

Oxidation of sulfides with hydrogen peroxide catalyzed by 10,10'-linked bisflavinium perchlorates

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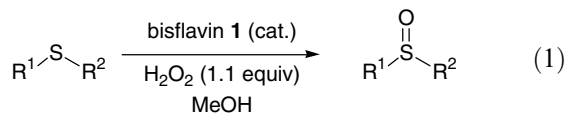
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Abstract—A series of bisflavinium perchlorates linked with methylene spacer at N¹⁰-position exhibit high catalytic activities for the oxidation of sulfides with hydrogen peroxide affording the corresponding sulfoxides. The kinetic studies revealed that the reaction rates are dependent on the spacer length of the catalysts due to their specific intramolecular electrochemical behaviors.

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Organocatalytic oxidations with hydrogen peroxide attract much attention as an important tool for environmentally benign oxidative transformations,¹ since they have potential designability for a variety of catalyses bearing high selectivity and sustainability. A limited number of electrophilic compounds including ketones,² sulfonylimines,³ and flavins⁴ are reported as efficient organocatalysts for the oxidations of olefins,² sulfides,^{3,4a–c} amines,^{4a,d} and ketones^{4e,f} with hydrogen peroxide. During the course of our studies on the creation of flavin-based molecular devices, we examine dynamic behaviors and functions of polyflavins connected with flexible methylene spacers. In this Letter, we wish to describe the synthesis of novel 10,10'-linked bisflavinium perchlorates **1** and their catalytic activities for the oxidation of sulfides with hydrogen peroxide, Eq. 1.



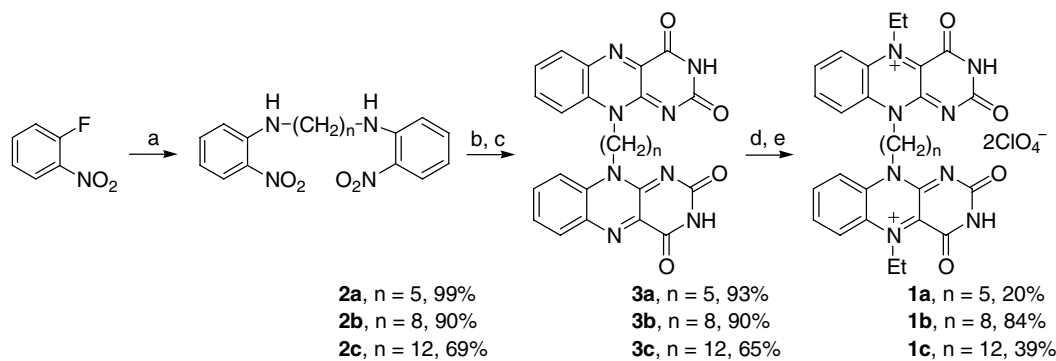
A series of bisflavinium perchlorates **1** were prepared starting from *o*-fluoronitrobenzene as shown in Scheme 1. Treatment of 1,ω-diaminoalkanes with *o*-fluoronitrobenzene gave nitroanilines **2**. Reduction of the nitro group and subsequent condensation with alloxan⁵

afforded bisflavin derivatives **3**. Reductive ethylation followed by oxidation with NaNO₂⁶ gave **1**, which was characterized by UV–vis, IR, and HRMS analyses.⁷

The catalytic activities of bisflavins **1a–c** (0.5 mol %) were examined for the reaction of 4-(methylthio)toluene (**4**, 2.95 × 10^{−2} M) with hydrogen peroxide (1.1 equiv) in MeOH-*d*₄ by means of ¹H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. Initial consumption rates of **4** (−d[**4**]/dt = *k*_{obs}) at 298 K were determined to be 4.66 × 10^{−5} M s^{−1} (**1a**), 5.33 × 10^{−5} M s^{−1} (**1b**), and 5.50 × 10^{−5} M s^{−1} (**1c**). The results indicate that bisflavins bearing longer methylene spacers exhibit higher catalytic activity. The *k*_{obs} value of **1c** is comparable to that of 5-ethylisoalloxazinium perchlorate (1.0 mol %, 6.83 × 10^{−5} M s^{−1}), which is the best monoflavin catalyst among those examined.^{4a} Although initial rates of the present oxidation are altered by spacer length of **1**, all of the bisflavin catalysts gave full conversion of various sulfides within 6 h affording the corresponding sulfoxides in excellent yields. Representative results are summarized in Table 1.⁸

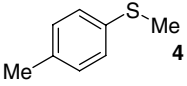
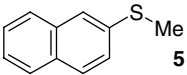
The mechanism of flavin-catalyzed oxidations with hydrogen peroxide has been established by the previous studies.^{4a} Flavinium cation (FlEt⁺) reacts with hydrogen peroxide to give active hydroperoxy species (FlEtOOH), which undergoes oxygen transfer to substrates and subsequent rate-determining dehydration of hydroxyflavin (FlEtOH) to regenerate FlEt⁺. The observed spacer dependency of the oxidation rates can be rationalized by the mechanism as shown in Scheme 2. After the

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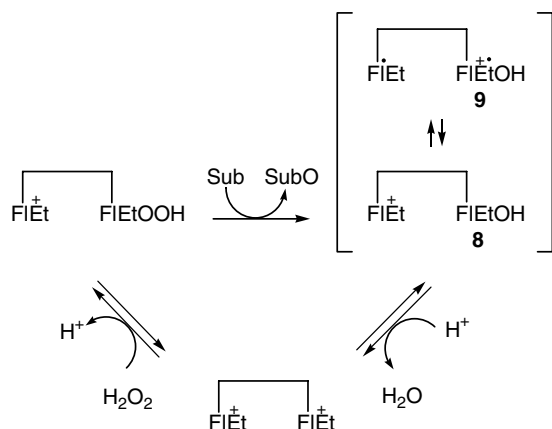
Scheme 1. Synthesis of bisflavinium perchlorate **1**. Reagents and conditions: (a) $\text{NH}_2(\text{CH}_2)_n\text{NH}_2$, Na_2CO_3 , DMSO, 140°C , overnight; (b) Zn, AcOH, 60°C , 1 h; (c) alloxan monohydrate, $\text{B}(\text{OH})_3$, AcOH, rt, overnight; (d) CH_3CHO , NaBH_3CN , $\text{Na}_2\text{S}_2\text{O}_4$, DMF, 60°C , 3 h and (e) HClO_4 , NaNO_2 , NaClO_4 , NH_3 aq, H_2O , rt, 1 h.

Table 1. Bisflavin-catalyzed oxidation of sulfides^a

Substrate	Catalyst	Time (h)	Yield ^b (%)
	1a	5	96
4	1b	5	97
4	1c	5	97
	1a	6	99
5	1b	6	93
5	1c	6	99
$(\text{C}_4\text{H}_9)_2\text{S}$ 6	1a	4	90
6	1b	4	96
6	1c	4	97
$(\text{C}_8\text{H}_{17})_2\text{S}$ 7	1a	6	88
7	1b	6	99
7	1c	6	99

^a The oxidation was carried out in the presence of a catalyst (1 mol %) and 30% H_2O_2 (1.1 equiv) in MeOH (1 mL) at 25°C .

^b Isolated yields.



Scheme 2. Proposed mechanism for the bisflavin-catalyzed oxidation with H_2O_2 .

similar oxygen transfer to substrates, bisflavin catalysts are converted into partially hydroxylated species **8**, which is in fast equilibrium with species **9** via single elec-

tron transfer.^{5b,9} This equilibration reduces the concentration of **8**, which leads to retardation of the rate-determining dehydration of the present catalytic cycle. Thus, the higher catalytic activity of **1c** is ascribed to specifically mobile flavin moieties arising from long methylene spacer. Further studies are currently underway to obtain detailed mechanistic information.

Acknowledgment

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- Characterization data for **1**. Compound **1a**: UV (acetonitrile) λ_{max} (log ϵ) 346 (4.13), 539 (3.80) nm; IR (KBr) 1650 (C=O) cm^{-1} ; HRMS (FAB) calcd for $\text{C}_{29}\text{H}_{31}\text{O}_4\text{N}_8$ ($\text{M}-2\text{ClO}_4^- + \text{H}^+$) 555.2468. Found 555.2446. Compound **1b**: UV (acetonitrile) λ_{max} (log ϵ) 329 (4.07), 541 (3.82) nm; IR (KBr) 1663 (C=O) cm^{-1} ; HRMS (FAB) calcd for

$C_{32}H_{37}O_4N_8$ ($M-2ClO_4^-+H^+$) 597.2924. Found 597.2936. Compound **1c**: UV (acetonitrile) λ_{max} ($\log \epsilon$) 376 (3.88), 543 (3.67) nm; IR (KBr) 1670 (C=O) cm^{-1} ; HRMS (FAB) calcd for $C_{36}H_{45}O_4N_8$ ($M-2ClO_4^-+H^+$) 653.3564. Found 653.3476.

8. A mixture of sulfide (0.22 mM), bisflavins **1a–c** (1 mol %) and 30% H_2O_2 aqueous solution (1.1 equiv) in MeOH (1 mL) was stirred at room temperature. After extraction with CH_2Cl_2 , the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel or Kugelrohr distillation to afford sulfoxide.
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