Leaving Group Tendencies and the Rates of Mono-oxygen Donation by Hydrogen Peroxide, Organic Hydroperoxides, and Peroxycarboxylic Acids

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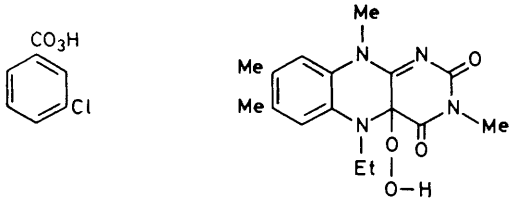
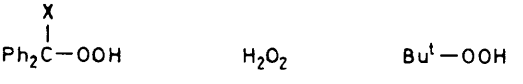
The log of the second-order rate constants for the sulphoxidation of thioxan, *N*-oxidation of *N,N*-dimethylbenzylamine, and oxidation of I^- to I_2 are linearly related to the pK_a of YOH when the mono-oxygen donors YOOH represent peroxycarboxylic acid, organic hydroperoxides, and hydrogen peroxide (the mechanism of mono-oxygenations by the biologically important 4a-hydroperoxyflavins find explanation through this correlation).

The transfer of an oxygen atom from hydroperoxides to organic substrates is of considerable interest to both organic and biological chemists.[1-3] The study[3] of 4a-hydroperoxy-5-alkylflavins and other electron-deficient organic hydroperoxides[2,4] has shown that organic hydroperoxides may possess considerable potential as mono-oxygen transfer agents in systems which do not require metal ions or other catalysts. The relationship of the mechanisms for hydroperoxide mono-oxygen and percarboxylic acid mono-oxygen transfers requires attention.

The oxygen donors *m*-chloroperbenzoic acid (**1**), 4a-hydroperoxy-5-ethyl-3-methyl-lumiflavin (**2**), diphenylhydroperoxyacetonitrile (**3**), methyl diphenylhydroperoxyacetate (**4**),hydrogen peroxide (**5**), and t-butyl hydroperoxide (**6**) have now been studied. Of these (**1**) is a peroxycarboxylic acid, (**2**) a close analogue of the 4a-hydroperoxyflavins generated at the active site of the flavin mono-oxygenase enzymes, and (**3**) and (**4**) (obtainable in high purity) have been found by Rebek[2] to be among the most useful alkyl hydroperoxides for the epoxidation of olefins. The reactions studied were the sulphoxidation of thioxan, the *N*-oxidation of *N,N*-dimethylbenzylamine, and the oxidation of I^- to I_2. The reactions with thioxan and *N,N*-dimethylbenzylamine were carried out in absolute Bu^tOH under an N_2 atmosphere and the oxidations of I^- in 95%



(**1**) (**2**)



(**3**) X = CN
(**4**) X = CO_2Me
(**5**)
(**6**)

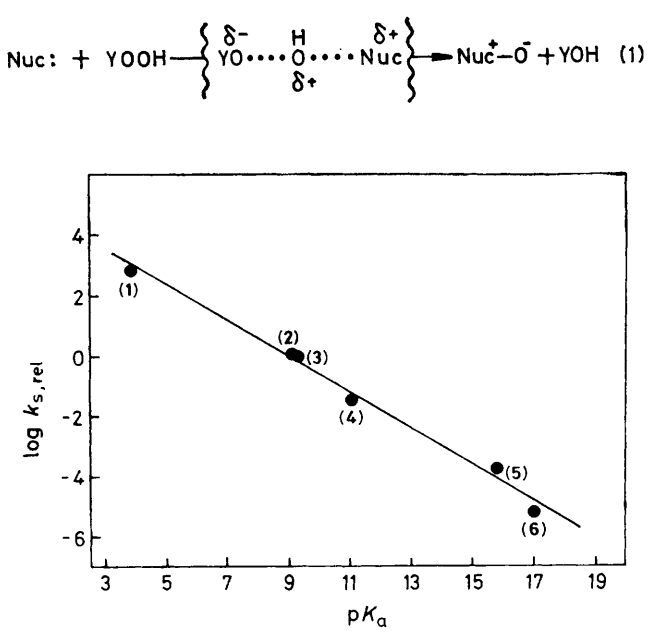
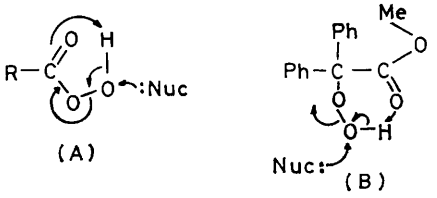


Figure 1. A plot of the log of the second-order rate constants [relative to the rate constant for (**2**)] for sulphoxidation of thioxan ($k_{s,rel}$) by the YOOH species *vs.* the pK_a of YOH species. (Solvent abs. Bu^{t}OH for rate constants and H_2O for pK_a values, at 30 °C.)

EtOH (30 °C).[5] All reactions were found to be first-order in substrate and hydroperoxide. Plots of the log of the second-order rate constants for sulphoxidation of thioxan (k_S) *vs.* the log of the second-order rate constants for *N*-oxidation of *N*,*N*-dimethylbenzylamine and *vs.* the log of the second-order rate constants for I^- oxidation were linear with slopes of 1.0 and 1.1 respectively. These results establish that the free energies of activation for mono-oxygen donation, from the peroxycarboxylic acid and the hydroperoxides, are equally dependent on changes in the structures of YOOH with nucleophiles as divergent as the negatively charged, polarizable I^-, the neutral, less polarizable, and non-basic dialkyl sulphide, and the neutral but basic tertiary amine.

The common mechanism, for the reactions under consideration, has been suggested to involve nucleophilic displacement upon the β-hydroperoxy-oxygen atom (equation 1).[6] Figure 1 is a plot of the log of the relative [to (**2**)] second-order rate constant for the sulphoxidation of thioxan by the YOOH compounds *vs.* the pK_a values† of YOH. The slope of the correlation line in Figure 1 ($\beta_{lg} = -0.6$) relates to the fractional negative charge on the leaving α-oxygen of the YO moiety in the transition state (T.S.) 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[6] as +0.2 which supports an early T.S. The position of the proton in the T.S. is not certain. For the sulphoxidation of thioxan in absolute dioxan by Bu^{t}OOH, the kinetic order in Bu^{t}OOH has been reported as two.[7] In all the present studies in Bu^{t}OH and EtOH solvents the kinetic orders in YOOH systems are one.[5,6] Perhaps in the aprotic solvent, the second Bu^{t}OOH molecule acts as a proton transfer agent and this role is also played by Bu^{t}OH and EtOH solvents. 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 (A and B),[2] does not provide a driving force for mono-oxygen 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) peroxycarboxylic acids, organic hydroperoxides, and hydrogen peroxide compose a common series of YOOH oxygen donors, the advantage of peroxycarboxylic 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 to 9.5.

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† 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, whilst those of $Ph_2C(CN)$-OH, $Ph_2C(CO_2Me)OH$, and Bu^{t}OH have been calculated employing the pK_a of MeOH (ref. 8), $\rho_I = -8.2$, and σ_I values of +0.1 (Ph), +0.56 (CN), +0.34 (CO_2Me), and −0.05 (Me), (ref. 9). The pK_a of the alcohol (FlEt-4a-OH) corresponding to the 4a-hydroperoxyflavin (**2**) cannot be determined by titration owing to its rearrangement (ref. 10). A reasonable model for FlEt-4a-OH is [Ph(Et)N](H$_2$NCO)(HCONHCO)C-OH. The σ_I values employed which give a pK_a of 9.4 are 0.17 (PhNEt) (calc. from tabulation of ref. 11), 0.27 ($CONH_2$, ref. 9), and 0.31 (calc. from tabulation of ref. 9).

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