalytic agent from **5** must occur by both an [O_2]-independent and [O_2]-dependent process. The essence of the overall reaction may be considered in the frame of Scheme I. When $CHCl_3$ replaces t-BuOH as the solvent, the epoxide is stable in the presence of **5** (6.4×10^{-3}–3.33×10^{-1} M) so that t-BuOH likely plays a role in the autocatalysis (see Discussion).

The remaining results pertain to epoxidation reactions carried out under strictly anaerobic conditions and with trace metal free precautions (see Experimental Section). Hydroperoxide concentrations were kept low to obviate the previously noted auto-

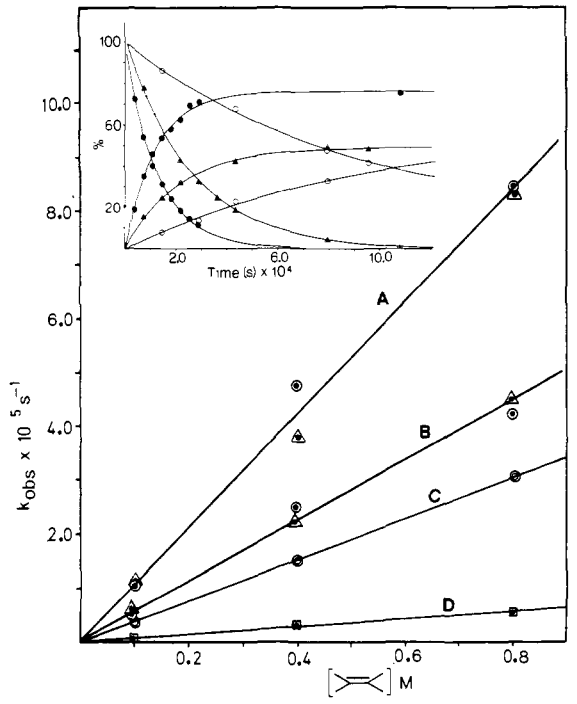
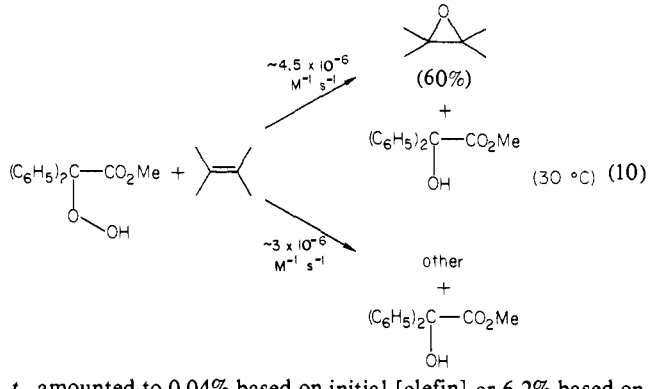


Figure 7. Plots of k_{obsd} for the reaction 2,3-dimethyl-2-butene with hydroperoxides under anaerobic conditions. Initial concentrations of hydroperoxides at 6.4×10^{-3} M. [(A) **5** at 60 °C in t-BuOH, (B) **4** at 30 °C in t-BuOH, (C) **5** at 30 °C in $CHCl_3$ (grade-B solvent), and (D) **5** at 30 °C in t-BuOH.] Duplicate points indicate reactions followed by GC determination of epoxide and iodometric determination of hydroperoxide. The inset contains representative first-order rate law fits for the disappearance of the hydroperoxide **5** in t-BuOH at 30 °C (initial [**5**] = 6.4×10^{-3} M) and appearance of epoxide (initial olefin concentrations 0.1, 0.4, and 0.8 M).

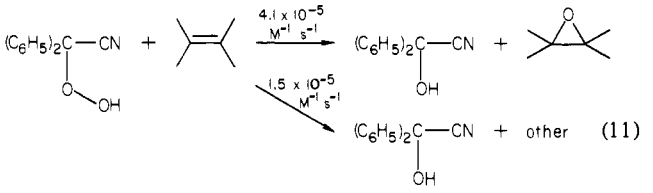
catalytic consumption of epoxide. Under these pseudo-first-order conditions, at either 30 or 60 °C (t-BuOH) with [**5**] (=6.4×10^{-3} M) and [olefin] (=0.1, 0.4, and 0.8 M), the disappearance of **5** *and* formation of epoxide followed the first-order rate law to $8t_{1/2}$ (Figure 7, inset). Plots of the pseudo-first-order rate constants (k_{obsd}) vs. [olefin] were linear (Figure 7). The calculated second-order rate constants are 7.48×10^{-6} M^{-1} s^{-1} (30 °C) and 1.05×10^{-4} M^{-1} s^{-1} (60 °C). Thus, in the absence of O_2 and trace metals and at low initial [**5**], the epoxidation of olefin is first order in [**5**] and first order in [olefin]. Also, the alcohol formed from **5** was found to be present in 96% yield based on initial [**5**] [by GC comparison to standard curves constructed by use of authentic $(C_6H_5)_2C(OH)CO_2Me$]. However, the yields of epoxide were not quantitative (at 30 °C: 72%, 55%, and 57% at 0.8, 0.4, and 0.1 M olefin). The less than quantitative yield of epoxide could not be attributed to the impurity of the hydroperoxide sample employed which assayed at 98% by iodometric titration. These results suggest two pathways (parallel pseudo first order) for reaction of **5** with olefin (eq 10). At 60 °C the allyl peroxide present at



t_∞ amounted to 0.04% based on initial [olefin] or 6.2% based on the initial value of [**5**]. At 30 °C, the allyl peroxide present at

t_∞ was determined at all olefin concentrations and found to be 0.002%, 0.009%, and 0.003% based upon initial [olefin]. The product marked "other" in eq 10 was nonvolatile and, therefore, possibly polymeric. The second-order rate constant for reaction of **5** with olefin in $CHCl_3$ (Figure 7) was determined as 4.5×10^{-5} M^{-1} s^{-1} (30 °C). Thus, the rate of epoxidation with **5** is increased by 6-fold on transfer from *t*-BuOH to $CHCl_3$ solvent (anaerobic). In $CHCl_3$, epoxidation is quantitative.

The reaction of **4** (6.4×10^{-3} M) with 2,3-dimethyl-2-butene (0.1–0.8 M) was also investigated under metal-free and anaerobic conditions in absolute *t*-BuOH. As with hydroperoxide **5**, the appearance of epoxide and disappearance of **4** followed the first-order rate law at all concentrations of olefin employed. Inspection of Figure 7 shows that the rate constant for appearance of epoxide is that for disappearance of hydroperoxide. From plots of k_{obsd} for hydroperoxide disappearance and epoxide appearance vs. [olefin], there was obtained the second-order rate constant of 5.58×10^{-5} M^{-1} s^{-1} (30 °C) for the bimolecular reaction of **4** with olefin (Figure 7). Again, however, epoxide formation was not quantitative. At [olefin] = 0.1, 0.4, and 0.8 M, the percent yields of epoxide based upon **4** employed were 70%, 72%, and 75%, respectively. The constancy of the percent yields of epoxide with change in olefin concentration is suggestive of the parallel paths of eq 11.

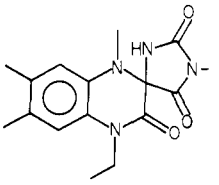


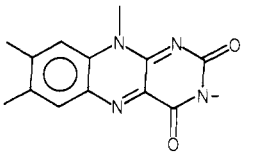
(11)

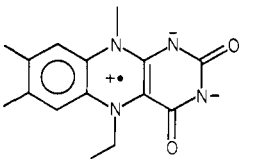
Unlike the bimolecular reactions of **4** and **5** with 2,3-dimethyl-2-butene, **6** (6.4×10^{-3} M) did not produce epoxide when in the presence of excess olefin (0.1 M, 0.4 M and 0.8 M) in absolute *tert*-butanol under metal-free conditions and in the absence of O_2 at 60 °C. The disappearance of **6** was initiated only after a lag period of up to 5 days and followed the sigmoidal curve anticipated for an autocatalytic reaction. The lag period became shorter with increase in [olefin]. A bimolecular reaction of **6** with olefin is obviously not involved. It has been shown that olefins may induce the decomposition of hydroperoxides.[19] Traces of allyl hydroperoxides A and B (0.09%, 0.14%, and 0.18% based on initial [olefin]) were found to be formed. The same concentrations of allyl peroxides were formed, however, in the absence of **6**. One may conclude that neither **6** nor any decomposition product of **6** reacts with the olefin to yield epoxide at 60 °C in *t*-BuOH under metal-free conditions and in the absence of O_2.

4a-Hydroperoxy-5-ethyl-3-methyllumiflavin (2) and its 1-carba-1-deaza analogue (3) do not react with 2,3-dimethyl-2-butene in the solvents *t*-BuOH and DMF, respectively, under either anaerobic or aerobic conditions. The slow disappearance of **2** and **3** follow the first-order rate law in both solvents and the addition of alkene (to 0.8 M) has no influence upon the rate constants for the decomposition reactions. The disappearance of **2** was followed spectrophotometrically (370 nm)[6] and by iodometric titration. In *t*-BuOH, the rate constants obtained by both analytical procedures in the presence and absence of alkene (to 0.8 M) ranged from 1.5×10^{-4} s^{-1} to 2×10^{-4} s^{-1} at the initial concentration of [**2**] = 3.2×10^{-3} M. The decomposition of **3** was followed at 378 nm.[2a] The first-order rate constants for decomposition of **3** were not influenced by addition of alkene to 0.8 M ($k = 1.08 \times 10^{-4}$ s^{-1} without alkene and $k = 1.0 \times 10^{-4}$ s^{-1} with 0.8 M alkene, solvent DMF). The various experiments were repeated employing initial [**2**] = 3.2×10^{-3} M and GC analysis for epoxide showed that none had been formed. The addition of either **5** (1.6×10^{-4} M), N^5-ethyllumiflavin radical (10^{-5} and 2×10^{-4} M), benzoyl peroxide (1.6×10^{-4} M), or N^5-ethyllumiflavin perchlorate (1.6×10^{-4} M) to solutions 1.6×10^{-3}–3.2×10^{-3} M in **2** and 0.8–1.6 M in alkene did not lead to the formation of epoxide or to an enhancement in the rate of decomposition of **2**.

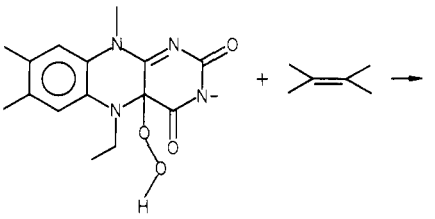
The transfer of **2** from *t*-BuOH or DMF solvent to anhydrous $CHCl_3$ greatly increases the rate of disappearance of **2** from solution. In spite of the instability of **2** in $CHCl_3$, efforts were made to determine if **2** could epoxidize 2,3-dimethyl-2-butene in this solvent. The reason for doing so was based on the moderate enhancement (10-fold) in the reactivity of **5** toward alkene in $CHCl_3$ as compared to *t*-BuOH. Three grades of $CHCl_3$ were employed: (A grade) washed with H_2O, dried over $CaCl_2$, distilled from P_2O_5, passed through basic alumina (Sigma WB-2, grade 1), and distilled (the last three operations under N_2); (B grade) washed with H_2O, dried over $CaCl_2$, and distilled from P_2O_5 under N_2; (C grade) 20% of spectroscopic grade chloroform boiled away under N_2 and residual cooled under N_2. These chloroform samples were stored in the dark under N_2. The stability of **2** and the products formed on decomposition of **2** (C, D, E) were determined

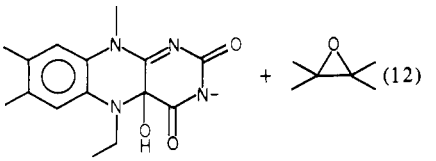

C
λ_{max} 305 nm ($CHCl_3$)


D
λ_{max} 472 (s) nm ($CHCl_3$)
447 nm
425 (s) nm


E
604 nm ($CHCl_3$)
645 nm

by using the three grades of chloroform. (Studies with **5** and **6**, loc. cit., were carried out with grade-B $CHCl_3$.) The decomposition of **2** (1×10^{-4} M) in grade-A $CHCl_3$ was found to follow a sequential first-order route (**2** → X → products) with decreasing absorbance (370 nm) for both steps (4.4×10^{-2} s^{-1} and 1.1×10^{-2} s^{-1}) and to yield as the final product oxidized flavin (D) as the only species absorbing above 300 nm. If **2** were to react with olefin to yield epoxide, the flavin products would be the alcohol 4a-FlEtOH (eq 12). Prior to the investigation of the question of


4a-FlEtOOH or **2**


(12)

4a-FlEtOH

epoxidation of olefin by **2** in chloroform, the stability of 4a-FlEtOH must be known in this solvent. In grade-A $CHCl_3$, 4a-FlEtOH (1×10^{-4} M) decomposes by a first-order process followed by a sudden sigmoidal decay in absorbance—as anticipated for a radical chain reaction—to yield D and the radical species E (comparable yield) plus an unknown absorbing maximally at 328 nm. In grade-B $CHCl_3$, **2** decomposes by the same sequential kinetic path

(19) Walling, C.; Heston, L. *J. Am. Chem. Soc.* **1965**, *87*, 38.

as seen with grade-A $CHCl_3$ (k's = 1.7×10^{-2} s^{-1} and 1.5×10^{-3} s^{-1}) to yield 15% D and 85% 10a-spirohydantoin C [determined by spectral and HPLC (silica with AN) comparison to authentic samples]. The decomposition of 4a-FlEtOH, in grade-B $CHCl_3$, followed a biphasic first-order kinetic scheme (k's = 3.5×10^{-4} s^{-1} and 1.4×10^{-5} s^{-1}) to yield about equal quantities of D and E plus the unknown absorbing maximally at 328 nm. In grade-C $CHCl_3$, the decomposition of **2** is again sequential first order (k's = 6.3×10^{-3} s^{-1} and 6.0×10^{-4} s^{-1}), providing a 75% yield of 4a-FlEtOH plus small amounts of C–E. The 4a-FlEtOH species is stable in grade-C $CHCl_3$. This may be due to an exchange reaction of 4a-FlEtOH with remaining EtOH antioxidant to yield 4a-FlEtOEt. These results establish that the stability of **2** decreases on purification of the chloroform solvent. This finding is not surprising since it is known that $CHCl_3$ undergoes free radical reactions which are initiated by the decomposition of peroxides[20] and the susceptibility to induced radical reactions increases with the purity of the chloroform. However, we also find that the stability of 4a-FlEtOH markedly decreases with an increase in the purity of the chloroform solvent. This finding cannot be attributed to a peroxide decomposition and presumably involves $1e^-$ transfer from the N^5-position of 4a-FlEtOH to $CHCl_3$. The same could be true for the decomposition of **2** and this would explain its instability in chloroform when compared to the reactive hydroperoxides **4** and **5**. In this regard, it should be pointed out that **2** is also unstable in CH_2Cl_2.

The rate constant for the decomposition of **2** (1×10^{-4} M) in grade-C $CHCl_3$ was found to be virtually invariant on addition of 2,3-dimethyl-2-butene (0.1–0.8 M). The same was found to be true when employing grade-B $CHCl_3$. Reaction of olefin with **2** does not compete with the "spontaneous" decomposition of **2** in these solvents and, therefore, there exists no kinetic evidence for the reaction of **2** with olefin in $CHCl_3$. Evidence for epoxide formation was sought by using grade-B $CHCl_3$ as the solvent. All of the studies enumerated before in $CHCl_3$ were carried out under strictly anaerobic conditions. Reactions for which epoxide yields were determined were carried out under anaerobic and aerobic conditions employing initial [**2**] = 3.2×10^{-3} M. The sample of **2** employed in these experiments was assayed at 89% **2** by iodometric titration. The chief impurity (~10%) is 4a-FlEtOH. Yields of epoxide and 4a-FlEtOH (when corrected for 4a-FlEtOH impurity in **2**) are provided in Table III.

A search for chemiluminescence on addition of 4, 5, and 6 to solutions of *p*-tolualdehyde was carried out. In a typical experiment a solution of the hydroperoxide was placed in the top compartment of a Thunberg cuvette and mixed with a solution of *p*-tolualdehyde contained in the bottom portion of the Thunberg. All solutions were prepared under a nitrogen atmosphere, the cuvette closed and transferred from the nitrogen glove box. Mixing of components was carried out just prior to the initiation of photon counting. The final concentrations of **4**, **5**, and **6** and *p*-tolualdehyde varied from ~10^{-4} to 10^{-2} M. In no instance could counts be detected over background.

Discussion

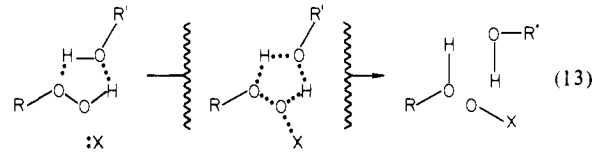
The oxidation of I^-, >N: and >S: by hydroperoxides most reasonably involves an S_N2 displacement by an unshared pair of electrons of the heteroatom upon the terminal oxygen of the hydroperoxide accompanied by proton transfer to the α-oxygen atom.[2a] Edwards[15] observed that the oxidations of thioxane by *t*-BuOOH and by H_2O_2 in the aprotic solvent dioxane are second order in these hydroperoxide species. It was suggested that the second hydroperoxide moiety served as a spectator catalyst to transfer a proton from the β- to α-oxygen of the hydroperoxide in concert with nucleophilic attack upon the β-oxygen. In past studies, we have not observed a second-order dependence for monooxygen transfer from hydroperoxides in protic solvent.[2a] It is possible that protic solvents serve as hydrogen-bonding bridges

Table III. Percentage Yields of 4a-FlEtOH[a] and Epoxide Obtained in the Decomposition of 2 (3.2×10^{-3} M) in the Presence and Absence of 2,3-Dimethyl-2-butene (30 °C, Absolute $CHCl_3$ Solvent)

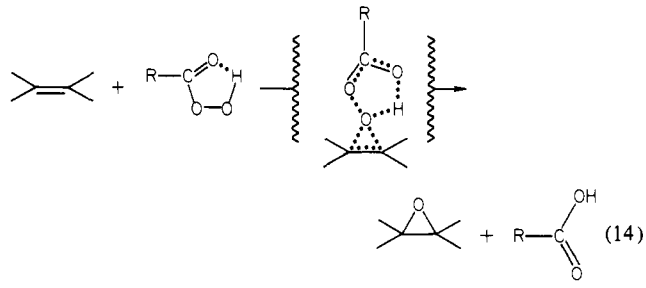
anaerobic			aerobic	
 (M)		4a-FlEtOH		4a-FlEtOH
0	0	0	0	0
0.1	14	0	27	1
0.4	31	4	50	11
0.8	31	6	50	18

[a] The concentration of 4a-FlEtOH was determined by injecting 93-μL aliquots of the reaction solution into 2.91 mL of 1 N HCl in *t*-BuOH and determining spectrally (λ_{max} = 350 mm, ϵ 6800 M^{-1} cm) the concentration of N^5-ethyl-3-methyllumiflavinium cation.

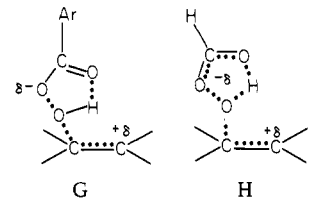
in the transition state for monooxygen transfer from hydroperoxide (eq 13). However, epoxidation of 2,3-dimethyl-2-butene in ab-


(13)

solute $CHCl_3$ by hydroperoxides **4** and **5** is not second order in the hydroperoxides. The mechanism of the epoxidation of olefins by percarboxylic acids was proposed by Bartlett[21] to involve a very delocalized and symmetrical transition state (eq 14) involving an


(14)

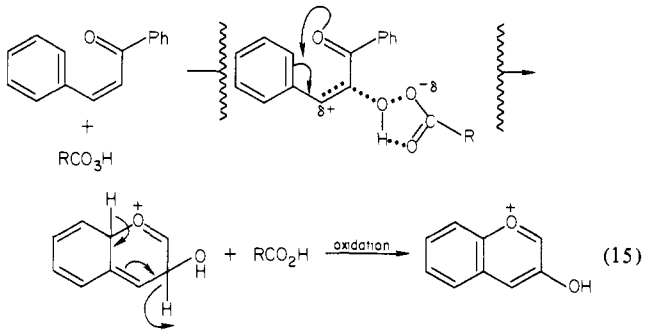
internal proton transfer. Mechanisms involving oxygen transfer from percarboxylic acid via a carbonyl oxide intermediate or oxygen transfer through a 1,3-dipolar addition mechanism involving a 1,2-dioxolane intermediate were suggested at a latter date.[22] Linear free-energy relationships and solvent effects are more in accord with the mechanism of eq 14 than that involving intermediate 1,2-dioxolane.[23] Recent experimental evidence has been presented both in support of carbonyl oxides as oxygen transfer agents[24] and in support of the contention that carbonyl oxides are rather poor electrophilic oxygen transfer agents.[25] Kinetic isotope effect data have been interpreted by Hanzlik and Shearer[26] to indicate that the critical transition state for percarboxylic acid epoxidation of olefins is not symmetrical and that there is involved little movement of the percarboxylic acid acidic hydrogen; unsymmetrical transition state G was suggested. Ab


G H

(20) Mayo, F. R. *J. Am. Chem. Soc.* **1943**, *65*, 2324. Kharasch, M. S.; Jensen, E. V.; Urry, W. H. *Science* (*Washington, D.C.*) **1945**, *102*, 128. Walling, C. "Free Radicals in Solution", Wiley: New York, **1957**, 248–252.

(21) Bartlett, P. C. *Rec. Chem. Prog.* **1957**, *31*, 419.
(22) Kwart, H.; Hoffman, D. M. *J. Org. Chem.* **1966**, *31*, 419.
(23) Kropf, H.; Yadanbachsch, M. R. *Tetrahedron* **1974**, *30*, 3455.
(24) Agarwal, S. K.; Murray, R. W. *Photochem. Photobiol.* **1982**, *35*, 31.
(25) Sawaki, Y.; Kato, H.; Ogata, Y. *J. Am. Chem. Soc.* **1981**, *103*, 3832.
(26) Hanzlik, R. P.; Shearer, G. O. *J. Am. Chem. Soc.* **1975**, *97*, 5231.

initio calculations have been offered in support of the unsymmetrical transition state H.[27] The percarboxylic acid conversion of *cis*-chalcone to 3-hydroxyflavylium cation, observed by Davidson and Norman,[28] would seem to support a fleeting unsymmetrical intermediate in epoxidation which is stabilized by electron delocalization (eq 15).



(15)

An objective of the present investigation has been to determine the relationships of the steric and electronic requirements for monooxygen donation, from hydroperoxides and a representative peracid (*m*-chloroperbenzoic acid, **1**) to the diverse nucleophiles I^-, S<, N< and >C=C<.

The hydroperoxides (**1**, **4**, **5**, and **6**) of this study react with the nucleophiles I^-, $C_6H_5CH_2N(CH_3)_2$, and the cyclic dialkyl sulfide, thioxane, to provide I_3^-, *N*-oxide, and sulfoxide, respectively, in reactions first order in hydroperoxide and first order in substrate (eq 2–4). The determined second-order rate constants are provided in Table I. The data in Table I has been combined with the second-order rate constants compiled in previous studies for the reaction of hydroperoxides with these same substrates in Table IV. The rate constants in Table IV are relative to the rate constants for the biologically important 4a-hydroperoxy-5-ethyl-3-methyllumiflavin (**2**). The relative second-order rate constants for the reaction of hydroperoxides with I^- (k_I) cover a range of 10^5 in magnitude. The relative second-order rate constants for the reactions with thioxane (k_S) and *N*,*N*-dimethylbenzylamine (k_N) cover a range of 10^8 and 10^6 in magnitude, respectively.

A plot of log k_S vs. log k_N (Figure 8) is linear and of slope 1.0. A plot of log k_S vs. log k_I exhibits some scatter, but a reasonable correlation line of slope 1.1 may be drawn. It may be concluded that N< and S< oxidations and the oxidation of I^- by hydroperoxides exhibit like sensitivities to changes in hydroperoxide structure. That the percarboxylic acid **1** reasonably fits the plot of log k_S vs. log k_I is also of interest. This feature suggests that there is a single reactivity series for oxygen donation from percarboxylic acids and hydroperoxides to nucleophiles as divergent as negatively charged and polarizable I^-, neutral, less polarizable and nonbasic dialkyl sulfide, and neutral, but basic amine. Convincing arguments have been presented in support of nonradical mechanisms for the N-oxidation reaction,[2a] and these considerations may now be extended to S-oxidation. From the plot of Figure 8 there may be extrapolated the relative second-order rate constant for the reaction of *m*-chloroperbenzoic acid with *N*,*N*-dimethylbenzylamine ($k_N = 2.14 \times 10^3$) in *t*-BuOH. The second-order rate constant for this reaction may, therefore, be taken as 2.6×10^2 M^{-1} s^{-1}.

In Figure 9 there is plotted the pK_a values[29] of YOH vs. the

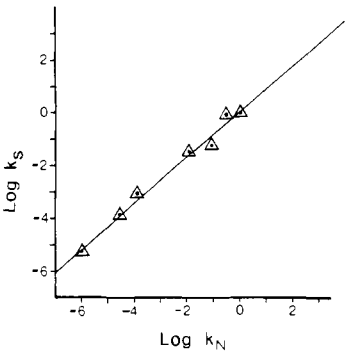


Figure 8. Relationship of the free energies of activation for reaction of hydroperoxides (Table II) with thioxane and *N*,*N*-dimethylbenzylamine. Plot of the logarithm of the relative second-order rate constants for reaction with thioxane (log k_S) vs. the logarithm of the relative second-order rate constants for reaction with *N*,*N*-dimethylbenzylamine (log k_N).

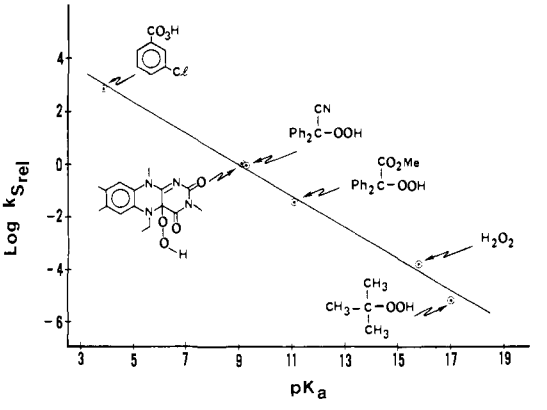


Figure 9. Plot of the log of the second-order rate constants (relative to the rate constant for **2**) for sulfoxidation of thioxane ($k_{S_{rel}}$) by the YOOH species vs. the pK_a of YOH species (solvent absolute *t*-BuOH for rate constants and H_2O for pK_a values, 30 °C).

log of the relative (to **2**) second-order rate constant for the sulfoxidation of thioxane by the YOOH compounds. The slope of the correlation line of the Figure ($\beta_{lg} = -0.6$) relates to the fractional negative charge on the leaving α-oxygen of the YO moiety in the transition state and to the positive character of the β-oxygen as a result of inductive polarization (i.e., YO ← OH) in the ground state. The value of β_{nuc} for the N-oxidation of amines by **2** has been determined[2a] as +0.2 which supports an early transition state. It should be noted that the correlation of log k vs. pK_a of YOH shows that intramolecular proton transfer, possible for certain YOOH species (as shown for epoxidation in eq 14 and in structures **5**, **9**, and **10**), does not provide a driving force for monooxygen transfer to S<, N<, or I^-.

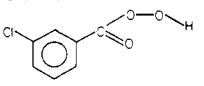
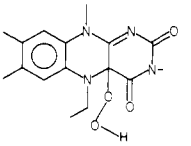
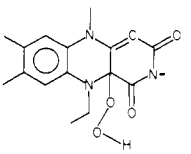
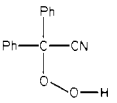
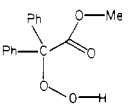
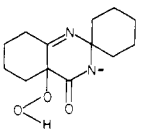
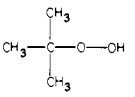
In conclusion, (i) the mechanism of oxygen transfer to :S<, :N<, and I^- by YOOH is equally dependent upon the ability of YO^- to support a negative charge ($\beta_{lg} = -0.6$), (ii) percarboxylic acid, organic hydroperoxides, and hydrogen peroxide compose a common series of YOOH oxygen donors, the advantage of percarboxylic acid being the greater stability of YO^-, and (iii) the great reactivity of the biologically important 4a-hydroperoxyflavins is due to the electronegativity of the 4a-position so that its derived YOH species possesses a pK_a of 9.1–9.5.

The epoxidation of alkenes by hydroperoxides has been a subject

(27) Plesuicar, B.; Tasevski, M.; Azman, A. *Ibid.* **1978**, *100*, 743.
(28) Davidson, A. J.; Norman, R. O. C. *J. Chem. Soc.* 1964, 5404.
(29) The pK_a values of YOH corresponding to the hydroperoxides YOOH were obtained as follows: values for *m*-ClC_6H_4COOH and H_2O were obtained from the literature. The pK_a values of $Ph_2C(CN)OH$, $Ph_2C(CO_2Me)OH$, and *t*-BuOH have been calculated by employing the pK_a of CH_3OH (ref 30), $\rho_I = -8.2$ and σ_I values of +0.1 (Ph), +0.56 (CN), 0.34 (CO_2Me), and −0.05 (Me) (ref 31). The pK_a of the alcohol (FlEt-4a-OH) derived from the 4a-hydroperoxyflavin (**2**) cannot be determined by titration due to its rearrangement (ref 32). A reasonable model for FlEt-4a-OH is (Ph(Et)N)(H_2NCO)(HCONHCO)C–OH. The σ_I values employed which give a pK_a of 9.4 are 0.17 (PhNEt) (calculated from tabulation of ref 33), 0.27 ($CONH_2$, ref 31), and 0.31 (calculated from tabulation of ref 31).

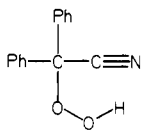
(30) Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 792.
(31) Charton, M. *J. Org. Chem.* **1964**, *29*, 1222.
(32) (a) Bruice, T. C.; Chan, T. W.; Taulane, J. P.; Yokoe, I.; Elliott, D. L.; Williams, R. F.; Novak, M. *J. Am. Chem. Soc.* **1977**, *99*, 6713. (b) Iwata, M.; Bruice, T. C.; Carrell, H. L.; Glusker, J. P. *J. Am. Chem. Soc.* **1980**, *102*, 5036.
(33) Hine, J. "Structural Effects on Equilibria in Organic Chemistry"; Wiley: New York, 1975.

Table IV. Comparison of the Second-Order Rate Constants [Relative to Those for **2**] for the Hydroperoxide Oxidation of I^- (k_I), S-Oxidation of Thioxane (k_S), and N-Oxidation of *N,N*-Dimethylbenzylamine (k_N)[a]

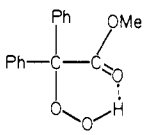
substrate no.	substrate structure	k_I	k_S	k_N
1		7.6×10^2	7.4×10^2	$(2.14 \times 10^3)^d$
2		1.0 ($6.0\ M^{-1}\ s^{-1}$)	1.0 ($0.12\ M^{-1}\ s^{-1}$)	1.0 ($0.12\ M^{-1}\ s^{-1}$)
3		3×10^{-1}	5.7×10^{-2} [a]	8.6×10^{-2} [b]
4		5.6×10^{-2}	8.7×10^{-1}	3.3×10^{-1}
5		5.5×10^{-2}	3.2×10^{-2}	1.1×10^{-2}
6		9.0×10^{-3}	9.2×10^{-4}	1.2×10^{-4}
7	H_2O_2	1.0×10^{-3}	1.4×10^{-4} [c]	2.8×10^{-5}
8		1.0×10^{-3}	5.8×10^{-5} [c]	$>1 \times 10^{-6}$

[a] With the exception of the special cases in footnotes *b* and *c*, the relative rate constants k_I pertain to EtOH solvent buffered with acetic acid and sodium acetate (see Experimental Section) while k_S and k_N values were determined in *t*-BuOH. [b] The values of k_N and k_S for 3 were obtained from kinetic measurements with 2 and 3 in DMF since 3 is of limited stability in *t*-BuOH.[39] [c] The values of k_S for 7 and 8 were obtained by comparisons of rate constants of 7 and 8 with the rate constants determined for 4a-hydroperoxy-5-trideuteriomethyl-3-methyllumiflavin in methanol.[40] [d] Value extrapolated from the plot of log k_S vs. log k_N (Figure 8).

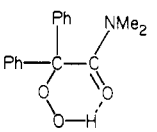
pursued by Rebek and collaborators.[5] Of the many hydroperoxides examined by Rebek, the following four proved to be most effective:



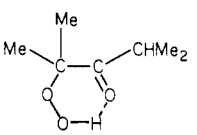
4



5

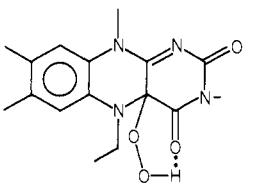


9

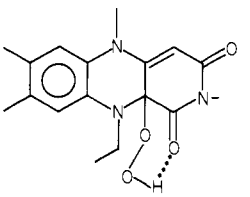


10

We have chosen, for this study, the hydroperoxides **4** and **5**. These have been reported to be the most reactive. Rebek attributed the effectiveness of **5**, **9** and **10**, in the epoxidation of olefins, to an internal hydrogen bond (as shown) between the hydroperoxy hydrogen and the α-substituent.[34] (In the instance of the most effective agent **4**, internal hydrogen bonding could only occur to the π electrons of the cyano group. The contribution of any hydrogen bonding of this nature to the driving force for epoxidation may be questioned.) Rebek has proposed that the reactivity of 4a-hydroperoxyflavins is due to a similar intramolecular hydrogen bonding of hydroperoxy hydrogen to the amide carbonyl at the 4-position of the isoalloxazine ring. There are included among the hydroperoxides that we have investigated not only the 4a-hydroperoxide of 3-methyllumiflavin (**2**) but also that of 1-carba-1-deaza-3-methyllumiflavin (**3**) and **6**. Examination of Stuart-Briegleb models of **4** and **5** and **2**, **3**, and **6** does not indicate



2



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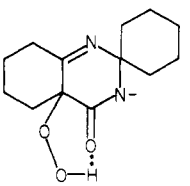


6

that hydrogen bonding in the latter three would be any less favorable than in the case of the first two. Also, the approach of the π cloud of 2,3-dimethyl-2-butene to the terminal oxygen of the hydroperoxy substituents of **2**–**6** is not influenced by steric effects.

(34) Rebek, J., Jr.; McCready, R. *J. Am. Chem. Soc.* **1980**, *102*, 5602.

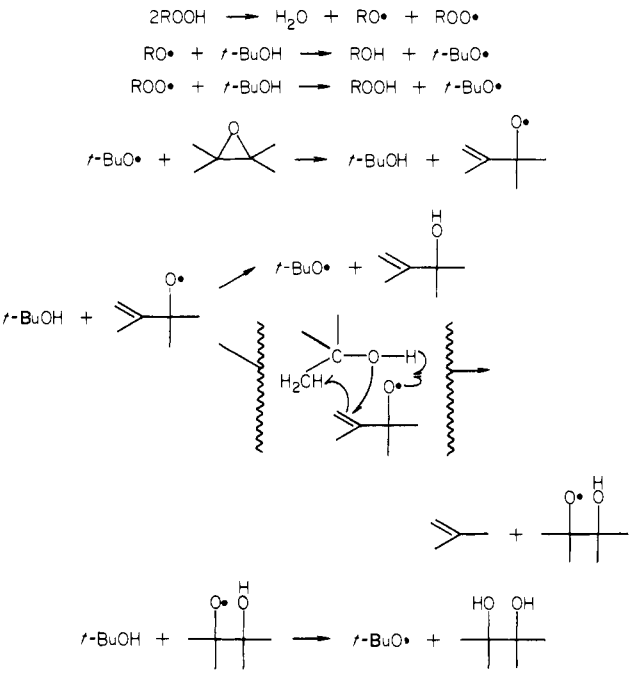
The epoxidation of 2,3-dimethyl-2-butene by 4, 5, and 6 is dependent upon the solvent employed, the concentration of hydroperoxide, and the presence or absence of O_2. These features will be discussed first, followed by a consideration of the results obtained under the pseudo-first-order restraints of [olefin] ≫ [hydroperoxide] and O_2 and trace metal free conditions. Results with the flavin peroxides **2** and **3** will be discussed separately. The following pertains to the disposition of olefin in the presence of **6**. In $CHCl_3$ solvent (aerobic) at 60 °C, a solution initially 0.33 M in both **6** and alkene contained, after 24 h, 48% yield of epoxide. Replacement of $CHCl_3$ by aerobic *t*-BuOH (reactants at 1×10^{-2} M) resulted in a slow sigmoidal disappearance of **6** (an autocatalytic reaction), and even after 8 days when [**6**] had decreased by ~50%, there was present only 2% epoxide. When aerobic DMF was used as solvent (initial [**6**] = 6.4×10^{-3} M, [alkene] = 0.1–0.8 M), the formation of epoxide was found to increase with [olefin] and after 24 h there was found to be present greater than 100% yield of epoxide based upon initial [**6**]. These cursory observations, on O_2 containing solutions of **6** and alkene, suffice to show that solvent has a great effect upon epoxidation, an autocatalytic decomposition of hydroperoxide may occur, and an O_2 autoxidation of olefin may also occur to yield epoxide, and the rate of this autocatalytic reaction is markedly dependent upon solvent.

When the reaction of olefin with **5** was studied in *t*-BuOH solvent in the presence or absence of O_2 there was found to be an epoxidation of the olefin. If the concentration of hydroperoxide was high ([**5**] = 3.33×10^{-1} M), the epoxide was subsequently converted to pinacol and allyl alcohol (Figure 6). At any time during the course of reaction, the total yields of epoxide, pinacol, and allyl alcohol equaled the concentration of hydroperoxide that had reacted. In separate experiments, under both aerobic and anaerobic conditions, it was shown that **5** catalyzes the disappearance of epoxide but it is not appreciably consumed. Thus, **5** epoxidizes olefin in a reaction first order in **5** and olefin, and **5** acts as an autocatalytic agent for conversion of epoxide to pinacol and allyl alcohol. The initiation of the autocatalytic reaction is greater than first order in **5**. This was shown to be so from the finding that at lower concentrations of **5**, the epoxide is completely stable. Further, the autocatalytic agent derived from **5** arises from both an O_2-dependent and O_2-independent path. Thus, consumption of epoxide exhibits a shorter lag phase in the presence of O_2 than in its absence. If $CHCl_3$ is employed as the solvent, **5** epoxidizes olefin but does not act as an autocatalytic agent for epoxide decomposition. Presumably *t*-BuOH solvent supplies the radical chain carrier or $CHCl_3$ quenches the chain carrier. The overall reaction is depicted in Scheme I. Though the elucidation of the detailed mechanism for conversion of epoxide to allyl alcohol and pinacol is beyond the ambitions of the present study, the mechanism of Scheme II appears plausible. Ample evidence exists for alkyl hydroperoxide decomposition being greater than first order in hydroperoxide.[35]

The reaction of **5** with olefin (*t*-BuOH, 30 and 60 °C) was found to be first order in both reactants under the pseudo-first-order conditions of [olefin] = 0.8, 0.4, and 0.1 M ≫ [**5**] = 6.4×10^{-3} M. The second-order rate constants for conversion of the hydroperoxide **5** to the corresponding alcohol and for conversion of olefin to epoxide were identical. The alcohol derived from the hydroperoxide was formed in 95% yield, however, the yield of epoxide was between ~60% and ~70%. Experiments with the hydroperoxide **4** were much the same as those obtained with **5**. The yield of epoxide was found to be ~72 ± 2% at initial [olefin] = 0.1–0.8 M. The competing parallel reactions of eq 10 and 11 pertain. Comparisons of eq 10 and 11 show that the reactivity of **4** with olefin to yield epoxide exceeds that of **5** by a factor of ~9. In the oxidation of thioxane and *N,N*-dimethylbenzylamine, **4** is 27 ± 1.5 times more reactive than is **5** (Table IV; Figure 9).

At 60 °C under strictly anaerobic conditions (*t*-BuOH solvent) or under aerobic conditions, there could be detected no reaction of **6** with alkene. After a lag period (5 days in the absence of O_2), **6** began to disappear from solution by way of an autocatalytic reaction. No epoxide was formed. The values of k_1, k_S, and k_N for **6** are but 0.17×, 0.03×, and 0.01× the like constants for **5**, respectively. The inability to detect epoxidation by **6** may simply reflect the very small rate constant that might be anticipated for the epoxidation reaction.

Scheme II



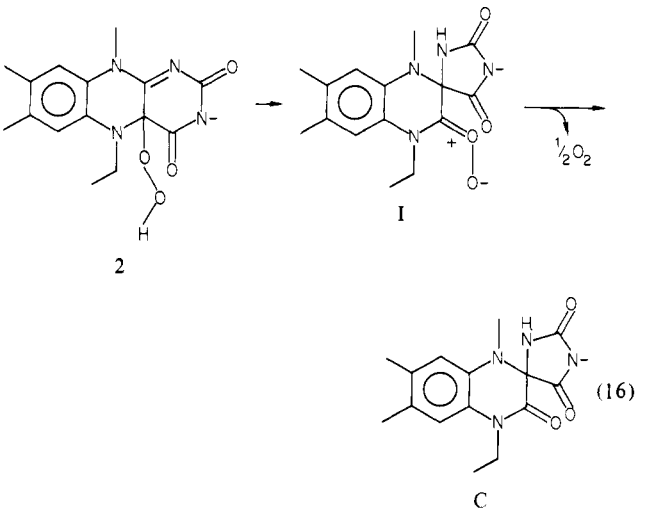
Evidence Could Not Be Obtained for the Bimolecular Reaction between 2,3-Dimethyl-2-butene and the 4a-Hydroperoxyflavins 2 and 3. In dry and anaerobic solvents, **2** (*t*-BuOH or DMF) and **3** (DMF) decompose slowly in an exponential manner. The addition of alkene to 0.8 M does not increase the rates of disappearance of **2** or **3** from solution. Epoxide could not be detected in reaction solutions at t_∞. If one is to compare the epoxidation of alkene by **4** and **5** to the experimental results with the flavin hydroperoxides **2** and **3**, then it is essential to take into account the fact that **2** and **3** decompose in solution whereas **4** and **5** are much more stable. Does lack of epoxidation by **2** and **3** simply result from the inability of the epoxidation reaction to compete with the rates of decomposition of **2** and **3**? At 0.8 M 2,3-dimethyl-2-butene, the pseudo-first-order rate for epoxidation of alkene by **4** is 4.1×10^{-5} s^{-1} (eq 11) and the rate of decomposition of **2** is 1.75×10^{-4} s^{-1}. If the rate for epoxidation by **2** equaled that for **4**, then it would follow that at t_∞ **2** should provide 29% epoxide. The reaction of **2** with thioxane and *N,N*-dimethylbenzylamine exceeds, in rate, the reaction of **4** with these reagents by 1.1 and 3.0, respectively. If **2** should possess the same rate advantage in the epoxidation reaction, then the percentage yield of epoxide with **2** would be 33% and 87%. Similar considerations with **2** and **5** predict that, if the epoxidation rate for **2** were equal to that of **5**, a 3% yield of epoxide would have been detected and, if **2** possessed the kinetic advantage in epoxidation over **5**, as shown in the reaction with thioxane and *N,N*-dimethylbenzylamine, then between 95% and 100% epoxide would have been formed. From these considerations of experiments in *t*-BuOH, one may conclude that the free-energy relationships (Figures 8 and 9) of hydroperoxides reacting with I^-, :S<, and :N< do not apply to the epoxidation of 2,3-dimethyl-2-butene in absolute *t*-BuOH under anaerobic conditions.

Preparative epoxidations with hydroperoxides are often reported in $CHCl_3$ as the solvent.[5] Attempts were made to realize the epoxidation of 2,3-dimethyl-2-butene by **2** in $CHCl_3$. The decomposition of **2** is rapid in $CHCl_3$ (30 °C), and both the rate constants and the products of decomposition are markedly dependent on the "purity" of the solvent (see Results). The use of a $CHCl_3$ sample of high purity does not help. The formation of

(35) Hiatt, R.; McCarrich, T. *J. Am. Chem. Soc.* **1975**, *97*, 5234.

epoxide (Table III) to 31% under anaerobic conditions is probably due to formation of epoxide by reaction of alkene with a decomposition product of **2**. The probability of this being so stems from the lack of effect of olefin on the rate constant for disappearance of **2** from solution. Also, the direct transfer of an oxygen from **2** to olefin to form epoxide should produce the flavin-derived alcohol 4a-FlEtOH in yield comparable to that of epoxide (eq 12). This was not found to be the case (Table III). Though 4a-FlEtOH decomposes in the chloroform solvent employed, the rate constant for this reaction is sufficiently slow to allow a reasonable determination of the percent yield of 4a-FlEtOH. The principal (90%) decomposition product of **2**, in these experiments, was the 10a-spirohydantoin C. The formation of 10a-spirohydantoins as decomposition products of flavin 4a-hydroperoxides have been noted previously,[36,32b] and their structures have been established by X-ray crystallography.[32b] Spirohydantoin C does not form from 4a-FlEtOH in $CHCl_3$ so that the high yield of C determined in the epoxidation reactions assures the low yield of 4a-FlEtOH and proves that the epoxide does not arise by direct reaction of **2** and olefin (eq 12). Mager reports that a suspension of **2** in H_2O yields C and molecular oxygen (stoichiometry not reported) and proposed the reaction to occur through the carbonyl oxide I (eq 16).[36] The driving force for the formation of I from **2** is not apparent, but if the proposal of the formation of I should be correct, it would supply an epoxidizing species. As previously noted, the hydroperoxide **2** does decompose in $CHCl_3$ by a kinetically apparent two-step mechanism as required by Mager's proposed reaction. The rate constants associated with neither step is, however, changed by the presence of alkene. This feature does not support I as an epoxidation agent in the decomposition of **2**. Perhaps epoxidation occurs by reaction of olefin with oxygen liberated on decomposition of **2** (eq 16). One might note that the yield of epoxide is doubled when **2** and alkene are combined in $CHCl_3$ in the presence of air (Table III).

4a-Hydroperoxylflavins Are the Only Known Hydroperoxides Which Exhibit a Chemiluminescent (CL) Oxidation of Aldehydes.[37]



Thus, *no light* emission is noted when **4**, **5**, and **6** are allowed to react with *p*-tolualdehyde. The reaction of **2** with *p*-tolualdehyde in absolute *t*-BuOH provides CL with $\Phi \cong 5 \times 10^{-4}$.[38]

Acknowledgment. This work was supported by grants from the National Institutes of Health and the National Science Foundation.

Registry No. **1**, 937-14-4; **2**, 59587-26-7; **3**, 79075-90-4; **4**, 5233-67-0; **5**, 57272-44-3; **6**, 30152-69-3; **7**, 7722-84-1; **8**, 75-91-2; iodide, 20461-54-5; thioxane, 15980-15-1; *N,N*-dimethylbenzylamine, 103-83-3; 2,3-dimethyl-2-butene, 563-79-1; *p*-tolualdehyde, 104-87-0.

(36) Mager, H. I. X. *Tetrahedron Lett.* **1979**, 3549.

(37) Kemal, C.; Bruice, T. C. *J. Am. Chem. Soc.* **1977**, *99*, 7064.
(38) Shepherd, P. T.; Bruice, T. C. *J. Am. Chem. Soc.* **1980**, *102*, 7774.
(39) Ball, S.; Bruice, T. C. *J. Am. Chem. Soc.* **1981**, *103*, 5494.
(40) Kemal, C.; Chan, T. W.; Bruice, T. C. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 405.

Conformational Energies of Fenfluramine: Graphical Representation of Energy as a Function of Four Conformational Variables

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Abstract: We have investigated the low-energy conformations of the protonated form of fenfluramine [*m*-(trifluoromethyl)-*N*-ethylamphetamine] using CAMSEQ.[1-3] All four of the torsion angles in the (*N*-ethylamino)propyl side chain have been examined. The results are presented as (a) τ_1–τ_2 energy maps for both solution and vacuum, the in vacuo map shaded to show areas corresponding to particular τ_3–τ_4 conformations, and (b) "three-dimensional" representations illustrating variation in energy as a function of three variables, the fourth variables taken as a parameter. The in vacuo minimum-energy conformation found for fenfluramine has $\tau_1 = 240°$, $\tau_2 = 70°$, $\tau_3 = 300°$, and $\tau_4 = 300°$, and the barrier between the minimum-energy conformation and the extended form ($\tau_2 = 180°$) is ≈6.5 kcal/mol. Conformation changes in τ_1–τ_2 are shown to be coupled with changes in τ_3–τ_4. In aqueous solution the extended form of fenfluramine is found to be the more stable by ≈27 kcal/mol.

Fenfluramine is of interest pharmacologically because it functions as an appetite depressant in animals without simultaneously acting as a psychomotor stimulant.[4-11] Thus, it has potential use as an anorectic agent free from "drug abruse" dif-

(1) Weintraub, H. J. R. Ph.D. Dissertation, Case Western Reserve University, Cleveland, OH, 1975.

(2) Weintraub, H. J. R.; Hopfinger, A. J. *Int. J. Quantum Chem., Quantum Biol. Symp.* **1975**, *No. 2*, 203–208.

0002-7863/83/1505-2463$01.50/0