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THE MECHANISTIC MODE OF OXIDATION OF SUBSTITUTED N,N-DIMETHYLANILINES, THIOANISOLES, AND METHYL PHENYL SULFOXIDES BY 5-ETHYL-4a-HYDROPEROXY-3-METHYL-LUMIFLAVIN (4a-FlEt-OOH)

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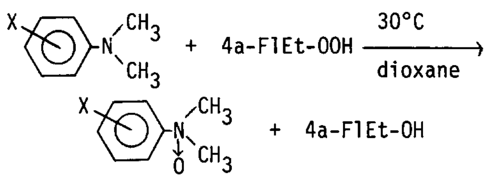
Summary: In the oxidation of the title compounds, 5-ethyl-4a-hydroperoxy-3-methyl-lumiflavin (4a-FlEt-OOH), was found to be an electrophilic oxidant similar to m-chloroperoxybenzoic acid. However, the stereoselectivity of the oxidation of cyclic sulfides to the corresponding sulfoxides by 4a-FlEt-OOH was less pronounced than that of the oxygenation with flavin-containing monooxygenase.

There are two different modes for the oxidation of amines and organosulfur compounds, i.e. electrophilic and nucleophilic.[1)] Electrophilic oxidation may proceed either by direct electrophilic attack of peroxidic oxygen on an electron-rich nitrogen or sulfur atom or by initial rate-determining electron transfer from the hetero-atom to the oxidant and subsequent oxygenation. The enzymatic oxygenation is not exceptional. The oxygenation of sulfides[2a,2b)] and sulfoxides[3)] by the aid of cytochrome P-450 and also with enzyme model systems,[4)] has been found to proceed via the two step mechanistic route involving the rate-determining electron transfer. In connection with our study on the enzymatic oxygenation of both tertiary amines and sulfides with the flavin-containing monooxygenase which is believed to be an enzyme which functions as an electrophilic oxidant,[5)] we have carried out the kinetic study on the oxidations of N,N-dimethylanilines to the N-oxides, of thioanisoles to corresponding sulfoxides and of these sulfoxides to the sulfones with a model enzyme system for flavin-containing monooxygenase, i.e.,4a-FlEt-OOH in dioxane.

4a-FlEt-OOH was synthesized by the known methods,[6)] while kinetic runs were conducted with a solution (3 ml) of 4a-FlEt-OOH containing substituted N,N-dimethylanilines (0.677 M) or substituted thioanisoles (0.133 M) or substituted methyl phenyl sulfoxides (0.555 M) in dry dioxane in a UV cell which was incubated at 30°C for 5 min. To this was added 50 μl solution of 4a-FlEt-OOH (1.5 x 10^{-3}M) in dry dioxane and the disappearance of absorption due to 4a-FlEt-OOH at 365 nm was monitored and pseudo first order rate constants were obtained at various concentrations of the amines, sulfides, and sulfoxides. Reaction products were analyzed; for examples, the N-oxide from the reaction of N,N-dimethylaniline with 4a-FlEt-OOH in dioxane was analyzed by the method of Ziegler and Pettit.[7] Analyses of the sulfoxide and the sulfone formed in the reactions of thioanisole and methyl phenyl sulfoxide with 4a-FlEt-OOH were carried out by initial isolation of products through column chromatography and subsequent identification of them by measurements of their IR spectra and m.p(s).

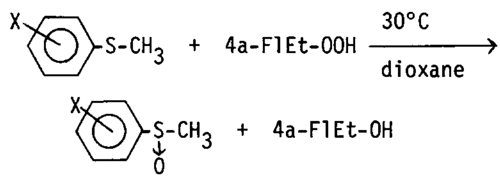
The rates were found to be of 2nd order in the 4a-FlEt-OOH and the substrate used. The effects of substituents on the rate of the reaction of substituted N,N-dimethylanilines, substituted thioanisoles and substituted methyl phenyl sulfoxides with 4a-FlEt-OOH were examined. The second order rate constants are listed in Table 1-3.

Table 1. Second order rate constants of the oxidation of substituted N,N-dimethyl-anilines with 4a-FlEt-OOH



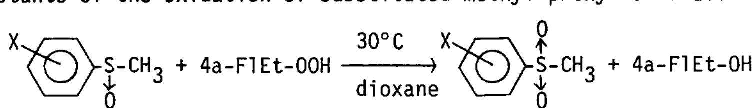
X	$k_2 x 10^4$ ($l \cdot mole^{-1} \cdot sec^{-1}$)
p-CH_3O	12.3
p-CH_3	7.76
(m-CH_3	1.89)
H	4.97
p-Cl	2.48
m-Cl	1.98

Table 2. Second order rate constants of the oxidation of substituted thioanisoles with 4a-FlEt-OOH



X	$k_2 x 10^2$ ($l \cdot mole^{-1} \cdot sec^{-1}$)
p-CH_3O	5.83
p-CH_3	2.85
m-CH_3	1.78
H	1.74
p-Cl	0.830
m-Cl	0.567
p-Br	0.781

Table 3. Second order rate constants of the oxidation of substituted methyl phenyl sulfides with 4a-FlEt-OOH

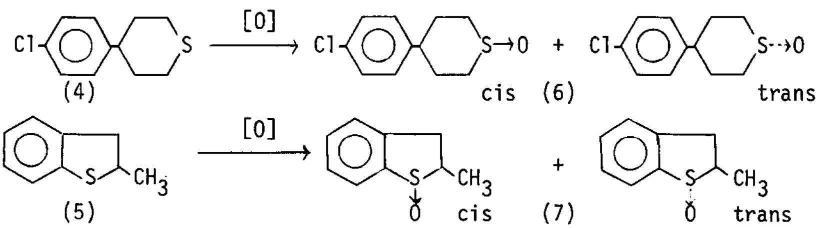


X	$k_2 x 10^4$ ($l \cdot mole^{-1} \cdot sec^{-1}$)	X	$k_2 x 10^4$ ($l \cdot mole^{-1} \cdot sec^{-1}$)
p-CH_3O	13.5	H	5.54
p-CH_3	7.46	p-Cl	2.67

The logarithms of these rate constants were nicely correlated with the Hammett σ-values (ρ = -1.23 for N,N-dimethylanilines, ρ = -1.47 for thioanisoles and ρ = -1.32 for methyl phenyl sulfoxides respectively). The electron-releasing substituent accelerates the reaction, as in the similar electrophilic oxidation of thioanisoles with hydrogen peroxide in ethanol (ρ = -1.13) by Modena et al.[8] All these results, along with recent works of Ball and Bruice and of Miller,[9] seem to reveal clearly that the oxidation of these amines, thioanisoles and aryl methyl sulfoxides with 4a-FlEt-OOH proceeds via the rate-determining electrophilic attack of the hydroperoxide on the electron-rich hetero-atoms, i.e. nitrogen and sulfur, but not through the two step mechanistic route involving the rate-determining electron-transfer from the hetero-atoms, which has been found to be the case in the oxygenation with the cytochrome P-450[2] and its enzyme model systems.[4]

A few selected cyclic sulfides were oxidized with 4a-FlEt-OOH and the ratios of the cis/trans isomers were determined by NMR spectra using a shift reagent, $Eu(DPM)_3$ or by gass chromatography. The results and related data on the oxidation of the sulfides are listed in Table 4.

Table 4. Comparison of the stereoselectivity of the oxidation of 4-p-chlorophenylthiane (4) and 2-methyl-2,3-dihydrobenzo[b]thiophene (5) with various oxidants.



Oxidants	(6) cis	(6) trans	(7) cis	(7) trans
4a-FlEt-OOH	33	66	18	82
FAD monooxygenase/O_2/NADPH[5]	6	94	92	8
Cyt. P-450/O_2/NADPH	34[10]	66[10]	19[2b]	81[2b]
m-CPBA	33[10]	67[10]	47[2b]	53[2b]
$NaIO_4$	76[11]	24[11]	48[2b]	52[2b]

Table 4 shows that the cis/trans ratio of the oxidation of (4) with 4a-FlEt-OOH is very close to those with m-CPBA and cyt. P-450 suggesting again the electrophilic nature of 4a-FlEt-OOH, but different from that found in the real enzymatic oxygenation of (4) in which the stereoselectivity is markedly high.[5]

Inspection of data in Table 4 undoutedly reveals that the ratio of cis and trans isomers formed in the oxidation of both (4) and (5) by 4a-FlEt-OOH is the lowest among the nonenzymatic oxidations of these sulfides, however, the stereospecificity as depicted by the cis/trans ratio is quite different from that found in the real enzymatic oxygenation of (5) with the flavin-containing monooxygenase of which the stereochemistry is controlled by the specific binding sites. While the electrophilic oxidation of most organic sulfide takes place predominantly on the less hindered side of the sulfide,[11] in the oxygenation with FAD-containing monooxygenase specific binding of the substrate in the enzyme cavity seems to be quite important in controlling the stereochemistry of the oxygenation.

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