Electronic and Steric Effects in Oxidations by Isoalloxazine 4a-Hydroperoxides

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Abstract: The reactivity of N^5-ethyl-N^{10}-(2,6-dimethylphenyl)-4a-hydroperoxy-N^3-methylisoalloxazine (**2a**) with para-substituted thioanisoles, alkyl phenyl sulfides, dialkyl sulfides, and benzylbutylamines has been determined. The transition state for reaction with thioanisoles has some single-electron-transfer (SET) character while the transition state for dialkyl sulfides lies closer to the S_N2 extreme. Comparisons with other work illustrate the problems associated with determining SET vs. S_N2 transition states on the basis of electronic, solvent, and/or product studies alone. The N^3,N^{10}-dimethylisoalloxazine N^5-oxide (**5**) does not effect oxidation of methyl 4-methylphenyl sulfide in acetic acid. Therefore, the N^5-oxide is not a viable intermediate in the oxidation of sulfides by FAD-containing monooxygenase (FADMO). The reactions with alkyl phenyl sulfides, dialkyl sulfides, and benzylbutylamines show a moderate steric effect which is, however, more characteristic of the oxidation reaction in general than it is of steric features of **2a**. Nonetheless, steric effects attending oxidations by FADMO can be at least partially explained by the steric effect associated with oxidations by flavin hydroperoxide.

Because of its ability to oxidize a variety of nitrogen- and sulfur-containing functional groups in xenobiotic substances, FAD-containing monooxygenase (EC 1.14.13.8, FADMO) is a mammalian enzyme of considerable interest.[1,2] The active site responsible for oxidation has been established as a 4a-hydroperoxyriboflavin.[3,4] Early model studies with 4a-hydroperoxyisoalloxazines (FlOOH) focused on the oxidation of nitrogen-containing substrates.[5] In 1982 we reported preliminary results on the reactivity of thioanisoles with a 4a-hydroperoxyisoalloxazine.[6] Subsequently, several groups have looked at similar sulfide oxidations.[7,8]

At the extremes there are two possible mechanisms for the oxidation of sulfides by a hydroperoxide. One involves nucleophilic attack of sulfur on the electrophilic oxygen to give trivalent sulfur[9] (S_N2 mechanism). This might occur with or without concerted proton transfer. The second involves single-electron transfer to give a divalent sulfur cation radical (SET mechanism). That there may be a continuum between these two extremes was intimated by Bruice in 1980: "The mechanisms of the N- and S-oxidation of [sic] 4a-FlOOH are best ascribed to nucleophilic displacements (perhaps with a radical character)".[10] It has been suggested by Pross that an S_N2-SET continuum has general significance.[11] Nonetheless, the possibility that transition states for sulfide oxidations might lie between the extremes has for the most part been ignored. Also, it has not been considered that cleavage products can arise via elimination from an intermediate (**1**, see Scheme I) from an S_N2 process.

Little is known about steric effects on the activity of FADMO. It has been reported that "sterically hindered amines" are not oxidized by FADMO, but specific examples were not given.[12]

Table I. Rates of Reaction of **3** with **2a** in *t*-BuOH at 30 °C

X[c]	rate,[a] M^{-1} s^{-1}	σ^b	σ^{+b}
CN	0.003 07	0.70	0.70
benzoyl	0.007 81	0.46	0.46
Cl	0.019 8	0.24	0.11
H	0.036 3 ± 0.003	0	0
CH_3	0.076 2	−0.14	−0.31
NHAc	0.081 5	−0.09	−0.6
OCH_3	0.103	−0.28	−0.78
NH_2	0.497	−0.57	−1.3

[a] With the exception of thioanisole, rates are the result of one determination. [b] Reference 19. [c] Para substituent on **3**.

Table II. Rates of Reaction of R_2S

R	rate, M^{-1} s^{-1}	rel rate	rel rate[a]	rel rate[b]
Me	0.470 ± 0.037[c]	53		
Et	0.276 ± 0.028[c]	31	111	
i-Pr	0.0375 ± 0.0034[c]	4.2	17	
t-Bu	0.008 94 ± 0.000 53[c]	1	1	
Et	0.36 ± 0.01[d]	33		0.77
t-Bu	0.0110 ± 0.0015[d]	1		0.82

[a] With singlet oxygen in MeOH (ref 38). [b] *t*-BuOH/dioxane. [c] With **2a** in *t*-BuOH, 30 °C. [d] With **2a** in dioxane, 30 °C.

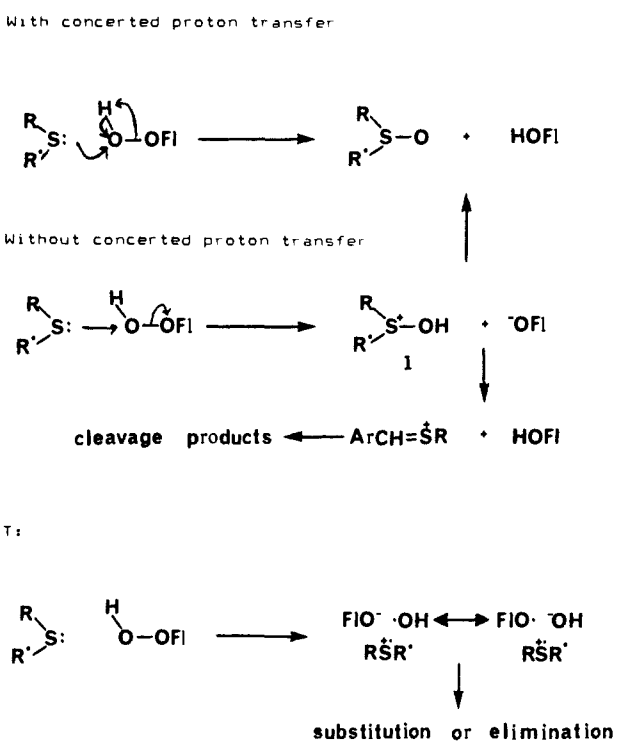
Moreover, it has been suggested that steric effects are responsible for the lack of oxidation of isothioureas by FADMO.[1] Finally, for some sulfur-containing pesticides, "...structural changes on the thioether moiety that affect the oxidation potential and/or increase steric hindrance of the sulfur atom ... apparently affect enzyme–substrate binding and decrease the rate of sulfoxidation."[13] It was our thought that steric effects could not only manifest themselves in enzyme–substrate interactions but also on the rate of reactivity of FlOOH with the substrate.

For the most part the literature indicates that steric effects have little influence on the reactivity of hydroperoxides. For example, in the oxidation of triphenylphosphine, the relative rates of reaction for *n*-BuOOH/*t*-BuOOH were only 3.5:1 in hexane at 21.5–22.5 °C and 2.1:1 in ethanol at 40 °C.[14] Qualitative work with phosphites and 1,1-diphenylpropyl hydroperoxide showed triethyl phosphite to be more reactive than isopropyl phosphite.[15] Finally,

(1) Ziegler, D. M. In *Enzymatic Basis of Detoxication*; Jakoby, W. B., Ed.; Academic: New York, 1980; Vol. 1, pp 201–227.
(2) Poulsen, L. L. In *Reviews in Biochemical Toxicology*; Hodgson, E., Bend, J. R., Philpot, R. M., Eds.; Elsevier/North Holland: New York, 1981; pp 33–49.
(3) Ziegler, D. M.; Poulsen, L. L. *J. Biol. Chem.* **1979**, *254*, 6449–6455.
(4) Beaty, N. B.; Ballou, D. P. *J. Biol. Chem.* **1979**, *254*, 4619–4625.
(5) (a) Ball, S.; Bruice, T. C. *J. Am. Chem. Soc.* **1980**, *102*, 6498–6503. (b) Ball, S.; Bruice, T. C. *J. Am. Chem. Soc.* **1979**, *101*, 4017–4019.
(6) Miller, A. *Tetrahedron Lett.* **1982**, *23*, 753–757.
(7) Oae, S.; Asada, K.; Yoshimura, T. *Tetrahedron Lett.* **1983**, *24*, 1265–1268.
(8) Doerge, D. R.; Corbett, M. D. *Mol. Pharmacol.* **1984**, *26*, 348–352.
(9) Dankleff, M. A. P.; Curci, R.; Edwards, J. O.; Pyun, H. Y. *J. Am. Chem. Soc.* **1968**, *90*, 3209–3218.
(10) Bruice, T. C. In *Biomimetic Chemistry*; Dolphin, D., McKenna, C., Murakami, Y., Tabushi, I., Eds.; American Chemical Society: Washington, DC, 1980; pp 89–118.
(11) Pross, A. *Acc. Chem. Res.* **1985**, *18*, 212–219.
(12) Rosen, G. M.; Finkelstein, E.; Rauckman, E. J.; Kitchell, B. In *Safe Handling of Chemical Carcinogens, Mutagens, Teratogens and Highly Toxic Substances*; Walter, D. B., Ed.; Ann Arbor Science: Ann Arbor, MI, 1980; pp 469–492.
(13) Hajjar, N. P.; Hodgson, E. *Biochem. Pharmacol.* **1982**, *31*, 745–752.
(14) Hiatt, R.; Smythe, R. J.; McColeman, C. *Can. J. Chem.* **1971**, *49*, 1707–1711.

0002-7863/86/1508-7773$01.50/0

Scheme I



FlOOH fell on a linear correlation of reactivity of YOOH with thioxane vs. pK_a of YOH, although there was a substantial deviation with a more hindered hydroperoxide.[16]

Peroxy acids also appear to show small effects. For example, the rate of reaction of perbenzoic acid with 2,4-dimethylpyridine and with 2,4,6-trimethylpyridine was the same.[17] On the other hand, while 2,6-dimethoxypyridine was oxidized slowly by perbenzoic acid in chloroform, 2,6-dibenzoxypyridine was not oxidized.[18]

In an exploration of the electronic and steric effects on the reactivity of flavin hydroperoxides with sulfides, the reactivity of N^5-ethyl-N^{10}-(2,6-dimethylphenyl)-4a-hydroperoxy-N^3-methylisoalloxazine (**2a**) with para-substituted thioanisoles, alkyl phenyl sulfides, and dialkyl sulfides has been investigated. The latter two groups of compounds contain alkyl groups with varying steric requirements. The results of these studies also led us to look at the relative reactivities of several benzylbutylamines.

Results

Rates of reaction of para-substituted thioanisoles, **3**, with **2a** are reported in Table I. A Hammett plot of these rates vs. σ[19] gave a ρ value of −1.68 (C = 0.14)[20,21] while a plot vs. σ^+ gave a ρ^+ value of −1.02 (C = 0.26). Plots vs. σ^+/σ^-, σ/σ^-, or σ° were also not as significant as the plot vs. σ. Furthermore, a plot of the log of relative rates of oxidation of dialkyl sulfides (Table II) vs. the sulfides' electrode potentials[22] showed very poor correlation (C = 4.38). Although still not very reliable, a plot of the log of relative rate vs. first ionization energy[23] gave a plot of much greater significance (C = 1.29).

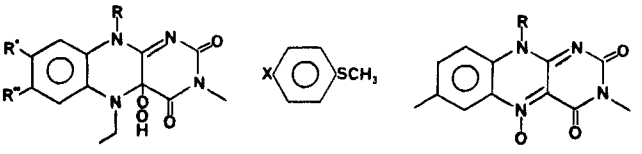
Table III. Rates of Reaction of **2a** with Alkyl Phenyl Sulfides in t-BuOH at 30 °C

compd	rate × 10^2, M^{-1} s^{-1}	rel rate
PhSMe	3.63 ± 0.15	7.3
PhSEt	2.67 ± 0.25	5.4
PhS(i-Pr)	1.08 ± 0.04	2.2
PhS(t-Bu)	0.495 ± 0.07	1
PhS(n-Pr)	3.01 ± 0.29	6.1
PhS(i-Bu)	2.06 ± 0.09	4.2

Table IV. Rates of Oxidation of Benzylbutylamines with **2a** at 30 °C

butyl	rate × 10^3, M^{-1} s^{-1}	rel rate[a]	rel rate[b]
n-Bu	5.74 ± 0.51[c]	5.6	0.36
i-Bu	7.96 ± 0.15[c]		
sec-Bu	3.76 ± 0.03[c]		
t-Bu	1.01 ± 0.09[c]	1	0.60
n-Bu	15.8 ± 0.1[d]	9.5	
t-Bu	1.67 ± 0.05[d]	1	

[a] n-Bu/t-Bu. [b] Solvent effect: t-BuOH/dioxane. [c] In t-BuOH. [d] In dioxane.



2a, R = 2,6-dimethylphenyl, R′ = R″ = H
b, R = methyl, R′ = R″ = H
c, R = R′ = R″ = CH_3
d, R = R′ = CH_3, R″ = H

3

4, R = tetraisobutyrylribityl

The relative rate of oxidation of thioanisole and methyl-d_3 phenyl sulfide (k_H/k_D) was 1.04 ± 0.01. On the other hand, qualitative results indicated that dimethyl-d_6 sulfide was more reactive than dimethyl sulfide with **2a**.[24]

The product of the reaction with p-methoxyphenyl methyl sulfide was the corresponding sulfoxide in essentially 100% yield. Even the oxidation of p-nitrobenzyl phenyl sulfide with **2a** showed only the formation of sulfoxide. No elimination products, neither p-nitrobenzaldehyde nor diphenyl disulfide, could be detected.

Rates of reaction of alkyl phenyl sulfides with **2a** are reported in Table III. Analysis of the data for the alkyl phenyl sulfides by the simple Taft equation (eq 1),[25] using the steric parameters of either Taft, Charton, or Dubois (developed from the hydrolysis of esters),[26,27] gives C values of 1.18–1.20 and r values of 0.84 in all cases. On the other hand, when the steric parameters developed by Charton for S–X, where X is alkyl, are used,[28] r is 0.91 and C is 0.87. While there is not enough data to do a significant correlation with the modified Taft equation (eq 2),[25] a simple inspection reveals that the correlation would be very poor.

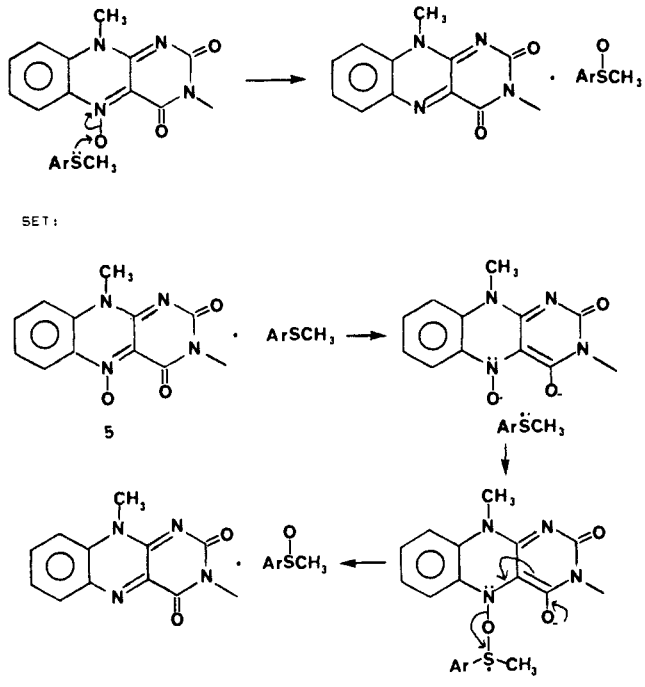
$$\log k/k_0 = \delta E_S \quad (1)$$

$$\log k/k_0 = \rho^*\sigma^* + \delta E_S \quad (2)$$

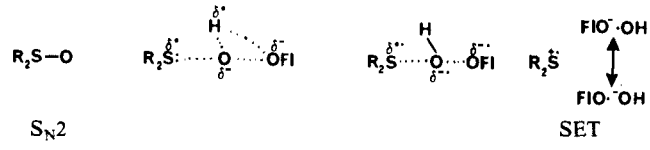
That the steric effect observed is not due to the bulk of the N^{10} substituent in **2a** is indicated by the relative rates of reaction of methyl phenyl and *tert*-butyl phenyl sulfides with **2b** (N^{10}-methyl substituent), which are 10.5:1.

(15) Kirpichnikov, P. A.; Mukmenova, N. A.; Pudovik, A. N.; Kolyubakina, N. S. *Dokl. Akad. Nauk. SSSR* **1965**, *164*, 965–968.
(16) Bruice, T. C. *Isr. J. Chem.* **1984**, *24*, 54–61.
(17) Modena, G.; Todesco, P. E. *Gazz. Chim. Ital.* **1960**, *90*, 702–708.
(18) Ames, D. E.; Grey, T. F. *J. Chem. Soc.* **1955**, 631–636.
(19) Hammett, substituent constants are taken from: Exner, O. In *Correlation Analysis in Chemistry*; Chapman, N. B., Shorter, J., Eds.; Plenum: New York, 1978; pp 439–540. In all cases the best "*B*" values (benzoic acid) were used.
(20) The C value first described by Wold (ref 21) and modified by Shorter is used as a criterion of significance. C as used in this paper is defined as Student's T value for a 99% confidence level divided by the T value for the data calculated. Thus, if this value is <1, the data are significant, and the closer this value is to 0, the more significant the correlation (ref 26).
(21) Wold, S.; Sjostrom, M. In *Correlation Analysis in Chemistry*; Chapman, N. B., Shorter, J., Eds.; Plenum: New York, 1978; pp 1–54.
(22) Cottrell, P. T.; Mann, C. K. *J. Electrochem. Soc.* **1969**, *116*, 1499–1503.
(23) Wagner, G.; Bock, H. *Chem. Ber.* **1971**, *107*, 68.
(24) Quantitative results were not obtained because the rate was at the limit of measurement by the Cary 219.
(25) Taft, R. W., Jr. In *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; Wiley: New York, 1956; pp 556–675.
(26) Shorter, J. *Correlation Analysis of Organic Reactivity*; Wiley: New York, 1982; Chapter 4.
(27) A complete listing of Taft steric parameters can be found in: Unger, S. H.; Hansch, C. *Prog. Phys. Org. Chem.* **1976**, *14*, 91–118.
(28) Charton, M.; Charton, B. I. *J. Org. Chem.* **1978**, *43*, 1161–1165.

Scheme II



Scheme III



Even with secondary amines, the benzylbutylamines, there is a steric effect on reactivity with **2a**. This effect is controlled somewhat by solvent: the relative reactivities of benzyl-*n*-butylamine and benzyl-*tert*-butylamine are more pronounced in dioxane than in *tert*-butyl alcohol (see Table IV). However, there is no such effect on the oxidations of sulfides (see Table II).

In 1981 Frost and Rastetter suggested that a possible mechanism for the hydroxylation of phenolates by appropriate flavoenzymes was the rearrangement of FlOOH to an N^5-oxide which then acted as an oxidizing agent.[29] Such an oxide, **4**, indeed effected hydroxylation of phenolates, mimicking the reaction of *p*-hydroxybenzoate hydroxylase. A similar pathway can be envisioned for the oxidation of sulfides either by an S$_N$2 or an SET mechanism (Scheme II). However, N^3,N^{10}-dimethylisoalloxazine N^5-oxide (**5**) does not effect oxidation of methyl 4-methylphenyl sulfide in acetic acid at 35 °C even after 18 h. Therefore, the N^5-oxide is not a viable intermediate in the oxidation of sulfides by FADMO. This result is substantiated by the fact that riboflavin N^5-oxide bound to monooxygenase apoenzymes does not oxygenate substrates.[30]

Discussion

Mechanism of Oxidation of Sulfides and Amines. Our results indicate that the transition state for oxidation of thioanisoles by **2a** lies at neither extreme of the S$_N$2–SET continuum (see Scheme III). The oxidation of the dialkyl sulfides lies closer to the S$_N$2 extreme than the oxidation of thioanisoles. These conclusions especially take into consideration the work of Pryor and Hendrickson, who discussed the problems associated with the use of substituent effects, solvent effects, and product studies to distinguish between SET and S$_N$2 mechanisms and who suggested that the nature of isotope effects would best indicate a certain mechanism.[31] Another similar investigation was the study of the oxidation of thioethers by peroxyhexanoyl nitrate.[32] The next sections discuss various parameters in regard to the mechanisms proposed as well as make some comments in regard to other studies. It will be seen that many of the conclusions in the literature regarding the mechanisms of oxidation of sulfides have been based on insufficient data.

Substituent Effects. The Hammett equation has been used to analyze oxidations of thioanisoles to the corresponding sulfoxides by many different agents. Depending on the bias of the investigators (including the present authors), ρ values, varying from −0.13 to −4.0, have been used as support for either an S$_N$2 or an SET mechanism. For example, it has been argued that a low ρ value (−2.07) for oxidation by Cr(VI) meant an SET mechanism[33,34] and that a low ρ value (−1.40) for oxidation by sodium periodate meant an S$_N$2 mechanism.[35,36] We earlier postulated an S$_N$2 mechanism for the oxidation of thioanisoles by FlOOH based on the size of the ρ value.[6]

Similarly, comparing correlations with σ, σ^+, and σ° can be misleading. Argument for an SET mechanism for the oxidation of thioanisoles by cytochromes P-450 was based on a better correlation with σ^+ rather than σ.[37] Nonetheless, in a reaction which seems to have some SET character, singlet oxygen oxidation (see below), the correlations are better with σ than with σ^+.[38,39] Furthermore, the solvolysis of 3-(arylthio)-3-methylbutyl *p*-toluenesulfonate with aryl-substituted sulfur participation to form a four-membered-ring intermediate is correlated best with σ° values,[40] while a related reaction to form three-membered sulfur-containing intermediates is correlated better with σ^+ values.[41,42] (For the former the ρ value was −1.58. It was suggested that this correlation meant that resonance with the sulfur was of minor importance.) This difference is surprising since both of these reactions should give sulfonium ion intermediates.

Good correlations of rates of oxidation with either electrode or ionization potentials of the sulfides[43] also cannot be interpreted unequivocally in favor of a particular mechanism. For example, the rates of oxidation of thioanisoles by iron(III) tetraphenylporphyrin and hydrogen peroxide, for which the data have been interpreted to mean an SET mechanism, correlate reasonably (C = 0.90) with electrode potential. However, the rates of reaction of thioanisoles with chloramine-T, which correlate considerably better with σ (C = 0.06) than σ^+ (C = 0.59), also correlate significantly (C = 0.64) with electrode potentials.[34] The data for the oxidation of thioethers by singlet oxygen are also confusing since there is a good correlation between electrode potential and

(29) Frost, J. W.; Rastetter, W. H. *J. Am. Chem. Soc.* **1981**, *103*, 5242–5245.

(30) Frost, J. W.; Massey, V.; Rastetter, W. H., unpublished results. Reported in: Wagner, W. R.; Spero, D. M.; Rastetter, W. H. *J. Am. Chem. Soc.* **1984**, *106*, 1476–1480.

(31) Pryor, W. A.; Hendrickson, W. H., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 7114–7122.

(32) van Noort, P. C. M.; Vermeeren, H. P. W.; Louw, R. *Recl.: J. R. Neth. Chem. Soc.* **1983**, *102*, 312–321.

(33) Srinivasan, C.; Chellamani, A.; Rajagopal, S. *J. Org. Chem.* **1985**, *50*, 1201–1205. σ and σ^+ plots gave essentially the same C values, 0.15 and 0.19, respectively. Data also correlated with E values (from ref 34; C = 0.31).

(34) Latypova, V. Z.; Zhuikov, V. V.; Chmutova, G. A.; Rydvanskii, Yu. V.; Kargin, Yu. M. *J. Gen. Chem. USSR (Engl. Transl.)* **1984**, *54*, 1380–1383.

(35) Ruff, F.; Kucsman, A. *J. Chem. Soc., Perkin Trans. 2* **1985**, 683–687.

(36) Recalculation of the data indicates essentially the same correlation (C = 0.30, 0.29) for either a σ or a σ^+ plot. A plot of four points vs. $E_{1/2}$ values (ref 34) gave C = 1.14.

(37) Watanabe, Y.; Iyanagi, T.; Oae, S. *Tetrahedron Lett.* **1980**, *21*, 3685–3688.

(38) Kacher, M. L.; Foote, C. *Photochem. Photobiol.* **1979**, *29*, 765–769.

(39) Monroe, B. M. *Photochem. Photobiol.* **1979**, *29*, 761–764.

(40) Eliel, E. L.; Knox, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 2946–2952.

(41) Harris, J. M.; Paley, S. M.; Hovanes, B. M.; McManus, S. P., unpublished results.[40]

(42) The correlation of several oxidations of thioanisoles with σ° values is not as good as that for other kinds of σ values. These include our oxidations, the singlet oxygen oxidations (ref 38 and 39), bromine oxidation (ref 50), and sodium periodate oxidation (ref 35).

(43) Without exception the C value for the calculations performed was always lower for correlations with electrode potential than with ionization potentials taken from: Bernardi, F.; Distefano, G.; Mangini, A.; Pignataro, S.; Spunta, G. *J. Electron Spectrosc. Relat. Phenom.* **1975**, *7*, 457–463.

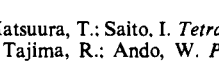
log k for thioanisoles[39] (C = 0.48) but a poor correlation for a mixture of aliphatic and aromatic thioethers[38] (C = 2.9). (However, see next paragraph.)

The inconsistencies in the linear free energy correlations for the oxidation reactions are probably due to a change in mechanism with a change in the electronic character of the substituents. When substituents are more electron-donating, the mechanism will change to more SET character. However, this could give such slight differences that they might be hidden in experimental error. Such a change in mechanism seems likely for the singlet oxygen oxidations of thioanisoles in which only the intermediates from electron-rich thioanisoles,[44] having an oxidation potential less than 0.5 V vs. SCE, dissociate to some superoxide as product.[45] This change in mechanism with structure could account for the differences in correlation with electrode potential for the oxidations of aliphatic and aromatic sulfides mentioned above. Finally, the mechanism of oxidation of thioanisoles with manganese(III) tetraphenylporphyrin chloride and iodosobenzene appears to change with substituents,[46] more of which need to be investigated to substantiate this preliminary result.

In sulfide oxidations by cytochromes P-450, several products can be rationalized on the basis of a radical mechanism (see below). However, as pointed out by Pryor and Hendrickson,[31] this may not reflect the transition state for a reaction. That the SET mechanism proposed for this reaction does not rest on a firm basis can be seen by an analysis of the rate studies. First, the C values for the Hammett plots are quite high, 1.02 for the σ^+ plot and 2.02 for the σ plot. The data include only five points, one of which is omitted from the correlation because it deviates substantially from the others.[37] The low value of ρ^+, −0.14, suggests either an early transition state, precluding full SET character, or a rate determined by more than one step. Because of the ambiguities still remaining concerning the rate-determining step(s) for oxidations by P-450 enzymes,[47] the meaning of the better σ^+ plot remains obscure.

Thioanisole oxidations by dopamine β-hydroxylase appear to be unusual. A correlation of rates of four 2-aminoethyl aryl sulfides with σ^n values has been reported to give a ρ value of −3.6.[48] This value, while considerably higher than the ρ values for many oxidations of alkyl aryl sulfides, is similar to that for some of the reactions where a sulfonium ion intermediate is proposed. Examples include the reaction of thioanisoles with V(V)[49] (ρ^+ = −3.25) and with bromine[50] (ρ = −3.2).[51] A recalculation of the data shows that the plot of the relative rates vs. σ (ρ = −3.99) is considerably more significant (C = 0.50) than the σ^n plot (C = 0.70) or the σ^+ plot (C = 6.57). Unfortunately, the study was limited to four thioanisoles whose substituents had σ values between 0 and 0.26 because of steric constraints of the enzyme. With more variety in substituents the ρ value could change significantly and still give a good correlation. More recently the enzymic process has been proposed as SET for the rate-determining step, followed by coupling with oxygen bound to copper to give sulfoxides as products.[52]

(44) It has been established that either a persulfoxide or an ion pair is an intermediate in singlet oxygen oxidations of diethyl sulfide (ref 63).



persulfoxide ion pair

(45) Inoue, K.; Matsuura, T.; Saito, I. *Tetrahedron* **1985**, *41*, 2177–2181.
(46) Takata, T.; Tajima, R.; Ando, W. *Phosphorus Sulfur* **1983**, *16*, 67–78.
(47) (a) Guengerich, F. P.; Macdonald, T. L. *Acc. Chem. Res.* **1984**, *17*, 9–16. (b) Ortiz, De Montellano, P. R. In *Reviews in Biochemical Toxicology*; Hodgson, E., Bend, J. R., Philpot, R. M., Eds.; Elsevier: New York, 1984; Vol. 6, pp 1–26.
(48) May, S. W.; Phillips, R. S.; Mueller, P. W.; Herman, H. H. *J. Biol. Chem.* **1981**, *256*, 8470–8475.
(49) Satyanarayana, D. V. V.; Nageswara, R. Y.; Nageswara, R. N. *Indian J. Chem., Sect. A* **1985**, *24A*, 34–36.
(50) Miotti, U.; Modena, G.; Sedea, L. *J. Chem. Soc. B* **1970**, 802–805.
(51) In the former case the σ^+ plot is more significant, and in the latter the σ plot is more significant.
(52) Padgette, S. R.; Wimalasena, K.; Herman, H. H.; Sirimanne, S. R.; May, S. W. *Biochemistry* **1985**, *24*, 5826–5839.

Table V. Relative Rates of Oxidation of Alkyl Phenyl Sulfides

oxidizing agent	rel rate R = CH_3/R = *t*-Bu	rel rate R = Et/R = *t*-Bu
peroxydisulfate[a]	58	23
peroxydiphosphate[b]	17	11
2a	7.3	5.4
hydrogen peroxide[c]	1.7	1.8

[a] Srinivasan, C.; Kuthalingam, P.; Arumugam, N. *Can. J. Chem.* **1978**, *56*, 3053. [b] Srinivasan, C.; Kuthalingam, P.; Arumugan, N. *J. Chem. Soc., Perkin Trans. 2* **1980**, 170. [c] Modena, G. *Gazz. Chim. Ital.* **1959**, *89*, 834.

Table VI. Amine Reactions and Interactions

reactant	solvent	plot[a]	slope	C	ref
2c	*t*-BuOH	pK_a 3° amines vs. log k_2[b]	0.44	0.83	5
2c	dioxane	pK_a DMA[c,d] vs. log k_2	0.39	0.48	7
		Hammett, σ^+	−0.72	0.77	
		Hammett, σ	−1.24	0.22	
2d	MeOH	pK_a anilines vs. log k_2	0.96	0.72	8
		Hammett, σ^+	−1.34	0.82	
		Hammett, σ	−2.46	0.95	
$^1O_2$	MeOH	pK_a DMA[c] vs. log k_2	0.46	0.29	53
		Hammett, σ^+	−1.01	0.66	
		Hammett, σ	−2.03	0.32	
		Hammett, σ,σ^-	−1.55	0.16	

[a] pK_a's taken from: Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution*; Butterworths: London, 1965, p 35. [b] Apparently, the plot shown in the reference did not include *N,N*-dimethylaniline as a point, but the C value is much lower when this amine is included (0.83 vs. 2.3). [c] Substituted *N,N*-dimethylanilines. [d] This reference omitted its data for *m*-CH_3 in its calculations, and so do we. Substituents used do not permit a σ,σ^- plot.

Interpretations of rate data for oxidations of amines are also equivocal, and more data are necessary before any definite mechanistic conclusions can be reached. For example, Hammett σ and/or Brønsted plots for amines and flavin hydroperoxides have been used in support of the S_N2 mechanism.[5,7,53] On the other hand, the solvent effect (relative rates in MeOH/freon = 590:1) on the quenching of singlet oxygen by substituted *N,N*-dimethylanilines was interpreted in terms of a charge-transfer (SET-like) process,[54] although the σ plot is much better than the σ^+ plot. The Brønsted plot is also highly significant, and the β values for this data and for the oxidation of tertiary amines by FlOOH are similar (see Table VI). Furthermore, anodic oxidation of tertiary amines, undoubtedly a SET process, has been correlated both with Hammett σ values and with pK_a's.[55] Thus, conclusions concerning the amount of charge transfer in the transition state based on the significance of σ vs. σ^+ plots or on the Brønsted β values are unwarranted.

The slope of nearly 1 for the Brønsted plot in the case of FlOOH oxidation of anilines[8] means a much later transition state[56] than for FlOOH oxidation of other amines. This could be due to a hydrogen bond from the NH of the aniline to the C-4 carbonyl or, more likely, because of the greater strength of the hydrogen bond, from the nitrogen of the aniline to the hydrogen of the hydroperoxide. Either of these would have to be broken before the reaction could proceed, leading to a later transition state. The better plot vs. σ^+ in the case of para-substituted anilines in methanol[8] suggests SET character, since an sp^3-hybridized nitrogen would not be expected to show such a correlation. It would be

(53) Oae, S.; Mikami, A.; Matsuura, T.; Ogawa-Asada, K.; Watanabe, Y.; Fujimori, K.; Iyanagi, T. *Biochem. Biophys. Res. Commun.* **1985**, *131*, 567–573.
(54) Young, R. H.; Martin, R. L.; Feriozi, M. D.; Brewer, D.; Kayser, R. *Photochem. Photobiol.* **1973**, *17*, 233–244.
(55) Lindsay Smith, J. R.; Masheder, D. *J. Chem. Soc., Perkin Trans 2* **1976**, 47–51. Since the rate data were not given, it could not be recalculated.
(56) Bell, R. P. In *Correlation Analysis in Chemistry*; Chapman, N. B., Shorter, J., Eds.; Plenum: New York, 1978; pp 55–84.

of interest to have the data for the *N,N*-dimethylanilines in methanol for comparison purposes.

Solvent. Solvent effects on the reactivity of **2a** with amines and sulfides (see Tables II and IV) are small. Similarly, the relative reactivity of **2c** and *N,N*-dimethylaniline in *t*-BuOH/dioxane is 2:1.[5,7] These small solvent effects suggest transition states in which there is little charge separation, compatible with either SET or S_N2.

Products. Product studies also give confusing results unless interpreted with caution. Thus, anodic oxidation, i.e., SET oxidation, of thioanisole gives exclusively the corresponding sulfoxide.[57] Even in the reaction of singlet oxygen with electron-rich thioanisoles, sulfoxide was the sole organic product isolated in good yield.[45] Only in the oxidation of sulfides substituted with an electron-withdrawing group in a benzylic position have cleavage products been observed. Nonetheless, these products could readily arise by elimination from **1** (Scheme I) as well as from radical intermediates which could be produced subsequent to the rate-determining step.

Our product study with *p*-nitrobenzyl phenyl sulfide (**6**) indicates that if radicals are produced, they readily couple to give sulfoxide rather than elimination products. As pointed out by others,[31] a lack of products from radicals does not mean an S_N2 rather than SET mechanism and vice versa. Oae and co-workers found that **6** gave more *p*-nitrobenzaldehyde than sulfoxide as product when it was oxidized by either liver microsomes or a reconstituted cytochrome P-450 system.[58] For these oxidations a sulfur cation radical was formulated as an intermediate. Oxidation of **6** in a control was not reported although we found that **6** is very readily air-oxidized (to give the corresponding aldehyde and disulfide, among other products). Perhaps the difference in observations is due to the difference in solvent systems; oxygen would be much more soluble in organic solvent and thus effect more oxidation than in the aqueous enzymatic systems. On the other hand, it is surprising that only a small amount of phenacyl phenyl sulfide was oxidized to diphenyl disulfide upon chromatography on alumina ($CHCl_3$),[58] while this compound was reported to undergo proportionately even more oxidation to diphenyl disulfide vs. sulfoxide than *p*-nitrobenzyl phenyl sulfide with cytochrome P-450.[57] It is also surprising that phenacyl phenyl sulfide was not oxidized in dioxane in the dark at room temperature to at least some diphenyl disulfide.[53]

Isotope Effects. The isotope effect of 1.04 observed in the oxidation of thioanisole suggests SET character in the transition state for the reaction.[59-61] Nonetheless, the product study with **6** indicates that, after the transition state, the nucleophilic substitution product is formed exclusively. Thus, this reaction lies between the S_N2 and SET extremes (Scheme III), and in analogy to the reaction of thioanisoles with singlet oxygen, with easily oxidized sulfides there should be slightly more SET character to the transition state.

The qualitative result for dimethyl sulfides indicates that the transition state for this oxidation lies closer to the S_N2 extreme than the oxidation of thioanisoles. This is consistent with the expected larger stabilizing effect of the aryl group on a sulfur cation radical as well as the larger size of phenyl since larger steric effects are expected for the S_N2 mechanism.[11]

Steric Effects on Sulfide and Amine Oxidations. The relative reactivities of the alkyl phenyl sulfides with **2a** correlate well only with Charton's sulfur parameters. It is Charton's contention that the differences in electronic effect for alkyl substituents on sulfur are minimal so that relative reactivity can be attributed primarily to steric effects.[20] However, our correlation appears to be fortuitous since the relative reactivities of the dialkyl sulfides were not correlated significantly using the same parameters. That the two sets of compounds do not correlate in the same way is not surprising. As others have pointed out, changing the bulk of the alkyl group on sulfur will change the electronic interaction of the sulfur with the aromatic ring,[62] and this may lead to a cancellation of various effects. Furthermore, as discussed above, a change of electronic structure (from aromatic to aliphatic thioether) could cause a shift in mechanism. Likewise, since SET should be less susceptible to steric effects,[11] the mechanism may change within a series as the steric demand of the substituents changes.

A comparison of the relative reactivities of alkyl phenyl sulfides with **2a** and other oxidants is shown in Table V. The steric effect in the oxidations with **2a** is small compared to some oxidants but larger than that for hydrogen peroxide. However, the relative rates of oxidation of dialkyl sulfides by singlet oxygen (see Table II) have a wider range than those for FlOOH oxidation of the same substrates. Thus, the steric effect must not be due to some intrinsic property of FlOOH but to the position of the transition state on the reaction coordinate. Ostensibly, the oxidations by **2a**, hydrogen peroxide and singlet oxygen, do not involve initial formation of a sulfurane intermediate which might be expected to show a larger steric effect.[11,32,45,63] We have not detected any apparent trend in steric effects between a variety of oxidants and either alkyl phenyl sulfides or dialkyl sulfides.

The relative rates of oxidation of the benzylbutylamines can also be explained by a steric effect.[64] The fact that the relative reactivities of benzyl-*n*-butylamine and benzyl-*tert*-butylamine are more pronounced in dioxane than in *tert*-butyl alcohol while a similar effect is not observed for the dialkyl sulfides can be attributed to hydrogen-bonding interactions of the amine nitrogen with the proton of *tert*-butyl alcohol. This decrease of relative reactivities of nucleophilic substitutions in hydrogen-bonding solvents has been observed in other cases.[65]

The better significance of the Brønsted plot for oxidation of *N,N*-dimethylanilines by **2c**[7] than that for similar oxidations of assorted tertiary amines[5] (see Table VI) suggests that there are subtle effects on the rates due to steric effects. That is, with the substituted *N,N*-dimethylanilines, steric effects should be the same and the correlation of rate data should be better.

The steric effects observed for model FlOOH oxidations cannot be related directly to FAD-containing monooxygenase because the steric requirements of the N^5-ethyl substituent of the model and the N^5 position on the enzyme are expected to be different. Nevertheless, steric effects on the enzyme can be at least partially explained by the steric effect associated with oxidations by FlOOH. Finally, although a steric effect on the epoxidation of 2,3-dimethyl-2-butene with N^5-ethyl model flavins was rejected by considering molecular models,[66] experimental verification is warranted on the basis of our work.

Conclusions

This work has shown that oxidations of sulfides by FlOOH involve some SET character. Comparisons with other work illustrate the problems associated with determining SET vs. S_N2 transition states on the basis of electronic, solvent, and/or product studies alone.

Experimental Section

Materials. Thioanisole and the dialkyl sulfides were purchased from Aldrich Chemical Co. These compounds were distilled, and a middle

(57) Uneyama, K.; Torii, S. *Tetrahedron Lett.* **1971**, 329-332.
(58) Watanabe, Y.; Numata, T.; Iyanagi, T.; Oae, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1163-1170.
(59) Compare with isotope effects reported in Table XI of ref 31. Also, because the isotope effect (k_H/k_D = 1.2) for microsomal oxidation of $PhSCH_2COPh$ was determined by product ratios (ref 58), a meaningful comparsion with our transition state for oxidation is precluded.
(60) This isotope effect is identical with that reported for the potassium hexacyanoferrate(III) oxidation of di-*n*-butylmethylamine for which electron-transfer oxidation was concluded (ref 61).
(61) Lindsay Smith, J. R.; Mead, L. A. V. *J. Chem. Soc., Perkin Trans 2* **1973**, 206-210.
(62) Ruff, F.; Komoto, K.; Furukawa, N.; Oae, S. *Tetrahedron* **1976**, *32*, 2763-2767.
(63) Liang, J.-J.; Gu, C.-L.; Kacher, M. L.; Foote, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 4717-4721.
(64) Apparently, branching in the β position has less of an effect than branching in the α position.
(65) (a) Grob, C. A.; Schlageter, M. G. *Helv. Chim. Acta* **1977**, *60*, 1884-1889. (b) Jencks, W. P.; Haber, M. T.; Herschlag, D.; Nazaretian, K. L. *J. Am. Chem. Soc.* **1986**, *108*, 479-483.
(66) Bruice, T. C.; Noar, J. B.; Ball, S. S.; Venkataram, U. V. *J. Am. Chem. Soc.* **1983**, *105*, 2452-2463.

fraction was collected. All other thio compounds and the benzylbutylamines were synthesized by literature procedures. Liquids were purified by fractional distillation under reduced pressure; solids were recrystallized to a constant melting point. Compound **2a** was synthesized by the literature procedure.[67] Compound **2b**, N^5-ethyl-4a-hydroperoxy-N^3,N^{10}-dimethylisoalloxazine, was synthesized in a like manner from N^3,N^{10}-dimethylisoalloxazine, prepared by the method of Yoneda,[68] While **2b** was too unstable for analysis, its precursor, N^5-ethyl-N^3,N^{10}-dimethylisoalloxazinium perchlorate, was recrystallized to a constant melting point of 196-197 °C from acetonitrile/ether: IR 1710 (s), 1620 (s), 1610 (s), 1560 (s), 1100 (s), 760 (s) cm^{-1}. Anal. C, H, N, Cl. The *tert*-butyl alcohol for kinetic studies was dried by refluxing over calcium hydride for at least 2 days, usually at least 5, and distilled with protection from moisture. The dioxane was refluxed overnight with sodium and benzophenone, distilled under nitrogen with protection from moisture, and used immediately for kinetic runs.

Isolation of *p*-Methoxyphenyl Methyl Sulfoxide. A solution of 0.020 g (0.05 mmol) of **2a** in 100 mL of *tert*-butyl alcohol was treated with 0.010 g (0.065 mmol) of *p*-methoxythioanisole in 5 mL of *tert*-butyl alcohol. The mixture was allowed to stand in the dark for several days. Removal of the solvent in vacuo followed by thick-layer chromatography (silica gel GF, ethyl acetate, eluant) gave 0.009 g (106%) of a pale-yellow oil whose infrared spectrum was identical with that of authentic *p*-methoxyphenyl methyl sulfoxide.[69] TLC showed that N^5-ethyl-4a-hydroxy-N^3-methyl-N^{10}-(2,6-dimethylphenyl)isoalloxazine was the major product from **2a**.

Reaction of *p*-Nitrobenzyl Phenyl Sulfide (6) with 2a in Dry, Degassed 1,4-Dioxane. In a glovebag purged with nitrogen, 12.3 mg (0.051 mmol) of **6** was dissolved in 25 mL of dry, degassed 1,4-dioxane. The solution was magnetically stirred as 20.6 mg (0.052 mmol) of **2a** was added. The reaction mixture was monitored by TLC (silica gel, 50:50 hexane/ether), but after 3 days, TLC still showed unreacted **6**. The reaction mixture was concentrated in vacuo to approximately 1-2 mL, and a TLC of this concentrate showed, besides decomposition products of **2a**, only the unreacted **6** and *p*-nitrobenzyl phenyl sulfoxide, by comparison with authentic samples. No *p*-nitrobenzaldehyde or diphenyl disulfide could be detected. Attempts to separate (in the air) the components of the reaction mixture by preparative TLC resulted in extensive decomposition, and no pure products could be isolated.

Kinetic Studies. A known amount of an approximately 2.5×10^{-4} M solution of FlOOH was pipetted into a cuvette. The samples were thermally equilibrated at 30 °C in a Cary 219 spectrophotometer for at least 0.5 h, and then a known amount of neat liquid sulfide or amine or a solution of sulfide of known concentration was pipetted into the cuvette. The concentrations of substrate were approximately 50-500 times that of FlOOH. The absorbance at 400 nm was measured continuously for the fast oxidations and at precise time intervals for the slow oxidations. Almost always the reactions were followed to at least 3 half-lives, and excellent pseudo-first-order kinetics were observed. Plots of first-order rate constants vs. concentration of substrate gave the second-order rate constants which are reported. All rate constants were determined by the least-squares method. With the exceptions noted, duplicate runs were performed.

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Registry No. **2a**, 73475-07-7; **2b**, 96837-33-1; **3** (X = CN), 21382-98-9; **3** (X = PhC(O)), 23405-48-3; **3** (X = Cl), 123-09-1; **3** (X = H), 100-68-5; **3** (X = Me), 623-13-2; **3** (X = AcNH), 10352-44-0; **3** (X = MeO), 1879-16-9; **3** (X = NH_2), 104-96-1; **6**, 7703-38-0; FADMO, 37256-73-8; Me_2S, 75-18-3; Et_2S, 352-93-2; *i*-Pr_2S, 625-80-9; *t*-Bu_2S, 107-47-1; PhSEt, 622-38-8; PhS-*i*-Pr, 3019-20-3; PhS-*t*-Bu, 3019-19-0; PhS-*n*-Pr, 874-79-3; PhS-*i*-Bu, 13307-61-4; *n*-BuNHCH$_2$Ph, 2403-22-7; *i*-BuNHCH$_2$Ph, 42882-36-0; *sec*-BuNHCH$_2$Ph, 46120-25-6; *t*-BuNHCH$_2$Ph, 3378-72-1; *p*-MeOC$_6$H$_4$S(O)Me, 3517-99-5; N^3,N^{10}-dimethylisoalloxazine, 4074-59-3; N^5-ethyl-N^3,N^{10}-dimethylisoalloxazinium perchlorate, 104550-31-4; 4a,5-dihydro-N^5-ethyl-4a-hydroxy-N^3-methyl-N^{10}-(2,6-dimethylphenyl)isoalloxazine, 76030-62-1.

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Very High 1,2- and 1,3-Asymmetric Induction in the Reactions of Allylic Boron Compounds with Chiral Imines

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Abstract: The reaction of allyl-9-borabicyclo[3.3.1]nonane (allyl-9-BBN) with chiral imines **3** produced the Cram isomer **4** either exclusively or very predominantly. The very high 1,2-asymmetric induction is explained by a six-membered chairlike transition state, in which the imine R group occupies an axial position owing to the stereoelectronic effect of imines (RCH=NR'). The reaction of allyl-9-BBN with the chiral imine **11** also gave the Cram isomer **12** very predominantly. The very high 1,3-asymmetric induction is accounted for by a similar transition state (**14**), in which the 1,2-axial–equatorial interaction between the R' group and the ligand L plays an important role for the high chiral induction. Very high enantio- and diastereoselective synthesis of amino acid derivatives was realized via the reaction of allylic 9-BBN with α-imino esters (**27**) having a chiral auxiliary at the R' group. The modified Cram (or Felkin) model (**9** or **9'**) is applicable to explain the 1,2-asymmetric induction. For the 1,3-asymmetric allylboration, the extended Cram model (**10**) is proposed.

The discovery of new methods for 1,2- and 1,3-asymmetric induction in acyclic systems has been a pressing concern in modern organic chemistry.[1] Especially, the Cram/anti-Cram problem has been one of the longstanding concerns. Although the Cram/anti-Cram selectivity of aldehydes has been intensely investigated during the last decade,[2] very few attempts have been made to elucidate such selectivity with imines.[3,4] It was rather curious that no such investigation had been performed at the outset of our work. The major reason is presumably owing to the complex

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