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Organocatalytic sulfoxidation in micellar systems containing amphiphilic flavinium salts using hydrogen peroxide as a terminal oxidant

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Abstract

Amphiphilic flavinium salt [10-dodecyl-5-ethyl-3,7,8-trimethylisoalloxazinium perchlorate (**1b**)], solubilized in micelles of sodium dodecyl sulfate (SDS), hexadecyltrimethylammonium chloride (CTAC), hexadecyltrimethylammonium nitrate ($CTANO_3$) or Brij 35, catalyzes the chemoselective oxidation of thioanisole (**2**) to its corresponding sulfoxide **4**. The sulfoxidation rates observed in micelles in the presence of **1b** exceeded, in most instances, those of the reactions catalyzed by its hydrophilic homologue [5-ethyl-3,7,8,10-tetramethylisoalloxazinium perchlorate (**1a**)] in homogeneous solutions. Reaction rates were strongly dependent on the type of micellar matrix and on the pH value. The highest acceleration rate was found in SDS micelles at pH 4.4 ($TOF = 3 \times 10^3\ h^{-1}$). In our experiments, micelles favoured the catalytic process rather than the non-catalyzed reaction, this effect being especially pronounced in cationic micelles, for which the non-catalyzed reaction was markedly suppressed. The ratio v_{cat}/v_0 of the catalyzed and non-catalyzed reaction rates was almost 40 in $CTANO_3$, while in homogeneous solution its value did not exceed 7.

Keywords: Sulfoxidation; Micelles; Organocatalysis; Green chemistry; Flavinium salts

1. Introduction

The oxidation of sulfides to sulfoxides has been the subject of intensive investigation due to the importance of sulfoxides as useful intermediates, or as chiral auxiliaries, in the process of organic synthesis [1–3]. Several sulfoxides, such as the proton pump inhibitors, omeprazol, lanzoprazol and rabeprazol, also exhibit biological activity [4,5]. Recently great interest has been focused on environmentally friendly oxidation systems, in particular those using hydrogen peroxide or oxygen as terminal oxidants [6,7]. One promising new sulfoxidation method uses the oxidation ability of flavin-4a-hydroperoxide (Fl-OOH, Scheme 1) [8], which is known to be a versatile oxidizing agent in flavin monooxygenases [9–11]. In the case of these enzymes, Fl-OOH derived from riboflavin ($R^1 = R^2 = H$ and R^3 = ribityl) acts as an oxidizing agent. In artificial systems, stable Fl-OOH can be prepared by the reaction of flavinium salts (Fl^+) with hydrogen peroxide, or by the reaction of their reduced form (FlH) with molecular oxygen (Scheme 1) [12].

Flavin-4a-hydroperoxides (Fl-OOH) were first used as stoichiometric agents in the oxidation of sulfides to sulfoxides [12–14]. More recently Bäckvall et al. described an organocatalytic system, in which Fl-OOH was generated in situ from flavinium salt (Fl^+) present in the reaction mixture in a catalytic amount (1–2% with respect to the substrate amount), and from hydrogen peroxide employed as a stoichiometric terminal oxidant (Scheme 2) [15–18]. Murahashi et al. described the oxidation of sulfides using molecular oxygen catalyzed by flavinium salts [19]. In this process, Fl-OOH was generated by the reaction of reduced flavinium salt (FlH) with oxygen in the air. A fluorinated solvent (e.g. trifluoroethanol) was used to ensure a sufficient concentration of oxygen in the reaction mixture. To keep the catalytic cycle in progress, this process required a stoichiometric amount of hydrazine to reduce the flavinium salt (Fl^+, Scheme 1).

Both of the systems described above are highly chemoselective and exclusively produce sulfoxides without overoxidation to sulfones [15–19]. Similar catalytic systems have been applied

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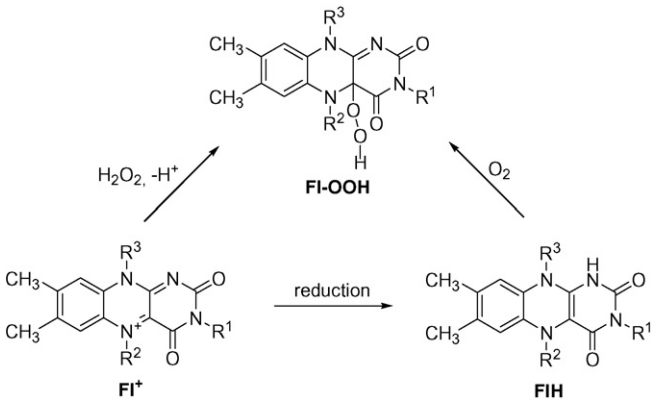
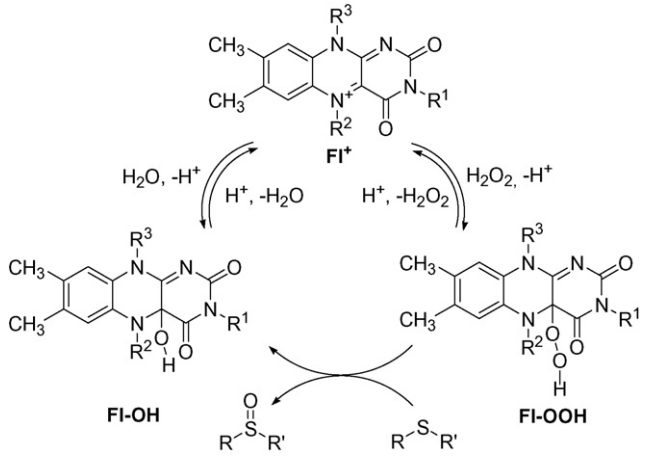


Scheme 1.

to the oxidation of tertiary amines to *N*-oxides [15,16], and to Baeyer-Villiger oxidation [20,21]. Some of these systems, employing chiral flavinium salts, have produced oxidation products with moderate enantioselectivity [22–24].

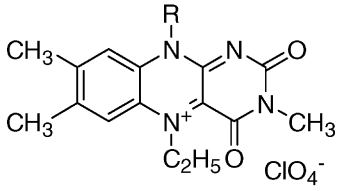
Hitherto, the oxidations catalyzed by flavin-4a-hydroperoxide (Fl-OOH) have been studied as homogeneous reactions in organic solvents. Recently Bäckvall [25] reported the use of ionic liquid as a reaction medium. Surprisingly however, until now no instances of flavin-catalyzed oxidations in nanoaggregates, such as micelles or microemulsions, have been reported despite the potential benefits; namely an increased reaction rate due to micellar catalysis [26,27], as well as the mild conditions and water-based reaction systems essential to green technologies [7,28,29].

Therefore, we decided to prepare and investigate micellar systems for catalytic oxidation based on amphiphilic flavinium salt **1b** comicellized with cationic, anionic or non-ionic surfactants. Using the oxidation of thioanisole (**2**) as a model reaction, we aimed to establish the influence of the micellar medium in each instance, as well as the influence of the micellar surface charge on the catalytic efficiency of flavinium salts. The efficiency of the prepared catalysts was compared with that of hydrophilic homologue **1a** in a homogeneous solution. We also focused on the effect of pH because two steps in the catalytic cycle involve acid–base equilibria (Scheme 2). To the best of our knowledge, ours is the first artificial oxidation system based on flavinium salts operating in an aqueous solution.



Scheme 2.

Formula **1**



1a: R = CH_3
1b: R = $C_{12}H_{25}$

2. Experimental

2.1. General methods

Temperature data were uncorrected. NMR spectra were recorded on a Varian Mercury Plus 300 (299.97 MHz for ^{1}H and 75.44 MHz for ^{13}C) and a Bruker Avance DRX 500 spectrometer (500.13 MHz for ^{1}H and 125.77 MHz for ^{13}C). Chemical shifts are given in ppm relative to tetramethylsilane ($\delta = 0.0$) used as an internal standard. TLC analyses were carried out on a DC Alufolien Kieselgel 60 F_{254} (Merck). Preparative column chromatography separations were performed on a silica gel Kieselgel 60 0.040–0.063 mm (Merck). Elemental analyses (C, H, N) were performed on a Perkin-Elmer 240 analyser; determination of Cl was made by argentometric titration. UV–vis spectra were recorded on a Varian Cary 50 spectophotometer. Starting materials and reagents used for the preparation of the catalyst were obtained from Aldrich, Lancaster and Fluka, and were used without purification. Solvents and substrates used for kinetic experiments (analytical grade) were purchased from Fluka and Penta. Concentration of hydrogen peroxide was determined by manganometric titration.

2.2. Procedure for synthesis and characterization of *1b*

Acetaldehyde (3.1 mL; 55.2 mmol) and palladium on carbon (10%; 0.080 g) were added to a suspension of 10-dodecyl-3,7,8-trimethylisoalloxazine (**3**) (0.217 g; 0.511 mmol) in acetic acid (62 mL) and water (6 mL). The resulting mixture was stirred for 4 days in an autoclave under H_2 (0.6 MPa) at room temperature. Then the catalyst was filtered off, the acetic acid was evaporated under reduced pressure, and the remaining green solid was dried in vacuo. The residue was suspended in 2 M perchloric acid (4 mL), and sodium perchlorate (1.397 g; 11.41 mmol) and sodium nitrite (0.525 g; 7.61 mmol) were added. Methanol (40 mL) was added to this system to form a homogeneous solution. The mixture was then stirred for 2 h at 10 °C. Methanol was evaporated under reduced pressure, and the precipitated violet solid was filtered off, washed with water and dissolved in methanol. The methanol was evaporated again, the solid residue was suspended in petroleum ether, filtered off and dried in vacuo. The yield of **1b** was 0.251 g (89 %).

Violet crystalline solid; mp 106–108 °C; ^{1}H NMR (CD_3CN, 500 MHz) δ 0.89 (t, $J = 6.6$ Hz, 3H, alkyl-CH_3), 1.30 (m, 16H,

(CH_2)$_8$), 1.55 (m, 2H, NCH$_2$CH$_2$CH_2), 1.79 (t, J = 6.9 Hz, 3H, N$^+$CH$_2$CH_3), 1.84 (m, 2H, NCH$_2$CH_2), 2.59 (s, 3H, 7-CH_3Ar), 2.65 (s, 3H, 8-CH_3Ar), 3.42 (s, 3H, NCH_3), 4.76 (m, 2H, NCH_2CH$_2$), 5.00 (bs, 1H, N$^+$CHH), 6.10 (bs, 1H, N$^+$CHH), 7.90 (s, 1H, 9-H$_{Ar}$), 8.23 (s, 1H, 6-H$_{Ar}$); ^{13}C NMR (CD$_3$CN, 125 MHz) δ 14.4 (alkyl-CH$_3$), 15.5 (N$^+$CH$_2$$CH_3$), 20.3 (7-$CH_3$Ar), 21.5 (8-$CH_3$Ar), 23.4 (alkyl-$CH_2$), 27.3 (alkyl-$CH_2$), 27.4 (alkyl-$CH_2$), 27.7 (alkyl-$CH_2$), 29.9 (alkyl-$CH_2$), 30.0 (N$CH_3$), 30.2 (alkyl-$CH_2$), 30.3 (alkyl-$CH_2$), 30.4 (alkyl-$CH_2$), 32.6 (alkyl-$CH_2$), 48.5 (N$CH_2$), 53.3 (N$^+$$CH_2$), 118.8 (9-$CH_{Ar}$), 121.7 (6-$CH_{Ar}$), 127.6 (9b-$C_{Ar}$), 131.3 ($C_{Ar}$), 136.7 (5b-$C_{Ar}$), 143.2 (CH$_3$-$C_{Ar}$), 150.2 ($C_{Ar}$), 153.8 (CH$_3$-$C_{Ar}$), 154.1 ($C$=O), 157.1 ($C$=O). For $C_{27}H_{41}ClN_4O_6.2H_2O$ calculated: C 55.05%, H 7.70%, N 9.51%, Cl 6.02%; found: C 55.25%, H 7.39%, N 9.34%, Cl 6.41%.

2.3. Kinetic measurements

The oxidation of thioanisole (**2**) (both in micellar and in homogeneous solutions) was performed in vials thermostated to 25.0 ± 0.5 °C. The reaction mixtures were prepared by mixing aliquot portions of stock solutions of reactants and other additives: thioanisole (**2**) ($c = 6.00 \times 10^{-1}$ mol L^{-1} in methanol), flavinium salt **1** ($c = 9.0 \times 10^{-3}$ mol L^{-1} in methanol, freshly prepared; it was not added in the blank experiments), surfactant ($c = 1.00 \times 10^{-1}$ mol L^{-1} in water), internal standard (1,3-dimethoxybenzene, $c = 3.0 \times 10^{-2}$ mol L^{-1} in 0.1 M solution of surfactant) and phosphate buffer ($c = 5.00 \times 10^{-1}$ mol L^{-1}). Diluted inorganic acids were used instead of the buffer in experiments performed at pH < 1.6: $HClO_4$ was used in SDS, Brij 35 and homogeneous solution; HCl was used in CTAC; HNO_3 was used in $CTANO_3$. The prepared mixtures were tempered for 20 min before the experiment was started. The reactions were initiated by the addition of 100 μL of hydrogen peroxide solution ($c = 4.50 \times 10^{-1}$ mol L^{-1}) to the prepared mixture. The resulting concentrations of reactants and auxiliaries in the reaction mixtures were as follows: thioanisole (**2**) 1.5×10^{-2} mol L^{-1}; hydrogen peroxide 2.25×10^{-2} mol L^{-1}; flavinium salt (**1**) 2.3×10^{-4} mol L^{-1}; 1,3-dimethoxybenzene 7.5×10^{-3} mol L^{-1}; buffer 1.0×10^{-1} mol L^{-1}; surfactant 1.0×10^{-1} mol L^{-1}.

The concentration of methyl phenyl sulfoxide (**4**) was monitored by HPLC using 1,3-dimethoxybenzene as an internal standard: 100 μL of the reaction mixture was diluted with 100 μL of acetonitrile and the sample was analyzed on an Ecom HPLC System (column: Separon SGX C18 column, 150 × 4.6 mm; eluent: methanol/water, 0.5 mL min^{-1}) using UV spectrophotometric detection. The presence of the corresponding sulfone was tested by HPLC after each experiment.

2.4. Study of flavinium salts 1–4a-hydroxyflavins 1-OH equilibrium

The apparent pK'_a values of **1** [30] were calculated using Origin 6.1 software (Boltzmann function) [31] by non-linear regression analysis of absorbance versus pH data (see supplementary data) at the maximum absorption wavelengths of **1** and **1**-OH. The pK'_a given in Table 1 are the averages of the obtained values. Either phosphate buffer (for pH > 1.6) or one of $HClO_4$, HCl or HNO_3 (for pH < 1.6) was used to adjust the pH values of the systems. Acidity function (H_0) values [33,34] were used instead of pH values for the $HClO_4$, HCl and HNO_3 solutions.

Table 1
Apparent pK'_a values of flavinium salt **1**–pseudobase (**1**-OH) equilibrium determined by UV–vis spectrometry[a]

Medium	pK'_a	λ_{max} (nm)	
		1	**1**-OH
H_2O/MeOH[b]	2.8[c]	548	360
SDS	3.9	547	353
CTAC	0.4	563	355
$CTANO_3$	0.6	547	352
Brij 35	1.4	552	354

[a] **1a** and **1b** were used in homogeneous and micellar solutions, respectively.
[b] 50:50 (v/v).
[c] 4.1 in water [32].

2.5. Binding constant of thioanisole (2) in Brij 35

The value of the binding constant K_S of **2** to micelles of Brij 35 [35] was estimated spectrophotometrically from the variation of absorbance A_{obs} at 255 nm with surfactant concentration c_{surf}. The binding constant was evaluated using Eq. (1) [36]

$$\frac{A_{obs} - A_w}{[D_n]} = A_M K_S - A_{obs} K_S \quad (1)$$

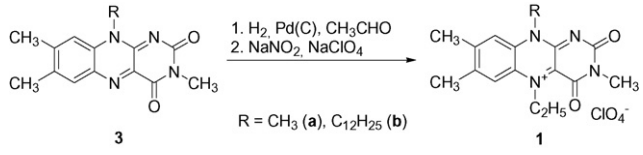
where A_{obs} is the observed absorbance, A_M and A_W are the corresponding absorbances of **2** in water and in micellar pseudophase and [D$_n$] is the concentration of micellized surfactant ([D$_n$] = c_{surf} − cmc).

The binding constant was obtained as a slope of the linear plot ($A_{obs} - A_w$)/[D$_n$] versus A_{obs}. A similar method was used by Blaskó et al. [37] and Bosco Bharathy et al. [38] for the estimation of binding constants of **2** in CTAX and SDS micelles.

3. Results and discussion

3.1. Preparation of flavinium catalysts

Flavinium catalysts **1** were synthesized from the corresponding 10-alkyl-3,7,8-trimethylisoalloxazines (**3**) by the reaction of reduced **3** with acetaldehyde, followed by the oxidation of 5-ethyl derivative with sodium nitrite in perchloric acid (see Scheme 3). Flavinium salt **1a** was prepared according to the procedure described by Mager and Tu [39] (for characterization of



Scheme 3.

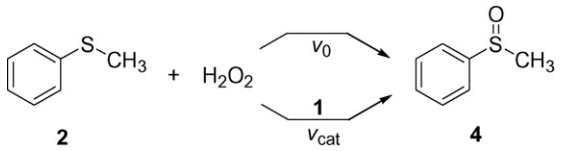
1a see supplementary data). The procedure for the preparation of its amphiphilic homologue **1b** was appropriately modified (see Section 2.2.). The synthesis of **3a** is described elsewhere [40,41]. Lipophilic isoalloxazine **3b** was prepared according to the procedures described for similar 10-alkyl derivatives [42], starting from 1,2-dimethyl-4,5-dinitrobenzene (for details see supplementary data).

3.2. Investigation of catalytic systems for sulfide oxidation

Amphiphilic flavinium salt **1b** was investigated as a catalyst for the oxidation of sulfides with hydrogen peroxide in three types of micelles: anionic, cationic and non-ionic. The micellar matrix consisted of "inert" non-reactive surfactants: sodium dodecyl sulfate (SDS), hexadecyltrimethylammonium chloride (CTAC), hexadecyltrimethylammonium nitrate ($CTANO_3$), and Brij 35. The surfactants employed in this study have been commonly used for the preparation of micellar catalysts in many other studies [26,27]. The reactivity of the prepared systems was examined by measuring the rate of model substrate (thioanisole (**2**)) oxidation. The measurements were performed under mild conditions (25 °C, buffered micellar solutions) at concentrations applicable to a preparative scale using a small excess of hydrogen peroxide (1.5 equivalents with respect to the substrate), a catalytic amount of flavinium salt **1** (1.5 mol%), and a relatively high concentration of surfactants ($c = 1.0 \times 10^{-1}$ mol L^{-1}) markedly exceeding their critical micelle concentrations [26]. The substrate concentration was selected to be as high as possible ($c = 1.5 \times 10^{-2}$ mol L^{-1}); the only limiting factor being its solubility in the micellar system.

It has been generally accepted [26,27,43] that micellar catalysis combines the effects of an increase in the effective concentration of the lipophilic substrate as well as of the lipophilic or amphiphilic catalyst in the aggregate, together with coulombic interactions between the charged reagent and the micellar surface. Quantification of these effects is possible [26,36,44], nevertheless, a qualitative interpretation of the kinetic data based only on simplistic assumptions concerning the hydrophobic and electrostatic interactions lead to interesting and applicable conclusions in many instances as well [45–47].

The current study was aimed to establish whether a micellar medium could provide some benefits in comparison with homogeneous reaction in the case of sulfoxidations catalyzed by flavinium salts **1**. Therefore, at this stage of the research we decided to discuss the obtained data on qualitative level only assuming simply the amphiphilic catalyst **1b** as well as its active form **1b**-OOH and intermediate **1b**-OH being localized in micellar pseudophase. It was also reasonable to assume that thioanisole (**2**) was almost completely solubilized in micellar pseudophase at the concentration of surfactants used in kinetic experiments ($c = 1.0 \times 10^{-1}$ mol L^{-1}). Localization of the substrate was supported by its binding constant K_S values [35] to micelles of SDS (180 M^{-1} [37]), CTAX (340 M^{-1} [37]) and Brij 35 (116 M^{-1}, see Section 2.5). According to NMR study performed by Bunton et al. [37] thioanisole (**2**) should be located near the micellar surface.



Scheme 4.

We found that the oxidation of **2** performed under the conditions described above is chemoselective, forming sulfoxide **4** as the only reaction product. The formation of methyl phenyl sulfone (the overoxidation product) was not observed in any instance; its presence in the reaction mixture being tested for after each kinetic run. Consequently we monitored the course of the reaction by measuring sulfoxide **4** concentration versus time dependence; the concentrations being determined using HPLC (for details see Section 2.3). In all kinetic experiments the reaction was monitored until 90% sulfoxide conversion was achieved.

Under the conditions of our experiments, slow sulfoxidation occurred even in the absence of the catalyst (Scheme 4). Therefore, the observed reaction rate v_{obs} consisted of the rate v_0 of the non-catalyzed reaction (blank) and the rate v_{cat} of the reaction catalyzed by flavinium salts **1** ($v_{obs} = v_0 + v_{cat}$). To determine the contribution of blank (v_0), we measured the rate of thioanisole (**2**) oxidation with hydrogen peroxide in respective reaction media in independent experiments.

With respect to the molar ratio of the reactants, the kinetics of non-catalyzed sulfoxidation is a second order reaction [48]. On the other hand, the same reaction in the presence of flavinium salts (if the contribution of the non-catalyzed process is negligible) follows first order kinetics, as is evident from the example given in Fig. 1. Bäckvall et al. reported the same type of kinetics for the oxidation of sulfides catalyzed by a flavinium salt [18]. Due to the different kinetics of sulfoxidation that apply in either

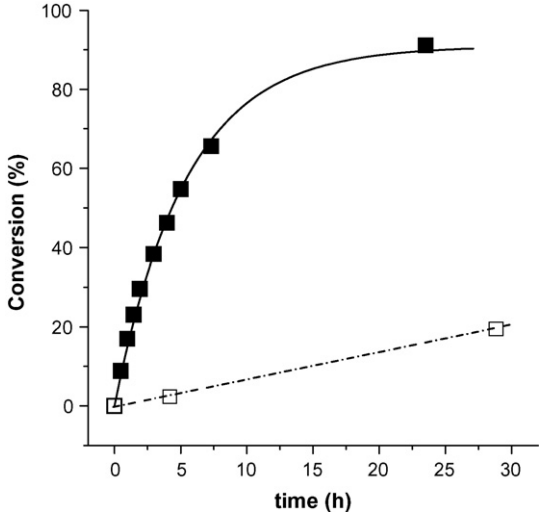


Fig. 1. Typical example of the course of oxidation of **2** with hydrogen peroxide. Conditions: CTAC, pH 2.4. Full symbols: concentration of sulfoxide **4** in reaction catalyzed by **1b**. Empty symbols: blank. The curve in the case of the catalyzed reaction was obtained by non-linear regression analysis of concentration vs. time data using a first order kinetic model.

the presence or the absence of salt **1**, the initial sulfoxidation rates (until 20% conversion) v_{obs} and v_0 were used to compare the catalyzed and non-catalyzed reactions. The same method has been used to evaluate the catalytic activity of various flavinium salts [15–17].

The initial reaction rates v_{obs} of thioanisole (**2**) oxidation in the presence of salt **1b**, as well as the rates v_0 of the corresponding blanks in anionic, cationic, and non-ionic micelles at various pH values, are shown in Fig. 2. For comparison, we also measured the sulfoxidation rate in a homogeneous solution catalyzed by water-soluble homologue **1a** under comparable conditions (pH, concentration of substrate and catalyst). The results obtained provided unequivocal evidence (i) that, under specific conditions, micelles as a reaction medium accelerate the oxidation of sulfides catalyzed by amphiphilic flavinium salt **1b** (ii) that in most instances micelles favour a catalytic process to a non-catalyzed reaction, and (iii) that the reaction rate depends on both the type of micellar matrix and on the pH value of the reaction mixture. These findings are discussed in detail below.

3.2.1. *Effect of pH and micellar medium on non-catalyzed sulfoxidation*

The non-catalyzed oxidation of sulfides by hydrogen peroxide was accelerated at pH values below 2; pronounced accelerations being observed in the homogeneous reaction, as well as in the reactions in anionic and non-ionic micelles. This is most likely attributable to the formation of hydroperoxonium ion, which is a more powerful oxidizing agent than its non-protonated form (by a factor of approximately 10^4) [48]. Despite the low basicity of hydrogen peroxide (the published pK_a value of hydroperoxonium ion ranges from −7.7 to −11 [48]), acid catalysis of oxidation by hydrogen peroxide has already been observed at pH values around 1 [48,49].

The remarkable increase in the sulfoxidation rate in SDS micelles at pH values below 2 is a consequence of the increased concentration of protons in Stern layer resulting from cation exchange (protons for sodium cations) close to the negatively charged micellar surface [50]. On the other hand, the non-catalyzed reactions of sulfides with hydrogen peroxide in cationic micelles were slower by a factor of 2–3 in comparison with reactions in both the homogeneous solution and the non-ionic micelles.

3.2.2. *Sulfoxidation in the presence of flavinium salts **1***

The sulfoxidation rates v_{obs} observed in the presence of amphiphilic flavinium salt **1b** in micelles exceeded those obtained for the homogeneous reaction in the presence of **1a** (Fig. 2), the highest acceleration being found in SDS micelles (TOF is ca. $3 \times 10^3\ h^{-1}$ at pH 4.4). In most instances the pH dependences of v_{obs} displayed a local maximum, the position of which depended on the type of micellar matrix. Furthermore, the oxidation rate in SDS micelles increased markedly at pH below 2. This increase can be explained by the acceleration of the non-catalyzed reaction discussed in the previous section.

The graphs in Fig. 2 show that the contribution of the non-catalyzed reaction in nanoaggregates was markedly suppressed when compared to the homogeneous reaction (with the exception of SDS at pH below 2). However, due to the significant contribution of the non-catalyzed reaction under certain conditions (low pH value in anionic micelles and homogeneous solution), the graphs in Fig. 2 do not allow for direct comparisson of the rate enhancement arising from catalysis by flavinium salts **1**. Therefore, we have expressed this rate enhancement as the relative reaction rates, $v_{cat}/v_0 = (v_{obs} - v_0)/v_0$. Fig. 3 shows the relative reaction rate versus pH dependences for each investigated reaction system.

Despite the highest overall sulfoxidation rate v_{obs} being found in anionic micelles of SDS, the most pronounced effect of the catalyst (v_{cat}/v_0) was observed in cationic micelles of $CTANO_3$, for which the rate enhancement factor was approximately 40. This is a consequence of the aforementioned suppression of non-catalyzed reactions in cationic micelles (see Section 3.2.1). Indeed, cationic micelles protect the substrate solubilized in the micellar interior against non-catalyzed oxidation.

The bell-shaped pH dependences of the catalyzed sulfoxidation rate v_{cat} in micelles arise from two opposing effects of protons on the catalytic cycle (Scheme 2). Protons participate in two steps of this cycle: in the decomposition of 4a-hydroxyflavin **1**-OH to flavinium salt **1**, and in the formation of flavin-4a-hydroperoxide **1**-OOH from salt **1**. The former step requires the protonization of the hydroxyl group of the pseudobase **1**-OH and is, therefore, facilitated in acidic medium. The latter step, on the other hand, proceeds with the loss of proton being disfavoured under the same conditions [51].

For each dependence in Fig. 3, the position of the maximum depends on the aggregate type. In non-ionic micelles it lies around pH 3.4. In anionic micelles it is shifted to a higher pH while in cationic micelles it shifts to a lower pH; in both cases by one unit. Most likely, it is the surface charge of the micelle which influences the position of the maximum either by supporting (in the case of anionic micelles) or by suppressing (in the case of cationic micelles) the transport of protons into the micellar pseudophase.

UV–vis spectroscopy was used to investigate the equilibrium between 4a-hydroxyflavin **1**-OH and flavinium salt **1** [30] (Scheme 5a) in all types of reaction media employed in this study. The obtained apparent pK'_a values characterizing this equilibrium are summarized in Table 1. The apparent pK'_a values found in anionic micelles were higher compared to those found in non-ionic micelles and in homogeneous solution, while the apparent pK'_a values obtained in cationic micelles were lower.

Concerning the micellar systems employed in this study, we first examined CTAC as an inexpensive and commercially available surfactant. However, Cl^- anion is a nucleophile that might attack position 4a of flavinium salt **1** under the formation of 4a-chloroflavin **1**-Cl (Scheme 5b). We were suspected that this equilibrium might reduce the concentration of salt **1** in the reaction system, and thus lower the catalyzed sulfoxidation rate. Therefore, we decided to also perform sulfoxidation in $CTANO_3$, a surfactant with a non-nucleophilic anion. Although, as expected, sulfoxidation in CTAC micelles was somewhat slower compared to that performed in $CTANO_3$ (Figs. 2 and 3), the differences observed were relatively small. Also noticeable

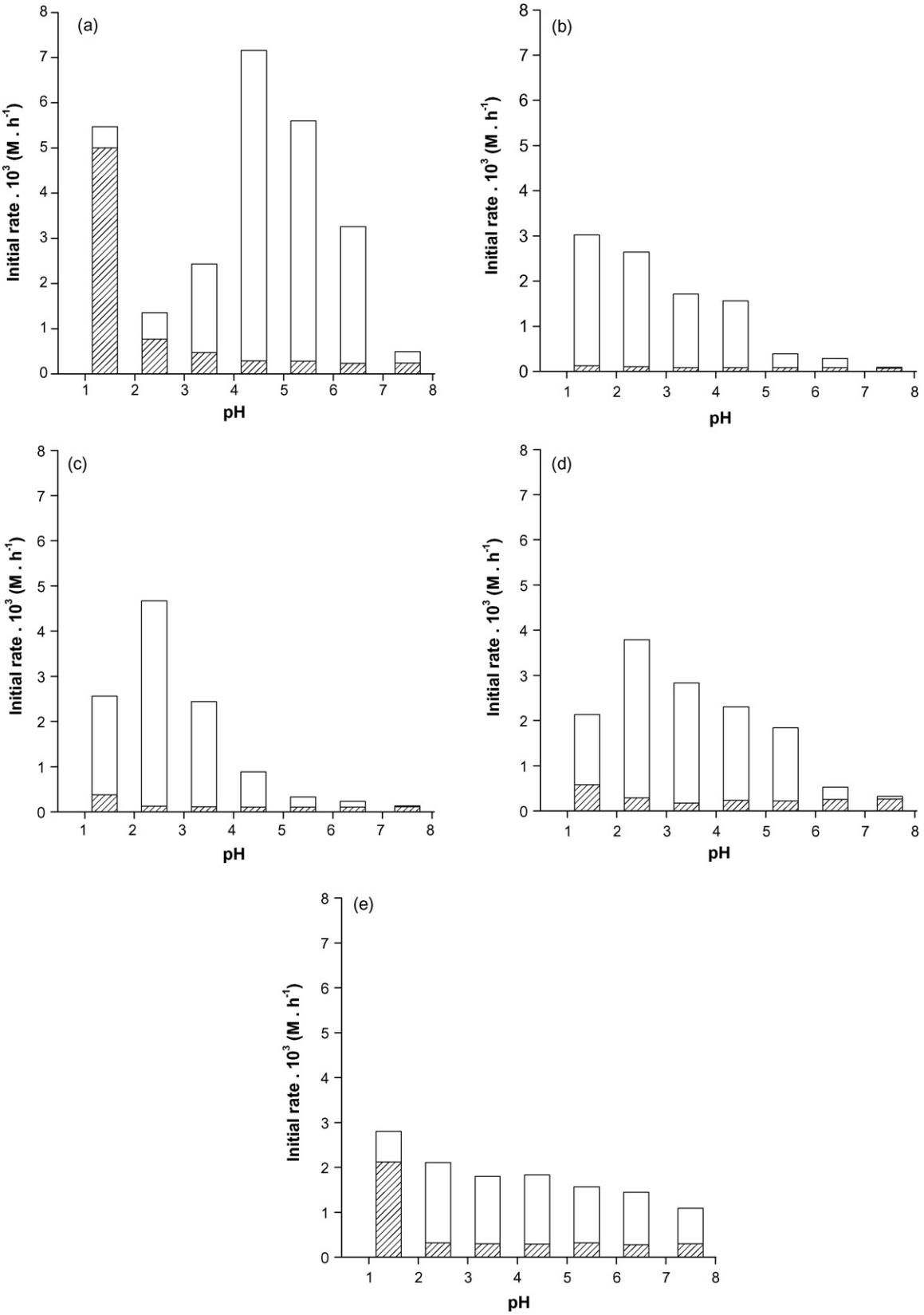


Fig. 2. Initial rates (v_{obs}) of thioanisole (**2**) oxidation with hydrogen peroxide in the presence of salt **1b** in SDS (a), CTAC (b), $CTANO_3$ (c), and Brij 35 (d), or using **1a** in aqueous-methanol (50:50, v/v) (e); shaded parts of the columns represent the contribution of the non-catalyzed reaction (v_0). Conditions: $c(\mathbf{2}) = 1.5 \times 10^{-2}$ mol L^{-1}, $c(H_2O_2) = 2.25 \times 10^{-2}$ mol L^{-1}, $c(\mathbf{1}) = 2.3 \times 10^{-4}$ mol L^{-1}, c(buffer) $= 1.0 \times 10^{-1}$ mol L^{-1}, and c(surfactant) $= 1.0 \times 10^{-1}$ mol L^{-1}, $t = 25\,^{\circ}C$.

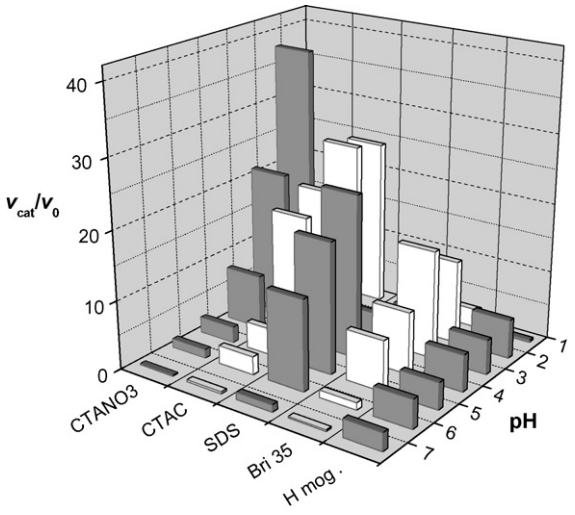
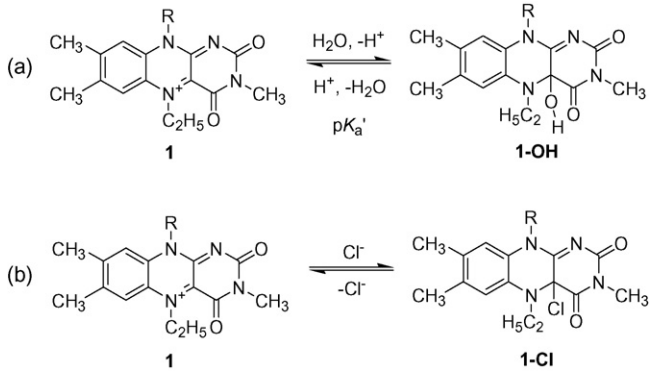


Fig. 3. pH dependence of the v_{cat}/v_0 ratio of initial rates of catalyzed and non-catalyzed oxidation of **2** with hydrogen peroxide in various reaction media. Flavinium salts **1a** and **1b** were used as catalysts in homogeneous solution and in micelles, respectively.



Scheme 5.

was the effect of Cl^- anion on the apparent pK'_a values found in the CTAC and $CTANO_3$ micelles.

4. Conclusion

We have shown that amphiphilic flavinium salt **1b** catalyzes the chemoselective oxidation of thioanisole (**2**) to sulfoxide **4** in various micellar systems. The efficacy of this catalyst is strongly dependent on both the pH value and the type of micelle used. For all micellar systems investigated, the sulfoxidation rate (v_{obs}) observed in the presence of flavinium salt **1** was higher compared to the reaction in homogeneous solution; the factor of acceleration ranging from approximately 1.5 (non-ionic micelles) to 3 (anionic micelles). Although the observed acceleration was moderate, it should be emphasized that the relative reaction rates (v_{cat}/v_0) in micelles were markedly higher compared to those in homogeneous solution. Suppression of the non-catalyzed reaction in micellar systems is interesting with respect to potential practical applications; for example, it could help to increase enantiomeric excess in the case of stereoselective oxidations mediated by chiral flavinium salts [22,24].

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molcata.2007.07.027.

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