Flavin–cyclodextrin conjugates as catalysts of enantioselective sulfoxidations with hydrogen peroxide in aqueous media†

Viktor Mojr,[a] Vladimír Herzig,[ab] Miloš Buděšínský,[b] Radek Cibulka*[a] and Tomáš Kraus*[b]

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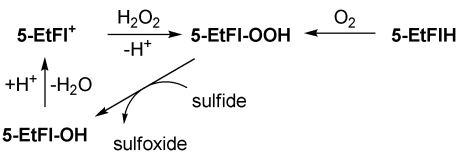
β-Cyclodextrin–flavin conjugates are highly efficient catalysts for the sulfoxidation of methyl phenyl sulfides with hydrogen peroxide in neat aqueous media operating at loadings down to 0.2 mol% and allowing for enantioselectivities up to 80% ee.

Enantiomerically pure sulfoxides are important chiral auxiliaries employed in asymmetric syntheses as well as active substances used in the pharmaceutical chemistry.[1] Enantioselective sulfoxidation of prochiral sulfides thus represents one of the key transformations in organic synthesis. Various chemocatalytic and biocatalytic systems for sulfoxidation have been developed, the use of transition metal complexes with chiral ligands as catalysts along with hydrogen peroxide as the terminal oxidant being studied in particular.[1–3] Metal-catalyzed sulfoxidations with hydrogen peroxide are usually highly enantioselective (ee > 90%) and require low loadings of the catalyst (1–2%). With most of these catalysts, however, high enantioselectivities are achieved partly by overoxidation of one of the sulfoxide enantiomers to sulfone (kinetic resolution) at the expense of the yield.[2,3] In contrast, sulfoxidations promoted by organocatalysts are devoid of excessive oxidation.[4] Among organocatalytic oxidation methods, those utilizing 5-ethylflavin hydroperoxides (5-EtFl-OOH) formed *in situ* from the corresponding flavinium salts (5-EtFl$^+$) and hydrogen peroxide seem to be the most promising for sulfoxidations.[5] Similarly, reduced 5-ethylflavins (5-EtFlH) were used[5] for the catalysis of oxidations by H_2O_2, being activated by oxygen in the first catalytic cycle (Scheme 1). When planarly chiral flavinium catalysts[6] were employed, substituted thioanisoles were oxidized with enantiomeric excess up to 65%,[6a] provided that relatively high loading of the catalyst (up to 12 mol%) was used.

Stereodiscrimination in oxidation reactions catalyzed by chiral flavin derivatives studied so far is induced by weak π–π interaction between an oxidant (flavin hydroperoxide) and an aromatic substrate.[6b,7] It can be expected that the catalytic properties of these systems could be further improved by an approach inspired by enzyme-like catalysis which utilizes a chiral substrate-binding site to control the stereoselectivity of the transformation. In particular, cyclodextrins and their derivatives have been extensively studied as enzyme mimics capable of significant enhancement of the reaction rates of various organic transformations in neat aqueous media.[8–11] In addition, cyclodextrin cavities provide a chiral environment, thus allowing, in principle, enantioselective reactions.[10] Aiming at the development of flavin-based organocatalysts for enantioselective sulfoxidations,[6b] we have considered the use of cyclodextrin macrocycle as chiral auxiliary covalently attached to the flavinium moiety hoping that preorganization of the substrate by complexation inside the cyclodextrin cavity could enhance both the rate and enantioselectivity of the sulfoxidation. Flavin–cyclodextrin conjugates have already been investigated[11] as catalysts (enzyme mimics) for redox reactions and were found to be active catalysts of oxidation of various substituted benzyl alcohols[11c,d] to corresponding aldehydes and phenylmethanethiols[11d] to disulfides. None of them, however, met all the requirements for a catalyst for oxidation by hydrogen peroxide. To this end, we have designed two new flavin–cyclodextrin conjugates **1** and **2** (Fig. 1) with N^5-ethylated dihydroalloxazine and dihydroisoalloxazine moieties which are bonded through N^1 and N^3 positions, respectively, to the primary C^6 carbon of β-cyclodextrin by amidomethylene linkage.

In this communication, we describe the syntheses of conjugates **1** and **2** and their abilities to catalyze enantioselective oxidation of aryl methyl sulfides by hydrogen peroxide. Their syntheses were achieved by PyBOP-promoted condensation reactions of the corresponding N^1- and N^3-carboxymethylflavin derivatives **3** and **4** with 6-amino-β-cyclodextrin (Scheme 2) which gave conjugates **5** and **6** in 72%



Scheme 1 Catalytic cycle of sulfoxidation by hydrogen peroxide mediated by flavinium salts **5-EtFl**$^+$.

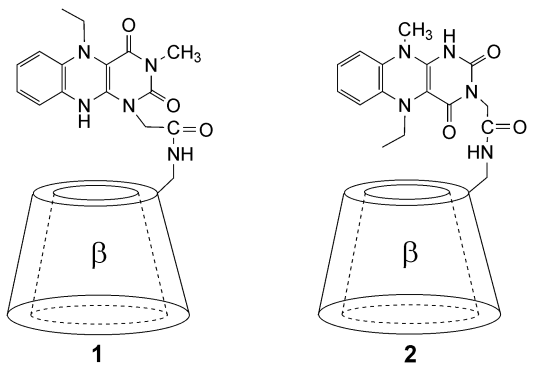


Fig. 1 Structures of flavin–cyclodextrin conjugates used in the study.

[a] *Department of Organic Chemistry, Institute of Chemical Technology, Prague, Technická 5, Prague 6, Czech Republic. E-mail: cibulkar@vscht.cz; Fax: +420 220444288*
[b] *Institute of Organic Chemistry and Biochemistry AS CR, v.v.i., Flemingovo nám. 2, 166 10 Prague 6, Czech Republic. E-mail: kraus@uochb.cas.cz; Fax: +420 220183560*

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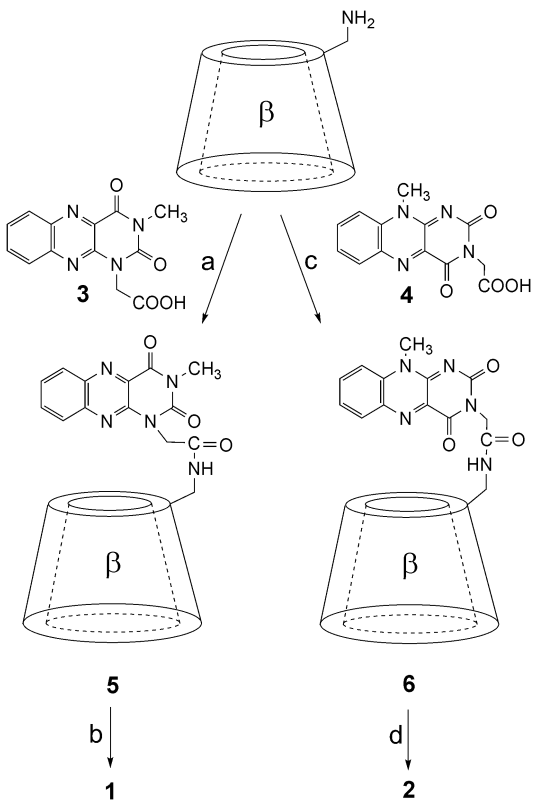
and 40% yields, respectively. In order to be catalytically active, the flavin moiety requires an alkyl (most often ethyl) substituent at the N^5 position. Thus, N^5-ethylation of **5** and **6** was accomplished by modified[12] reductive alkylation employing Pd-catalyzed hydrogenation and a large excess of acetaldehyde in a mixture of ethanol and water acidified with perchloric acid. Since N^5-ethylated flavins are sensitive to air oxidation, making direct monitoring of the course of the reaction by common techniques difficult, the progress of reductive alkylation was followed by testing the activity of the catalyst in the oxidation reaction of thioanisole. In this way, the optimal reaction time for the reductive alkylation was determined to be 24 hours. Parallel control experiments using native β-cyclodextrin in place of the conjugates revealed that the β-cyclodextrin macrocycle is stable under these reaction conditions. Despite our great efforts, we were unable to record clear NMR spectra of the N-alkylated conjugates in their reduced forms due to peak broadening, probably as a result of the presence of radical species. However, the expected structures of the N^5-alkylated conjugates were supported by high resolution mass spectra; peaks of reduced species could be observed in the spectrum of **2** recorded using a freshly prepared sample, whereas the presence of flavinium salts was evidenced in solutions of both **1** and **2** after exposing the samples to air oxygen.[13]

Next, the abilities of the N^5-alkylated alloxazine and isoalloxazine conjugates **1** and **2** to catalyze hydrogen peroxide-promoted oxidation of sulfides were tested using a series of six methyl phenyl sulfides (Table 1) differing in substitution in the *para* position. The reactions were conducted in buffered (sodium phosphate) aqueous solutions with 1 mol% loadings[15] of the catalysts along with an excess (2.3 equivalents) of hydrogen peroxide. While conjugate **1** provided optimal conversions at pH 7.5, the isoalloxazine analogue **2** was employed in the phosphate buffer at pH 2.9.[16]



Scheme 2 Syntheses of flavin–cyclodextrin conjugates **1** and **2**; (a) compound **3**, PyBOP, DIPEA, DMF; (b) CH_3CHO, Pd/C, H_2, EtOH, H_2O, $HClO_4$; (c) compound **4**, PyBOP, DIPEA, DMF; (d) CH_3CHO, Pd/C, H_2, EtOH, H_2O, $HClO_4$.

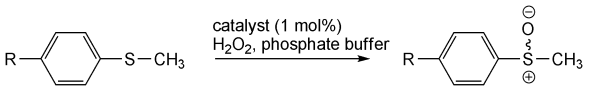
The starting thiols proved to be poorly soluble in the aqueous environment and tended to form emulsions or fine suspensions. It was found that vigorous shaking of the reaction vials with a wrist shaker provided the best reproducibility. In most cases the reaction mixture became homogeneous after several minutes of reaction time. The poor solubility of the starting materials in the reaction mixture did not allow determination of kinetics of the reactions and quantification of rate enhancements. Nevertheless, a comparison of efficiencies of the catalysts was made by determining (i) the conversions after a 10 minute period and (ii) the reaction time required to achieve at least 90% conversion.

In general, alloxazine conjugate **1** produced higher conversions for the oxidation reactions compared with isoalloxazine conjugate **2**. Under catalysis of **1** most substrates were oxidized with a conversion of over 90% within 10 minutes. The isoalloxazine conjugate showed lower acceleration [except for 4-(methylsulfanyl)phenol (entry 6) where it provided nearly quantitative oxidation within 10 minutes]. Nevertheless, with the exception of 4-(methylsulfanyl)benzoic acid (entries 11 and 12) all oxidation reactions catalyzed with conjugates **1** or **2** proceeded to at least 90% conversion within 90 minutes. 4-(Methylsulfanyl)benzoic acid proved to be a difficult substrate for oxidation for both catalysts, presumably because of the electron withdrawing nature of the carboxylic function and its very poor solubility in aqueous solutions. It is important to note that no over oxidation of sulfides to sulfones was observed in any of the oxidations catalyzed by **1** and **2**.

Analyses of the enantiomeric excesses of the isolated sulfoxides by HPLC on chiral phases (see Table 1 and ESI† for details) revealed that both catalysts **1** and **2** were able to exert various degrees of enantioselectivity across the series of thioanisole oxidations. Remarkably, conjugate **1** consistently provided enantioselectivities in the range 64% up to 80% ee, the highest value being observed in the case of the oxidation of methyl 4-methylphenyl sulfide (entry 13). The observed differences in enantioselectivities exhibited by **1** and **2** could be caused by different contribution of non-stereoselective intermolecular oxidation (reaction of flavin hydroperoxide with a sulfide outside the cavity) or by different orientation of the flavin moiety with respect to the bound substrate. Blank experiments (entries 3 and 4) carried out under the same conditions using a mixture of β-cyclodextrin and 5-ethyl-1,3-dimethylalloxazinium salt **7** or 5-ethyl-3,10-dimethylalloxazinium salt **8** (Fig. 2) in place of conjugates **1** and **2**, respectively, showed lower efficiency in terms of conversions and provided no detectable enantioselectivities, therefore proving that covalent linking of both flavin and β-cyclodextrin components is essential.

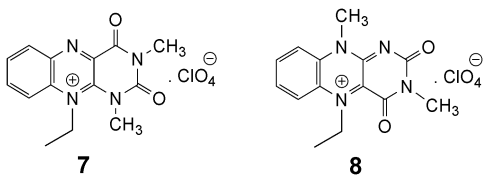
The high conversion rates achieved with conjugate **1** prompted us to further decrease the catalyst loadings. Thus, when 0.5 mol% of conjugate **1** was employed for the oxidation

Table 1 Enantioselective H_2O_2-sulfoxidations of aryl methyl sulfides catalyzed by conjugates **1** and **2**[a]



Entry	R	Catalyst[c]	Conv. 10 min (%)	Optimized conversion Time[d]/min	Conv. (%)	ee[e] (%)
1	H	**1**	83	20	93	64
2	H	**2**	20	90	99	21
3	H	**7** + **β-CD**[f]	17	120	80	0
4	H	**8** + **β-CD**[f]	17	120	82	0
5	OH	**1**	91	—	—	73
6	OH	**2**	95	—	—	9
7	OCH_3	**1**	97	—	—	72
8	OCH_3	**2**	78	36	90	28
9	OR[b]	**1**	98	—	—	76
10	OR[b]	**2**	46	30	96	21
11	COOH	**1**	30	60	34	73
12	COOH	**2**	4	120	23	35
13	CH_3	**1**	97	—	—	80
14	CH_3	**2**	18	120	95	41
15	CH_3	**1** (0.5%)	67	60	99	77
16	CH_3	**1** (0.2%)	35	60	79	77

[a] Conditions: substrate (0.1 mmol), H_2O_2 (2.3 equiv.), phosphate buffer pH 7.5 (for **1**) or 2.9 (for **2**), RT. [b] R=O(CH$_2$)$_2$O(CH$_2$)$_2$OCH$_3$. [c] Catalyst loading 1 mol% (related to the substrate) if not stated otherwise. [d] Time necessary to achieve at least 90% conversion, maximally 120 min. [e] Enantiomer ratios were determined by HPLC on a chiral stationary phase (see ESI†). [f] For structures of compounds **7** and **8**, see Fig. 2.



7 **8**

Fig. 2 Structures of flavin catalysts **7** and **8**.

of methyl 4-methylphenyl sulfide (entry 15), quantitative conversion was accomplished within 60 minutes of reaction time. With 0.2 mol% loading of **1** 79% conversion was achieved within the same period (entry 16). Further increase of reaction time produced no effect, indicating that the catalyst was inactive after 1 hour of reaction time.

In conclusion, we have synthesized two β-cyclodextrin–flavin conjugates, which proved to be highly efficient catalysts for the oxidation of electron-rich methyl phenyl sulfides to sulfoxides by hydrogen peroxide. In particular, the catalytic system based on β-cyclodextrin–alloxazine conjugate **1** is distinguished from other organocatalysts by *fast near-quantitative conversions* and *high enantioselectivities*, reaching up to 80% ee. It is also remarkable that the reactions proceed in *neat aqueous media* with *very low loadings* of the catalyst down to 0.2 mol% with a turnover number up to 395. Structural modifications of both the flavin and cyclodextrin components, which may bring about further improvement in efficiencies (namely stability of the catalyst) and enantioselectivities of the sulfoxidations as well as broadening the substrate scope, are under investigation in our laboratories.

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