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Chiral ethylene-bridged flavinium salts: the stereoselectivity of flavin-10a-hydroperoxide formation and the effect of substitution on the photochemical properties

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ABSTRACT

A series of chiral non-racemic N^1,N^{10}-ethylene bridged flavinium salts **4** was prepared using enantiomerically pure 2-substituted 2-aminoethanols (R = isopropyl, phenyl, benzyl, 4-methoxybenzyl, 4-benzyloxybenzyl) derived from amino acids as the sole source of chirality. The flavinium salts were shown to form 10a-hydroperoxy- and 10a-methoxy-adducts with moderate to high diastereoselectivity depending on the ethylene bridge substituent originating from the starting amino acid. High diastereoselectivities (*dr* values from 80:20 to >95:5) were observed for flavinium salts bearing benzyl substituents attached to the ethylene bridge. The benzyl group preferred the face-to-face (*syn*) orientation relative to the flavinium unit; thereby effectively preventing nucleophilic attack from one side. This conformation was found to be the most stable according to the DFT calculations. Consequently, the presence of benzyl groups causes intermolecular fluorescence quenching resulting in a significant decrease in the fluorescence quantum yield from 11% for **4a** bearing an isopropyl substituent to 0.3% for **4c** containing a benzyl group and to a value lower than 0.1% for the benzyloxybenzyl derivative **4e**.

1. Introduction

Flavin-dependent monooxygenases promote the insertion of an oxygen atom into a variety of biological substrates and xenobiotics.[1] The oxidative process is mediated by flavin co-factor **Fl** (FAD or FMN, see Scheme 1A) forming (upon reduction with NADPH, and the subsequent reaction with oxygen) flavin-4a-hydroperoxide **Fl-OOH**, which introduces one oxygen atom into the substrate molecule. After oxygen transfer, the co-factor is regenerated via the elimination of water (Scheme 1A).[2] Many of these enzymes, e.g. Baeyer–Villiger (B.V.) monooxygenases, have been found to oxidize prochiral substrates, cyclic ketones to lactones and sulfides to sulfoxides with high stereoselectivities.[3,4] Thus, several biocatalytic procedures with flavin-monooxygenases have been developed for these reactions and some of them have even been transformed into valuable technologies.[5]

In parallel, artificial flavin systems have been under investigation for chemoselective and stereoselective sulfoxidation and B.V. oxidation reactions.[6,7] In these procedures, instead of natural unsubstituted **FlOOH**, 5-ethylflavin-4a-hydroperoxide **5-EtFlOOH**, formed from 5-ethylflavinium salts **5-EtFl$^+$X$^-$**, were employed because of their significantly higher stability outside an enzyme (Scheme 1B).[8] Only very recently, has artificial unsubstituted **FlOOH** been utilized in oxidation reactions, which was allowed because of its intramolecular stabilization via a tripeptide unit.[9]

There is also a difference in the formation of hydroperoxide between biological and artificial systems. Unlike enzymes, artificial oxidative species are mostly generated using hydrogen peroxide as a stoichiometric oxidant, which undergoes addition to the flavinium catalyst (Scheme 1B). The biomimetic procedure involving the reduction of 5-alkylflavinium salt **5-EtFl$^+$X$^-$** to **5-EtFlH$_2$** using a sacrificial reducing agent followed by reaction with molecular oxygen has also been described for artificial monooxygenation, however, it has not been used in a stereoselective fashion to date.[6]

Leaving aside B.V. oxidations, in which the reaction is significantly influenced by the Criegee intermediate breaking down,[1c] the stereoselectivity of monooxygenation is controlled by two sequential steps: (i) The formation of hydroperoxide and (ii) the stereoselective transfer of an oxygen atom from the hydroperoxy group onto the substrate (Fig. 1). Both these steps must occur stereoselectively to produce one enantiomer of the sulfoxide in

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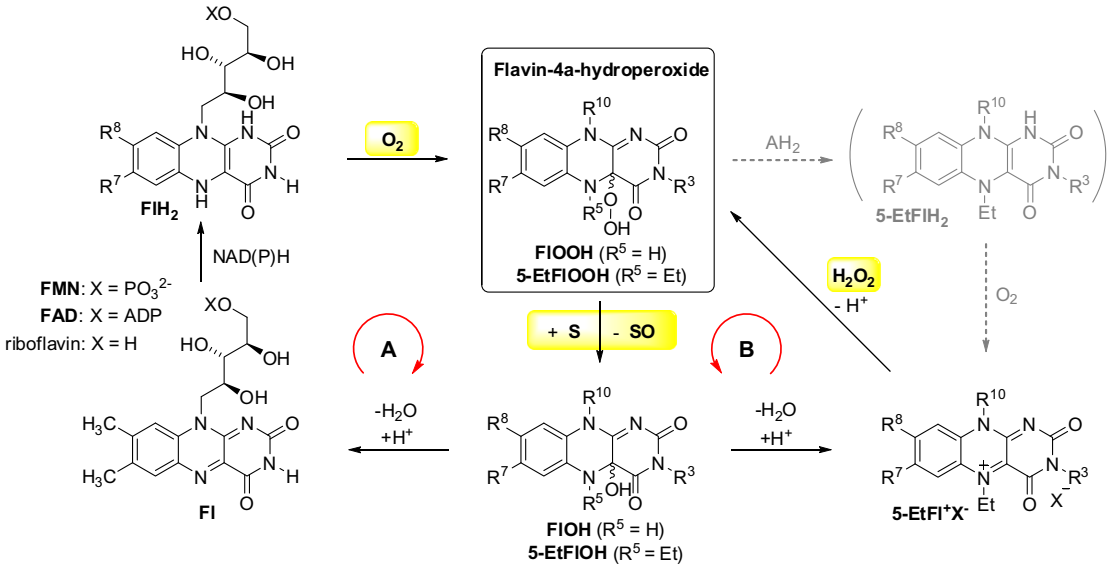


Scheme 1. Mechanism of monooxygenations promoted by flavin-4a-hydroperoxide and its generation in biological (A) and artificial (B) systems.

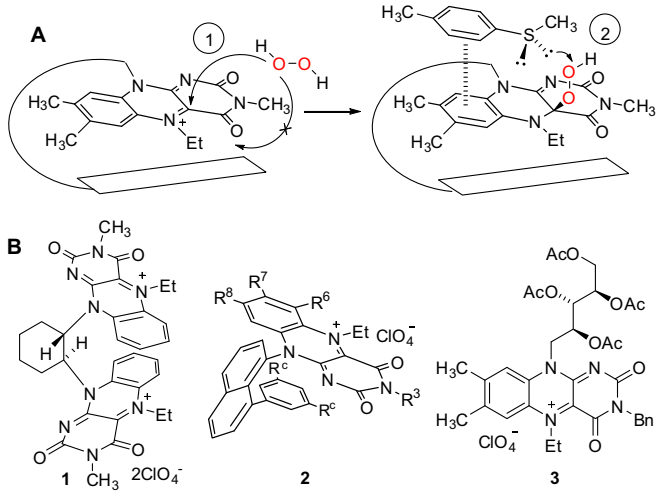
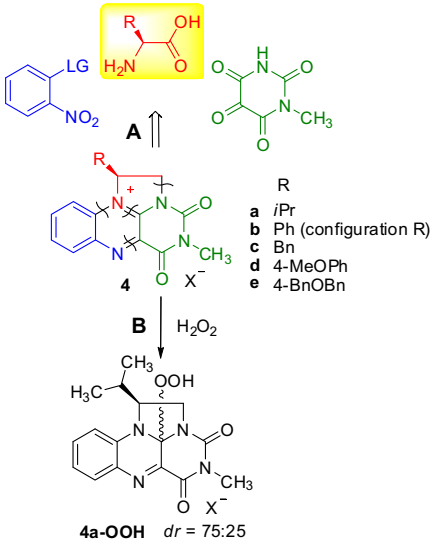


Figure 1. Origin of stereoinduction in monooxygenations mediated by flavinium salts shown on an example of sulfoxidation (A) and structures of selected chiral flavinium salts (B).



Scheme 2. Retrosynthesis of ethylene-bridged flavinium salts **4** (A) and the structure of flavin-10a-hydroperoxide **4a-OOH** (B).

excess. In enzymes, the stereoselectivity is controlled by the topography of the active site containing a chiral environment created by various amino acid residues. In artificial systems, two approaches have been applied: (i) Mimicking the binding site with a chiral cavity comprised of a cyclodextrin covalently bound to a flavin subunit[7b,10] or (ii) the introduction of a 'cap' allowing access of hydrogen peroxide from only one side (see catalysts **1** and **2**).[11] The second step, the transfer of oxygen, is believed to be controlled by π–π interactions between an aromatic substrate and flavin hydroperoxide (Fig. 1A). Catalysts **1** and **2** have been shown to catalyze the B.V. oxidation of phenylcyclobutanones[11c] and the sulfoxidation of aromatic sulfides[11a] with observed enantioselectivities up to 61 and 74%, respectively. Interestingly, a simple 5-ethyltetraacetylriboflavinium salt **3** was found to form a hydroxy adduct (a model of hydroperoxide) in 29% *de,* which was subsequently reflected by the stereoselective H_2O_2-sulfoxidation of methyl *p*-tolyl sulfide catalyzed by **3** (30% *ee*).[12]

In our preliminary communication,[13] we found that the chiral 1,10-ethylene-bridged flavinium salt **4a** bearing an amino acid residue (R = isopropyl) attached to the ethylene bridge can be straightforwardly prepared from valine (Scheme 2A). Salt **4a** is able to catalyze sulfoxidation reactions using hydrogen peroxide in a similar manner to that observed with 5-alkylflavinium salts (Scheme 2). This oxidation occurs through flavin-10a-hydroperoxide **4a-OOH** formed via the addition of hydrogen peroxide to **4a**.[14] Interestingly **4a-OOH** was found to be formed with *dr* = 75:25.

Having in mind their simple synthesis allowing the easy introduction of an amino acid residue and the ability to form adducts (e.g. hydroperoxides), salts **4** seem to be suitable models to study the effect of covalently attached amino-acid residues on the diastereoselectivity of hydrogen peroxide adduct formation. Herein, we report our investigation on flavins **4** with aromatic residues known to accompany flavin co-factors in various enzymes.[15] Besides their effect on adduct formation, we also observed the strong effect of the side chain structure on the spectroscopic properties of **4**. We believe these findings will help to design new efficient flavinium catalysts as well as to elucidate the