

Flavin Catalyzed Oxidations of Sulfides and Amines with Molecular Oxygen

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The metabolism of enzymes occurs under mild reaction conditions with high selectivity.¹ The simulation of the function of enzymes with simple organic catalysts may lead to the discovery of biomimetic, catalytic oxidations with molecular oxygen, which are environmentally benign.^{2,3} There is a strong need to have greener technology for clean catalytic aerobic oxidation; however, reports on aerobic oxidation incorporating the oxygen atom to organic substrates are still scarce.⁴

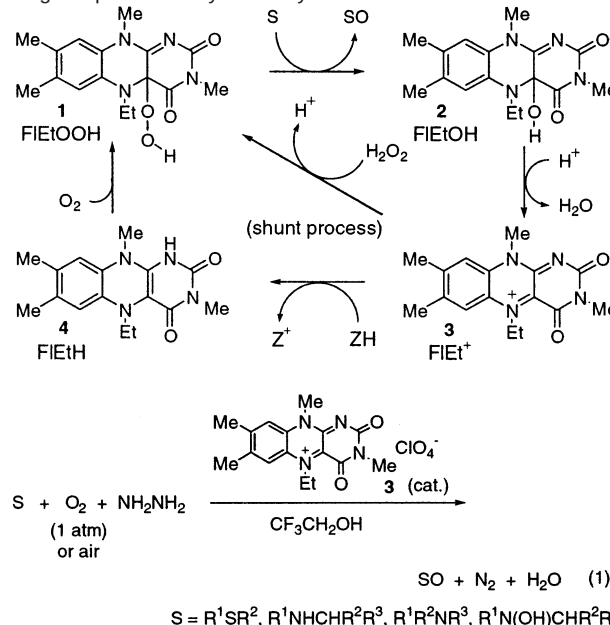
Microsomal FAD-containing monooxygenase (FADMO) activates molecular oxygen and oxidatively metabolizes xenobiotic substances in the hepatic tissue.⁵ The active site responsible for the oxidation has been established as the enzyme-bound 4a-hydroperoxyflavin.⁶ 4a-Hydroperoxylumiflavin has been prepared and subjected to the model study on stoichiometric oxidations.^{7,8} The catalytic cycle of FADMO is shown in Scheme 1 using simplified 5-ethyl-3-methylumiflavin.⁶ 4a-Hydroperoxyflavin (FIEtOOH, **1**) undergoes monooxygenation of substrate (S) to give oxidized product (SO) and 4a-hydroxyflavin (FIEtOH, **2**),⁸ which undergoes dehydration to give oxidized flavin (FIEt⁺, **3**). FIEt⁺ (**3**) is reduced upon treatment with ZH (hydrogen donor, NADPH) to give the reduced flavin (FIEtH, **4**), which reacts with molecular oxygen to generate FIEtOOH (**1**) to complete the catalytic cycle.

Detailed stopped-flow studies on the kinetics of FIEtOH (**2**) revealed that pseudo S_N1 type substitution of FIEtOH (**2**) with H₂O₂ occurs readily to give FIEtOOH (**1**),⁹ and in 1989 we discovered that the oxidation of amines and sulfides with H₂O₂ occurs in the presence of organocatalysts of flavins such as FIEtOOH (**1**), FIEtOH (**2**), FIEt⁺·ClO₄[−] (**3**), and FIEtH (**4**) highly efficiently (the shunt process in Scheme 1).⁹ Flavin catalyzed reactions are highly attractive, and related flavin catalyzed oxidations of tertiary amines,^{10,11} sulfides,¹² and ketones¹³ with H₂O₂ have been reported continuously. Another important aspect is asymmetric flavin catalyzed oxidation with H₂O₂.¹⁴ However, to the best of our knowledge, there is no report on the aerobic flavin catalyzed oxidation reactions, which may correspond to FADMO.

We wish to report that the aerobic oxidations of sulfides, secondary amines, *N*-hydroxylamines, and tertiary amines occur in the presence of FIEt⁺·ClO₄[−] catalyst (**3**) and hydrazine monohydrate in 2,2,2-trifluoroethanol (TFE) to give the corresponding oxidized compounds in excellent yields along with water and molecular nitrogen as the environmentally benign byproduct (eq 1). This is the first demonstration of environmentally benign oxidation using molecular oxygen and organic catalysts. It is noteworthy that, although molecular oxygen has been used for the oxidation of reduced flavins,^{9–12} its purpose is for the preparation of the catalyst for oxidation with H₂O₂.

The oxidation of the reduced flavin (FIEtH) with molecular oxygen occurs readily to give hydroperoxyflavins;¹⁵ therefore, the crucial step of the catalytic cycle of Scheme 1 is the transformation of FIEt⁺ to FIEtH with an appropriate reductant which may

Scheme 1. Catalytic Cycle for the Oxidation of Flavoenzyme Using Simplified 5-Ethyl-3-methylumiflavin

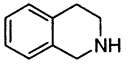
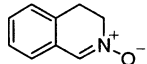
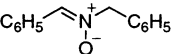
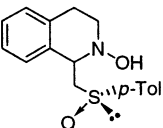
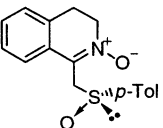
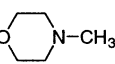
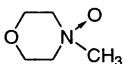
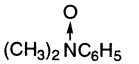


correspond to NADPH. We turned our attention on the fact that hydrazine derivatives are suicide inhibitors for flavoenzymes such as mammalian monoamine oxidase¹⁶ and found that hydrazine monohydrate serves as an excellent reductant. Oxidation of methyl *p*-tolyl sulfide (**5**) with molecular oxygen (1 atm, balloon) in the presence of 1 mol % **3** and hydrazine monohydrate in TFE at room temperature gave the corresponding sulfoxide in >99% yield along with the generation of water and molecular nitrogen.

The oxidized flavinium salt **3** is the most effective catalyst among those examined.⁹ The solvent effect for the aerobic oxidation is dramatic. Fluorinated alcohols such as TFE and 1,1,1,3,3,3-hexafluoro-2-propanol are essential for the aerobic oxidation. TFE is a common industrial solvent,¹⁷ and its solubility of molecular oxygen is very high.¹⁸ To clarify the stoichiometry of molecular oxygen and hydrazine monohydrate, the gas composition, the water content before and after the reaction, and the uptake and release of each gas and water were measured. When 1 equiv of sulfide **5** was oxidized, consumption of 1 equiv of molecular oxygen and production of 1 equiv of water and 0.5 equiv of molecular nitrogen were observed. The aerobic oxidation of **5** in the presence of 0.5 equiv of hydrazine monohydrate gave the corresponding sulfoxide in 96% yield. These results clearly indicate that hydrazine monohydrate reduces FIEt⁺ twice to give water and molecular nitrogen.

On the basis of these results, flavoenzyme-mimic aerobic oxidation has been accomplished using simple and stable lumiflavin catalyst **3**. The representative results are summarized in Table 1. Although 0.5 equiv of hydrazine is enough to oxidize sulfides to

Table 1. Flavin Catalyzed Aerobic Oxidations^a

entry	substrate	product	time	yield ^b
1	(C ₄ H ₉) ₂ S	(C ₄ H ₉) ₂ SO	2 h	96%
2	(C ₄ H ₉) ₂ S	(C ₄ H ₉) ₂ SO	4 h	95% ^c
3			2 h	97%
4			3 h	85% ^{d,e}
5	C ₆ H ₅ CH ₂ NHC ₆ H ₅		6 h	80% ^{d,e}
6			1 h	77% ^f
7			2 h	97% ^d
8	(CH ₃) ₂ NC ₆ H ₅		4 h	94% ^d

^a The aerobic oxidation was carried out in the presence of **3** (1 mol %) and NH₂NH₂·H₂O (1 equiv) in TFE (1 mL) at 35 °C under O₂ (1 atm).
^b Isolated yield. ^c Under air. ^d At 60 °C. ^e **3** (5 mol %) and NH₂NH₂·H₂O (1.1 equiv) were used. ^f **3** (5 mol %) was used.

sulfoxides, 1 equiv of hydrazine was used to complete the reaction within 2 h. The catalytic oxidation of sulfides with molecular oxygen (1 atm) for 2 h gave the corresponding sulfoxides in excellent yields without overoxidation to sulfones (entry 1). Importantly, the oxidation under air also proceeded smoothly, although a longer reaction time is required (entry 2). The oxidation of 1,3-dithiane gave monoxide exclusively (entry 3). The catalyst has a long-term stability, and a turnover number (TON) of 19 000 has been achieved for the oxidation of **5** with 0.005 mol % catalyst. The aerobic oxidation of secondary amines gave the corresponding nitrones (entries 4 and 5). Nitrones are highly valuable synthetic intermediates.¹⁹ It is noteworthy that the oxidation of the hydroxylamine bearing an optically active sulfoxide occurred without loss of optical purity (entry 6). The oxidation of tertiary amines gave the corresponding *N*-oxides in excellent yields (entries 7 and 8). The advantage of these aerobic oxidations with metal-free organic catalysts is no contamination of byproducts in the products which are used as pharmaceutical agents.

The reaction mechanism can be rationalized as follows. The intermediary of FIEtOOH was confirmed by composition of the relative rates of the oxidation of *para*-substituted phenyl methyl sulfides. Thus, the relative reactivity values for various sulfides with respect to X = H (k_X/k_H) were correlated well with the Hammett σ value of the substituents. A plot of Hammett σ versus $-\log(k_X/k_H)$ gave a ρ value of -1.60 ($R = 0.998$), which is similar to the ρ value obtained by the oxidation of sulfides with 4a-

FIEtOOH ($\rho = -1.47$)²⁰ and also is similar to the ρ value ($\rho = -1.90$) obtained by catalytic oxidation of sulfides with a H₂O₂ solution in the presence of the catalyst **3**, indicating that oxidation of sulfides with 4a-FIEtOOH occurs electrophilically to give sulfoxides and FIEtOH. The FIEtOH undergoes a pseudo S_N1 reaction to give H₂O and FIEt⁺,⁹ which is reduced with hydrazine monohydrate to give FIEtH. Thus, hydrazine would attack at the 4a(C) position of the isoalloxazine ring of FIEt⁺ to form the 4a-adduct (FIEtNHNH₂), which undergoes β -elimination of diazene (NH=NH) to afford FIEtH.¹⁶ Diazene thus formed again reacts with FIEt⁺ similarly to give FIEtN=NH, which undergoes β -elimination to afford FIEtH and molecular nitrogen. The FIEtH thus formed would undergo reaction with molecular oxygen to form FIEtOOH to complete the catalytic cycle.

In conclusion, we found that lumiflavin catalyzes oxidation of substrates such as sulfides and amines with molecular oxygen or even air in the presence of hydrazine monohydrate in TFE to give the corresponding oxides along with water and molecular nitrogen. This catalytic aerobic oxidation is extremely efficient and clean. Further extension of this unique catalytic reaction is under investigation.

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Supporting Information Available: Experimental procedures (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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