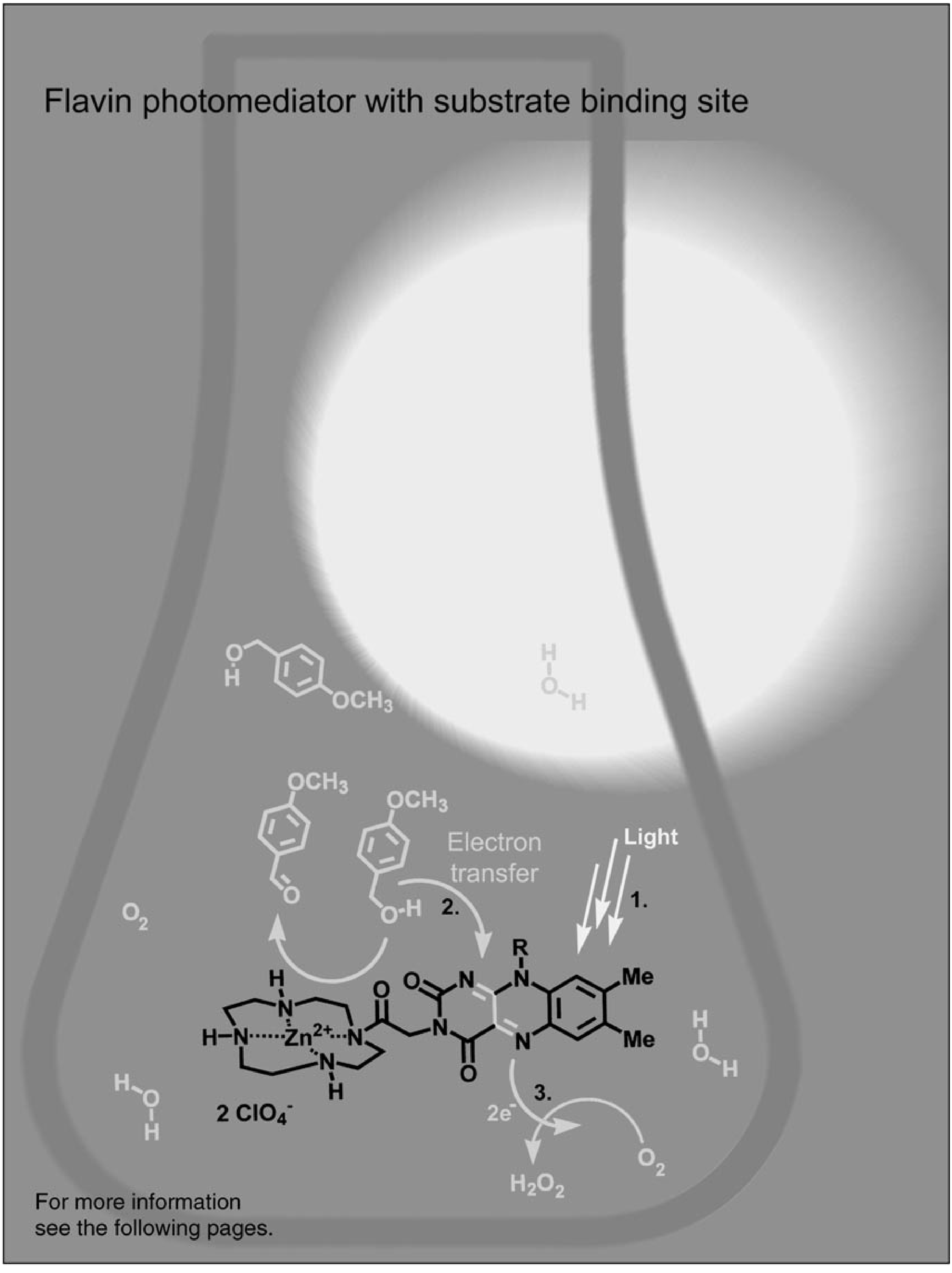

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Catalytic Photooxidation of 4-Methoxybenzyl Alcohol with a Flavin–Zinc(II)-Cyclen Complex

Radek Cibulka,*[a] Rudolf Vasold,[b] and Burkhard König*[b]

Abstract: Flavin–zinc(II)-cyclen **10** contains a covalently linked substrate binding site (zinc(II)–cyclen) and a chromophore unit (flavin). Upon irradiation, compound **10** effectively oxidizes 4-methoxybenzyl alcohol (**11-OCH$_3$**) to the corresponding benzaldehyde both in water and in acetonitrile. In the presence of air, the reduced flavin **10-H$_2$** is reoxidized, and so catalytic amounts of **10** are sufficient for alcohol conversion. The mechanism of oxidation is based on photoinduced electron transfer from the coordinated benzyl alcohol to the flavin chromophore. This intramolecular process provides a much higher photooxidation efficiency, with quantum yields 30 times those of the comparable intermolecular process with a flavin chromophore without a binding site. For the reaction in buffered aqueous solution a quantum yield of $\Phi = 0.4$ is observed. The turnover number in acetonitrile is increased (up to 20) by high benzyl alcohol concentrations. The results show that the covalent combination of a chromophore and a suitable binding site may lead to photomediators more efficient than classical sensitizer molecules.

Keywords: electron transfer · flavin · macrocyclic ligands · photooxidation · sensitizers

Introduction

Photoinduced electron transfer (PET) in reversible noncovalent assemblies of electron-donor and electron-acceptor moieties is studied intensively[1,2] because of its importance for related biological processes. However, utilization of PET for catalysis or sensitization of chemical reactions has so far mainly been restricted to diffusion-controlled collision processes. Only a limited number of systems with a defined reversible interaction between the photosensitizer and the substrate have been reported.[3,4] To improve the sensitizing efficiency of a photoactive molecule for a chemical reaction we have prepared a mediator containing a chromophore covalently tethered to a substrate binding site. In such a system, the bound substrate and the photoactive unit interact intramolecularly, thus increasing the efficacy of the electron-transfer process. The substrate–sensitizer interaction through coordinative bond formation is reversible, allowing a catalytic process.

As a model reaction for investigation of the sensitizing synthetic receptor, the photooxidation of benzyl alcohols has been used. The oxidation of alcohols to aldehydes is a key transformation in the chemical industry and also in biology, and numerous stoichiometric and catalytic reactions and reagents to mediate the process have been developed.[5] Investigations currently in progress are aimed at attempting to increase the efficiency of the reaction and to make it more environmentally benign.[6] New metal complexes[7] and metal-free systems[8,9] that catalyze oxidations with oxygen or hydrogen peroxide as the stoichiometric oxidant are sought after. The flavin–zinc(II)-cyclen complex reported here fulfils these criteria.

Results and Discussion

Design and synthesis: Molecule **10** (Scheme 1) consists of two covalently bound subunits: the flavin chromophore, which upon irradiation provides the necessary redox energy to transform the substrate into the product, and a coordinative binding site for the substrate. Riboflavin was selected as the chromophore because it becomes a strong oxidant upon irradiation,[10] and riboflavin-2′,3′,4′,5′-tetraacetate has previously been used for intermolecular PET oxidation of benzyl

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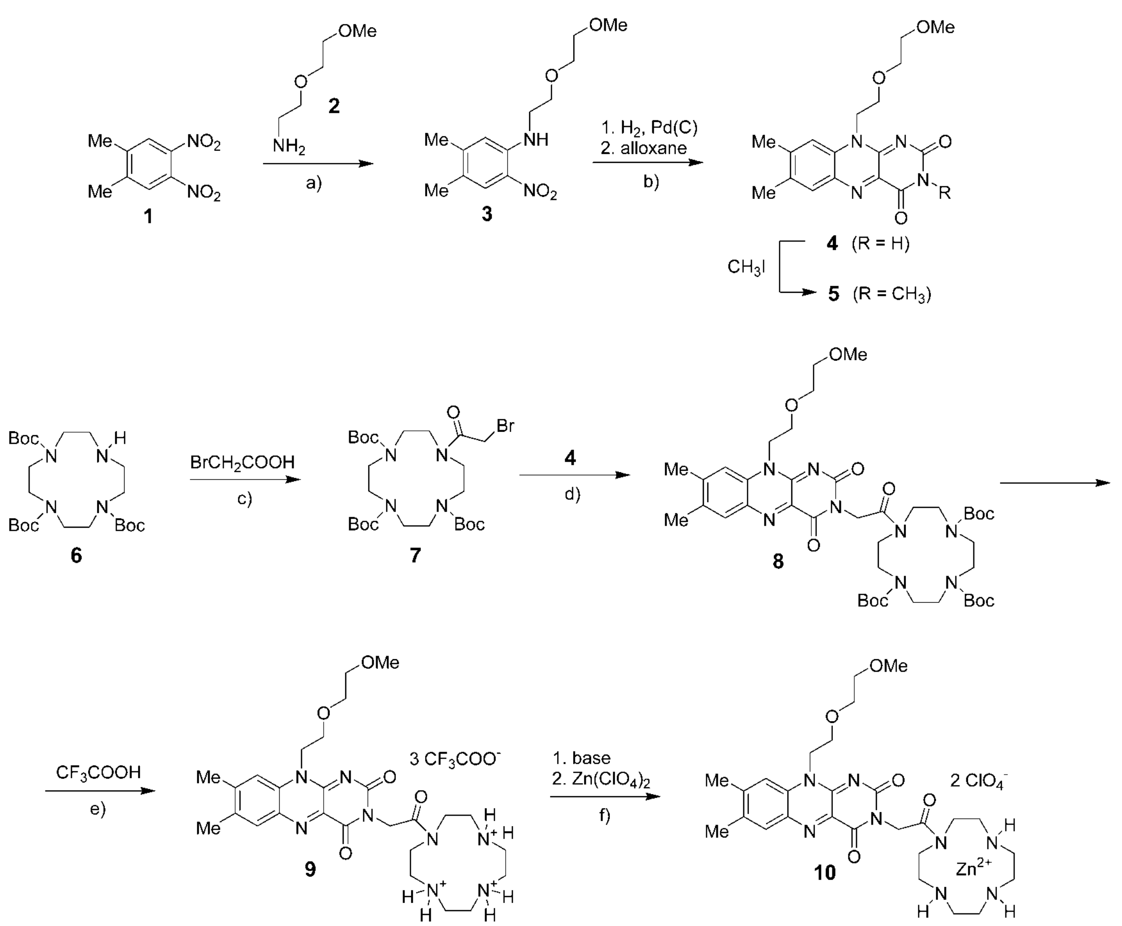


Scheme 1. Synthesis of flavin–zinc(II)-cyclen complex **10**. Reaction conditions: a) pyridine, reflux (82 %); b) acetic acid, RT (52 %); c) DCC, CH_2Cl_2, RT (72 %); d) K_2CO_3, DMF, RT (88 %) e) CH_2Cl_2, RT (99 %); f) 1. H_2O, ion exchange (OH^-); 2. CH_3CN, 60 °C (39 %).

alcohols.[9a,b,d] A diethylene glycol substituent was introduced into the 10-position to increase the solubility in water and thus to allow oxidation reactions in aqueous solutions.

Abstract in Czech: Flavin-Zn(II)-cyklen **10** obsahuje vazebné místo pro substrát (Zn(II)-cyklen), které je kovalentně vázané k chromoforu (flavin). Po ozáření oxiduje sloučenina **10** 4-methoxybenzylalkohol **11-OCH$_3$** na odpovídající aldehyd ve vodě a v acetonitrilu. Provádí-li se reakce v přítomnosti vzduchu, vznikající redukovaný flavin **10-H$_2$** se reoxiduje a pro oxidaci alkoholu tak postačuje pouze katalytické množství látky **10**. Mechanismus oxidace je založen na fotoindukovaném přenosu elektronů z benzylalkoholu koordinovaného k cyklenové jednotce na flavinový chromofor. Tento intramolekulární proces podstatně zvyšuje účinnost fotooxidace—její kvantový výtežek je třicetinásobný ve srovnání s kvantovým výtežkem intermolekulární oxidace flavinem bez vazebného místa. V pufrovaném vodném prostředí bylo dosaženo kvantového výtežku $\Phi = 0.4$. Počet dosažených katalytických cyklů v acetonitrilu se zvyšuje s koncentrací benzylalkoholu až na hodnotu 20. Výsledky ukazují, že kovalentní spojení chromoforu a vhodného vazebného centra může vést k fotomediátorům, které jsou účinnější než klasické fotosenzibilizátory.

Zinc(II)–cyclen was chosen as the binding site for the substrate, in view of the presence and functioning of Lewis acid zinc(II) ions in the active site of alcohol dehydrogenase.[11] Cyclen has a high affinity ($\lg K = 16.2$)[12] for zinc(II) ions, which precludes other binding equilibria. Moreover zinc(II)–cyclen is known to coordinate Lewis base substrates[13] such as water, alcohols,[11b,14] imides, or phosphate anions weakly and reversibly. Similar systems containing a crown ether unit covalently linked to a flavin moiety have already been reported.[15] In these cases, however, the crown ether is not a binding site for a substrate but only coordinates alkali metal or alkaline-earth metal ions, thus modulating the flavin redox potential and resulting in changes in the oxidation quantum yields of benzyl alcohol[15a] or alkali mandelates.[15b]

The flavin part of the molecule (compound **4**) was prepared by using the general method developed by Kuhn and co-workers:[16] synthesis of 1,2-dimethyl-4,5-dinitrobenzene (**1**), *ipso*-substitution of the nitro group with 2-(2-methoxyethoxy)ethylamine (**2**) in pyridine, the reduction of the second nitro group in **3** with dihydrogen and Pd/C, and subsequent condensation of the obtained diamine with alloxane. Triply *tert*-butyloxycarbonyl(Boc)-protected cyclen[17] was treated with bromoacetic acid in the presence of dicyclohexylcarbodiimide (DCC) to give **7**. The alkylation of flavin **4** in its 3-position has to be performed quickly to avoid decomposition of the molecule, so an excess of compound **7** was used in DMF with K_2CO_3 as base. The reaction in DMF was found to be ten times faster than that in acetonitrile. Deprotection of **8** with trifluoroacetic acid in dichloromethane gave the ammonium salt **9**, and the free amine form of **9** was obtained by use of a strong basic ion exchanger. Because of its low stability[18] the free base was immediately converted into the zinc(II) perchlorate complex **10**. All reactions starting from compound **4** were performed with exclusion of light to prevent photochemical degradation of the flavin moiety. For comparison, the 3-methylflavin **5**, which lacks the cyclen binding site, was also prepared.

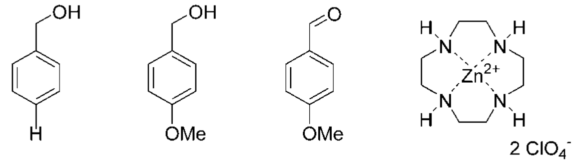
Cyclic voltammetry and fluorescence quenching: The abilities of flavin derivatives **4**, **5**, and **10** to oxidize benzyl alcohols were estimated from the ΔG values for electron transfer from the alcohol to the excited flavin. With the entropy changes from ground to excited state neglected, ΔG was calculated by the Rehm–Weller[19] equation [$\Delta G = 96.4\,(E^{ox}_{1/2} - E^{red}_{1/2}) - e^2/\varepsilon a - E^{0-0}$]. Redox potentials of flavin reduction and alcohol oxidation were experimentally determined by cyclic voltammetry (Table 1), and typical values[9a,b,10d] were used for the Coulombic term ($e^2/\varepsilon a = 5.4\,kJ\,mol^{-1}$) and the flavin excitation energy ($E^{0-0} = 241\,kJ\,mol^{-1}$). The reduction potential of flavin **10** with zinc(II)–cyclen substitution was found to be shifted in the positive direction by 200 mV in relation to flavins **4** and **5**, which may be interpreted in terms of the electron-withdrawing effect of the adjacent zinc(II) ion.

Table 1. Estimated thermodynamic oxidation parameters (ΔG) and emission quenching rate constants (k_q) for flavin derivatives **4**, **5**, and **10** in reaction with benzyl alcohol (**11-H**) and *para*-methoxybenzyl alcohol (**11-OCH$_3$**).

Flavin	τ [ns][a]	$E^{red}_{1/2}$ of flavin[b] [V]	$k_q \times 10^9$ [$M^{-1}s^{-1}$] 11-H	11-OCH$_3$	ΔG [kJ mol^{-1}] 11-H[c]	11-OCH$_3$[d]
10	5.4	−0.88	–	7.8	+11	−47
4	7.1	−1.08	–	5.7	+30	−28
5	6.4	−1.09	–	5.6	+31	−27

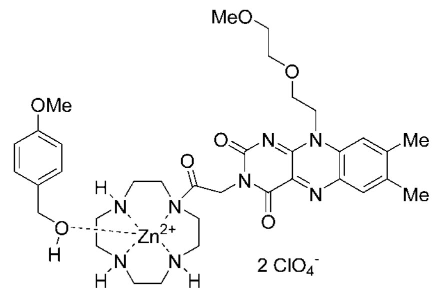
[a] Fluorescence lifetimes (single-exponential decay; measured in acetonitrile in the absence of benzyl alcohol). [b] Values obtained in acetonitrile versus ferrrocene/ferrocenium; $c_{Flavin} = 2\times10^{-3}$ M. [c] $E^{ox}_{1/2}$ (benzyl alcohol, **11-H**) = 1.79 V versus ferrocene/ferrocenium. [d] $E^{ox}_{1/2}$ (4-methoxybenzyl alcohol, **11-OCH$_3$**) = 1.19 V versus ferrocene/ferrocenium.

The thermodynamic data reveal that **11-OCH$_3$** (see Scheme 2) is a suitable substrate for flavin-mediated photooxidation. No flavin emission quenching is observed in the presence of benzyl alcohol (**11-H**), because the electron-transfer process for this redox couple is endergonic. The rate constants (k_q) of flavin emission quenching by 4-methoxybenzyl alcohol (**11-OCH$_3$**) given in Table 1 were estimated by use of the measured lifetimes and slopes (K_S) of Stern–Volmer plots (see Experimental Section for details). The values of k_q—of about $6\times10^9\,M^{-1}s^{-1}$—are virtually identical for all investigated flavins. However, the obtained Stern–Volmer plots for dynamic emission quenching of **4** and **5** with **11-OCH$_3$** are linear, while the nonlinear plot observed for **10** indicates a static quenching mechanism through a noncovalent interaction between **10** and **11-OCH$_3$**, as shown in Scheme 3 (see Supporting Information for data). An affinity constant of about 24 L mol^{-1} was estimated from the emission quenching data (see Supporting Information).



11-H **11-OCH$_3$** **12-OCH$_3$** **13**

Scheme 2. Benzyl alcohols **11** used for photooxidation, product of photooxidation (**12-OCH$_3$**), and zinc(II) cyclen bisperchlorate (**13**).



11-OCH$_3$ - 10

Scheme 3. Reversible complex of **10** and **11-OCH$_3$**.

Catalytic photooxidation of 4-methoxybenzyl alcohol in acetonitrile: The photooxidation of 4-methoxybenzyl alcohol (**11-OCH$_3$**) to 4-methoxybenzaldehyde (**12-OCH$_3$**) under mediation by the flavin–zinc-cyclen **10** was investigated in acetonitrile under atmospheric pressure of air. The presence of oxygen is necessary to reoxidize the reduced flavin[9a,10a] formed during photooxidation, so that catalytic amounts of **10** are sufficient. No aldehyde formation was observed after 60 min of irradiation of **11-OCH$_3$** in acetonitrile in the absence of any flavin (Table 2, entry 1) even if the solution contained an excess of hydrogen peroxide; hydrogen peroxide thus does not oxidize benzyl alcohol under these reaction conditions. Flavin–zinc(II)-cyclen **10** mediates the photooxidation, providing 51% conversion after 1 h of irradiation (Table 2, entry 2). The quantum yield of aldehyde formation is $\Phi = 3.8\times10^{-2}$.

In the presence of flavins **4** and **5**, without the zinc(II)–cyclen unit, the oxidation proceeds very slowly, and after 60 min of irradiation only small amounts of products were detected. The importance of covalently connected flavin and zinc(II)–cyclen for high photoconversion of benzyl alcohol is shown by comparison of the data for **10** with those obtained in the presence of equimolar amounts of 3-methylflavin **5**[20] and cyclen–zinc(II) perchlorate (**13**). The more positive reduction potential makes **10** the better oxidant, but the estimated change in ΔG is not sufficient to explain the observed significant differences in reactivity.[21] The highly effective

Table 2. Quantum yields of the photooxidation of 4-methoxybenzyl alcohol ($c = 2\times10^{-3}$ mol L^{-1}) in acetonitrile[a] mediated by different flavins ($c = 2\times10^{-4}$ mol L^{-1}).

Entry	Flavin	Conversion after 1 h of irradiation [%]	Rel. abs. at 444 nm after 1 h of irradiation[b] [%]	Quantum yield of aldehyde formation Φ[c]
1	none	0	–	–
2	**10**	51	45	3.8×10^{-2}
3	**2**	1	54	1.3×10^{-3}
4	**8**	1	54	9.1×10^{-4}
5	**5**+**13**	2	53	1.8×10^{-3}
6	**10**+Sc(TfO)$_3$[d]	70	52	1.1×10^{-1}

[a] The data were obtained from irradiation ($\lambda > 420$ nm) of an oxygen-saturated solution of flavin and **11-OCH$_3$** in acetonitrile under atmospheric pressure. [b] Relative absorbance of the reaction mixture at 444 nm after 60 min irradiation time relative to the absorbance at the beginning of the experiment. [c] Quantum yield calculated from the rate of aldehyde formation during irradiation for 5 min. [d] c(Sc(TfO)$_3$) $= 1\times10^{-2}$ mol L^{-1}.

intramolecular electron-transfer process from reversibly coordinated **11-OCH$_3$** to the excited flavin chromophore of **10** is clearly the origin of its photocatalytic function (Figure 1).

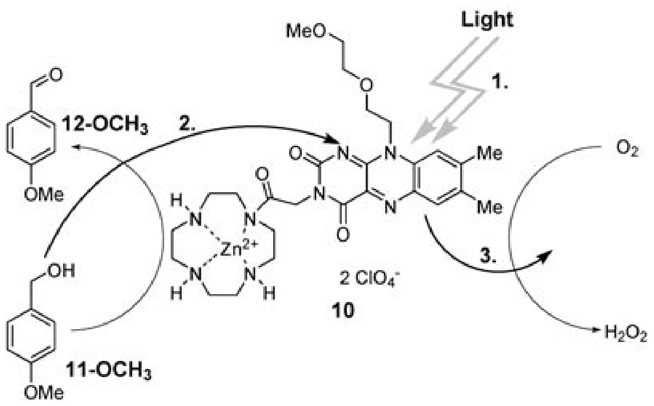


Figure 1. Proposed mechanism of catalytic photooxidation of benzyl alcohol **11-OCH$_3$** mediated by flavin **10** in the presence of dioxygen.

Unfortunately, degradation of the flavin molecule in solution was observed during irradiation by visible light, the typical flavin absorbance maximum intensity decreasing during the course of the reaction. Table 2 gives the relative decrease after 1 h. A similar degradation of the flavin is observed in the absence of benzyl alcohol (see Supporting Information).

Fukuzumi et al.[9a] have reported the stabilization of riboflavin-2,3,4,5-tetraacetate in the photocatalytic oxidation of benzyl alcohols by rare-earth-metal ion coordination to the carbonyl-oxygen donor atoms of the isoalloxazine ring. In an attempt to increase the stability of **10** we performed the oxidation of **11-OCH$_3$** in the presence of an excess of scandium(III) triflate (Table 2, entry 6). The observed rate of aldehyde formation is slightly higher with scandium triflate, but flavin decomposition is still severe, as indicated by a drop in the flavin absorption intensity to 52 % of its original value (45 % in the absence of scandium triflate) after 1 h of reaction time.

The formation of aldehyde **12-OCH$_3$** and hydrogen peroxide and the conversion of **11-OCH$_3$** during photooxidation in the presence of **10** was monitored analytically (Figure 2). The data show a clean conversion process that affords 90 % alcohol conversion after 2 h. This corresponds to a theoretical turnover number of 9 for the sensitizer **10**, but in view of its degradation during the course of the reaction its actual efficiency must be much higher.

To confirm the proposed electron-transfer mechanism, the oxidation of 4-methoxybenzyl alcohol (**11-OCH$_3$**) by flavin was performed under exclusion of oxygen. Irradiation of a deaerated acetonitrile solution containing flavin **10** and **11-OCH$_3$** with visible light ($\lambda > 420$ nm) resulted in the formation of **12-OCH$_3$** and the reduced flavin **10-H$_2$**. The process was monitored by ^{1}H NMR, UV/Vis spectrophotometry, and HPLC (see Supporting Information).

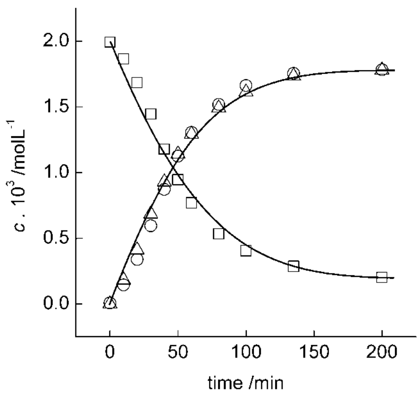


Figure 2. Concentrations of **11-OCH$_3$** (□), **12-OCH$_3$** (○), and hydrogen peroxide (△) during photooxidation of **11-OCH$_3$** ($c = 2\times10^{-3}$ mol L^{-1}) in oxygen-saturated acetonitrile in the presence of a catalytic amount of **10** ($c = 2\times10^{-4}$ mol L^{-1}).

The efficiency of photooxidation by flavins **10** and **5** increases with increasing alcohol concentration, reaching maximum turnover numbers of irradiation of about 20 and 1.6, respectively, after 60 min. (Figure 3). The flavin–zinc(II)-cyclen conjugate **10** is thus also significantly more efficient then flavin **5** at higher substrate concentrations.[22]

Photooxidation of 4-methoxybenzyl alcohol in water: The good solubility of **10** in water allows the mediated photooxidation of **11-OCH$_3$** to be studied in buffered aqueous solutions (borate buffer, pH 7.2). Irradiation of a deaerated aqueous solution of **10** and **11-OCH$_3$** afforded the corresponding benzaldehyde **12-OCH$_3$**, as detected by ^{1}H NMR and HPLC analysis. The photocatalytic efficiencies and quantum yields of flavins **5** and **10** in dioxygen-saturated aqueous solutions were compared by turnover number after irradiation for 60 min (Table 3). Generally, the rates of photooxidation in water are higher than those in acetonitrile,

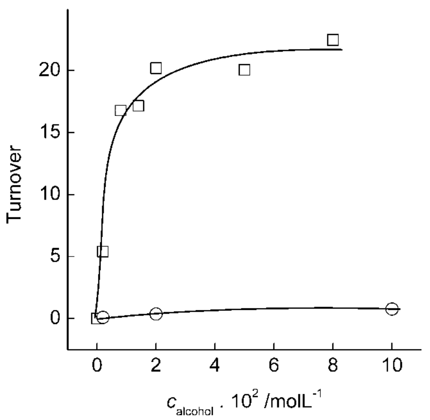


Figure 3. Dependence on the alcohol concentration of the flavin turnover numbers for photooxidation of **11-OCH$_3$** with **10** (□) and **5** (○) in acetonitrile ($c_{flavin} = 2\times10^{-4}$ mol L^{-1}) after 60 minutes irradiation.

Table 3. Comparison of the efficiency of flavin mediators ($c = 2\times10^{-4}$ mol L^{-1}) for the photooxidation of 4-methoxybenzyl alcohol in borate buffer, pH 7.2.[a]

Flavin	Concentration of **11-CH$_3$** [mmol L^{-1}]	Turnover after 1 h irradiation	Rel. abs. at 444 nm after 1 h irradiation[b] [%]	Quantum yield Φ[c]
none	2	0	–	–
10	2	7.6	57	0.23
5	2	8.3	79	0.11
5+**13**	2	8.3	73	0.14
10	20	10.9	76	0.40
10, pH 9.0	20	12.7	84	0.40

[a] The data were obtained after irradiation of oxygen-saturated solutions of the catalyst and substrate in water with light ($\lambda > 420$ nm) under atmospheric pressure. [b] Relative absorbance of the reaction mixture at 444 nm after irradiation for 60 min relative to the absorbance at the beginning of experiment. [c] Quantum yield calculated from the rate of aldehyde formation during irradiation for 5 min.

which can be interpreted in terms of the higher polarity of the medium.[23] At higher concentration of substrate ($c = 20$ mmol L^{-1}), a photooxidation quantum yield of $\Phi = 0.40$ was achieved with compound **10**. The quantum yield was not influenced by an increase in the pH from 7.2 to 9.0.

The turnover numbers for flavins **5** and **10** are fairly similar, in contrast with the results in acetonitrile. Flavin **10** suffers from its lower photostability, as is evident from the relative absorbance of the reaction mixture after 60 min of irradiation. However, the quantum yield calculated from the initial conversion in the first five minutes of the reaction indicates a higher efficiency for **10** than for **5** in the catalytic photooxidation. The observed difference in reactivity in aqueous solutions is smaller than in acetonitrile. The competition of benzyl alcohol and water binding to the coordination site of **10** may hamper the formation of the alcohol/flavin–zinc(II)-cyclen complex necessary for efficient intramolecular oxidation.

Conclusion

The flavin–zinc(II)-cyclen conjugate **10** has been prepared as a new sensitizer with a substrate binding site for the photooxidation of 4-methoxybenzyl alcohol to the corresponding aldehyde. The oxidation mechanism is based on photoinduced electron transfer, both in acetonitrile and in water. In the presence of dioxygen, the flavin is reoxidized and **10** acts efficiently in catalytic amounts. The role of the zinc(II)-cyclen unit is to coordinate the hydroxy group of the benzyl alcohol in reversible fashion, thus facilitating intramolecular electron transfer to the excited flavin. The efficiency of the intramolecular process with **10** is significantly higher than for flavins lacking the binding site. In summary, compound **10** operates as an efficient photosensitizer for the oxidation of 4-methoxybenzyl alcohol by oxygen. The reaction proceeds in aqueous solutions at pH 7.2 and at ambient temperature. The study demonstrates that sensitizers with increased efficiency for photochemical processes can be obtained through the combination of chromophores with suitable binding sites. Such systems may find applications in photooxidations or photoreductions of biomolecules, waste water treatment, selective photochemical transformations, or the chemical storage of light energy.

Experimental Section

General: 1,2-Dimethyl-4,5-dinitrobenzene (**1**),[16,24] 2-(2-methoxyethoxy)ethylamine (**2**),[25] and triply Boc-protected cyclen **6**[17b] were synthesized by known procedures. All other reagents used were commercially available reagent grade. Solvents were distilled and dried by standard procedures. Temperature data are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance instrument at 300 MHz and 75 MHz, respectively. Chemical shifts are reported in ppm, coupling constants (*J*) in Hz. Elemental analyses were performed on a Vario EL III analyzer. UV/Vis and fluorescence spectra were recorded on Varian Cary 50 Bio and Varian Eclipse spectrometers. Mass spectra were measured on Finnigan MAT 95, ThermoQuest Finnigan TSQ 7000, and Finnigan MAT SSQ 710 A spectrometers. TLC analyses were carried out on DC Alufolien Kieselgel 60H F254 (Merck). Gerundan Si 60 silica gel (0.063–0.200 mm; Merck) was used for column chromatography.

***N*-[2-(2-Methoxyethoxy)ethyl]-4,5-dimethyl-2-nitroaniline (3)**: A solution of 1,2-dimethyl-4,5-dinitrobenzene (**1**, 2.18 g, 11.11 mmol) and 2-(2-methoxyethoxy)ethylamine (**2**, 2.10 g, 17.62 mmol) in pyridine (270 mL) was heated to reflux for 15 h. A further portion of 2-(2-methoxyethoxy)ethylamine (1.05 g, 8.81 mmol) was added, and the solution was heated to reflux until all starting material had been converted into product (TLC, chloroform/methanol 100:3). The overall reaction time was 65 h. The reaction mixture was cooled, chloroform (400 mL) was added, and the solution was extracted with aqueous citric acid (10%, 10×250 mL) and with water (2×250 mL). The organic phase was dried over sodium sulfate, the solvents were evaporated in vacuum, and the crude product was purified by column chromatography (chloroform/methanol 100:1) to give compound **3** (2.45 g, 82%) as an orange oil. $R_f = 0.23$ ($CHCl_3$/MeOH 100:1); ^{1}H NMR ($CDCl_3$): $\delta = 2.17$ (s, 3H; $ArCH_3$), 2.26 (s, 3H; $ArCH_3$), 3.40 (s, 3H; CH_3O), 3.51 (t, ^3J(H,H) = 5.8 Hz, 2H; CH_2N), 3.59 (m, 2H; CH_3OCH_2), 3.67 (m, 2H; $CH_3OCH_2CH_2$), 3.77 (t, ^3J(H,H) = 5.6 Hz, 2H; OCH_2CH_2N), 6.63 (s, 1H; ArH), 7.92 ppm (s, 1H; ArH); ^{13}C NMR ($CDCl_3$): $\delta = 18.6$ (+), 20.7 (+), 42.7 (−), 59.2 (+), 69.3 (−), 70.6 (−), 71.9 (−), 114.1 (+), 124.5 (C_{quat}), 126.5 (+), 130.0 (C_{quat}), 144.1 (C_{quat}), 147.2 ppm (C_{quat}); MS (70 eV, EI): *m/z* (%): 268 (24) $[M]^+$, 179 (100) $[M-C_4H_9O_2]^+$; elemental analysis calcd (%) for $C_{13}H_{20}N_2O_4$ (268.3): C 58.19, H 7.51, N 10.44; found: C 57.61, H 7.24, N 10.27.

10-[2-(2-Methoxyethoxy)ethyl]-7,8-dimethyl-10*H*-benzo[*g*]pteridine-2,4-dione (4): Nitro compound **3** (1.30 g, 4.84 mmol) was dissolved in acetic acid (20 mL) and after addition of Pd/C (10%) was stirred for 23 h in an autoclave under dihydrogen atmosphere (600 kPa). The reaction mixture was filtered through Celite, and boric acid (2.7 g, 43.7 mmol) and alloxan monohydrate (2.48 g, 15.49 mmol) were added immediately. The mixture was stirred for 9 h under nitrogen at room temperature. The solution was diluted with chloroform (250 mL) and water (50 mL), the separated chloroform phase was washed with water (3×100 mL), and the organic phase was dried over magnesium sulfate. After evaporation of solvent in vacuo and recrystallization of the crude product from water, compound **4** (0.86 g, 52%) was obtained as orange crystals. M.p. 229 °C; ^{1}H NMR ($CDCl_3$): δ = 2.45 (s, 3H; $ArCH_3$), 2.54 (s, 3H; $ArCH_3$), 3.28 (s, 3H; CH_3O), 3.42 (m, 2H; CH_3OCH_2), 3.60 (m, 2H; $CH_3OCH_2CH_2$), 4.02 (t, ^3J(H,H) = 5.6 Hz, 2H; OCH_2CH_2N), 4.93 (t, ^3J(H,H) = 5.8 Hz, 2H; CH_2N), 7.77 (s, 1H; ArH), 8.03 (s, 1H; ArH), 8.46 ppm (s, 1H; NH); ^{13}C NMR ($CDCl_3$): δ = 19.5 (+), 21.4 (+), 45.9 (−), 59.0 (+), 68.0 (−), 70.8 (−), 71.8 (−), 117.0 (+), 132.16 (+), 132.22 (C_{quat}), 135.0 (C_{quat}), 135.8 (C_{quat}), 137.1 (C_{quat}), 148.1 (C_{quat}), 150.3 (C_{quat}), 155.2 (C_{quat}), 159.6 ppm (C_{quat}); UV/Vis (acetonitrile): λ_{max} (ε) = 225 (31000), 270 (31400), 345 (8400), 444 (11900); MS (70 eV, EI): *m/z* (%): 344 (2) $[M]^+$, 242 (100) $[M-C_5H_{10}O_2]^+$, 171 (58) $[M-C_7H_{11}NO_4]^+$, 156 (24) $[M-C_7H_{12}N_2O_4]^+$; elemental analysis calcd (%) for $C_{17}H_{20}N_4O_4$ (344.4): C 59.29, H 5.85, N 16.27; found: C 58.98, H 5.78, N 16.20.

Tri-*tert*-butyl 10-bromoacetyl-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate (7): A solution of triply Boc-protected cyclen **6** (2.5 g, 5.29 mmol), bromoacetic acid (0.85 g, 6.11 mmol), and DCC (1.09 g, 5.28 mmol) in anhydrous dichloromethane (60 mL) was stirred for 20 h under nitrogen at room temperature. White solid was filtered off, and the filtrate was washed with a solution of sodium hydroxide (2 M, 2×40 mL) and water (2×40 mL) and dried over sodium sulfate. The crude product obtained by evaporation of the solvents in vacuo was purified by column chromatography (ethyl acetate/petroleum ether 3:1). Product **7** (2.26 g, 72%) was obtained as a white solid. R_F = 0.70 (ethyl acetate/petroleum ether 3:1); m.p. 55 °C; ^{1}H NMR ($CDCl_3$): δ = 1.46 (s, 18H; $(CH_3)_3C$), 1.49 (s, 9H; $(CH_3)_3C$), 3.37–3.57 (m, 16H; CH_2N), 3.84 ppm (s, 2H; CH_2Br); ^{13}C NMR ($CDCl_3$): δ = 28.0 (+), 49.5–51.6 (−), 80.5 (C_{quat}), 80.7 (C_{quat}), 155.4 (C_{quat}), 157.3 (C_{quat}) ppm; MS (70 eV, EI): *m/z* (%): 592 and 594 (10) $[M]^+$, 513 (63) $[M-Br]^+$, 492 and 494 (17) $[M-C_4H_8-CO_2]^+$, 413 (40) $[M-C_4H_8-CO_2-Br]^+$, 371 (58) $[M-C_7H_{10}O_3Br]^+$, 357 (37), 57 (100) $[C_4H_9]^+$; elemental analysis calcd (%) for $C_{25}H_{45}N_4O_7$ (593.6): C 50.59, H 7.64, N 9.44, Br 13.46; found: C 50.18, H 7.21, N 9.16, Br 13.20.

Tri-*tert*-butyl 10-(2-{10-[2-(2-Methoxyethoxy)ethyl]-7,8-dimethyl-2,4-dioxo-4,10-dihydro-2*H*-benzo[*g*]pteridin-3-yl}acetyl)-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate (8): A mixture of **4** (0.34 g, 0.99 mmol), **7** (1.73 g, 2.91 mmol), and potassium carbonate (1 g) in dry dimethylformamide (50 mL) was stirred under nitrogen at room temperature until all **4** had been converted into the product (ca. 4 h). The progress of the reaction was monitored by TLC (ethyl acetate/methanol 5:2). A second portion of **4** (0.16 g, 0.46 mmol) was added, and the mixture was stirred at room temperature for 8 h, diluted with chloroform (200 mL), and washed with water (4×150 mL), and the organic phase was dried over magnesium sulfate. After evaporation of the solvents and purification of the crude product by column chromatography (ethyl acetate/methanol 4:1), compound **8** (1.1 g, 88%) was obtained as a yellow solid. R_F = 0.55 (ethyl acetate/methanol 4:1); m.p. 137–139 °C; ^{1}H NMR ($CDCl_3$): δ = 1.48 (m, 27H; $(CH_3)_3C$), 2.43 (s, 3H; $ArCH_3$), 2.53 (s, 3H; $ArCH_3$), 3.29 (s, 3H; CH_3O), 3.30–3.75 (m, 16H; CH_2N), 3.42 (m, 2H; CH_3OCH_2), 3.55 (m, 2H; $CH_3OCH_2CH_2$), 4.00 (t, ^3J(H,H) = 5.8 Hz, 2H; OCH_2CH_2N), 4.85–4.95 (m, 4H; CH_2N, CH_2Br), 7.75 (s, 1H; ArH), 8.04 ppm (s, 1H; Ar*H*); ^{13}C NMR ($CDCl_3$): δ = 19.5 (+), 21.3 (+), 28.42 (+), 28.46 (+), 28.58 (+), 45.4 (−), 50.03 (−), 50.06 (−), 50.29 (−), 51.50 (−), 59.0 (+), 68.1 (−), 70.7 (−), 71.7 (−), 80.2 (C_{quat}), 80.5 (C_{quat}), 116.9 (+), 132.1 (C_{quat}), 132.2 (+), 134.9 (C_{quat}), 135.5 (C_{quat}), 136.6 (C_{quat}), 146.7 (C_{quat}), 147.5 (C_{quat}), 149.0 (C_{quat}), 155.2 (C_{quat}), 155.6 (C_{quat}), 159.8 ppm (C_{quat}); MS (ESI, $CH_2Cl_2+CH_3OH+CH_3COONH_4$): *m/z* (%): 858 (100) $[M+H]^+$, 758 (26) $[M-C_4H_7-CO_2]^+$; elemental analysis calcd (%) for $C_{42}H_{64}N_8O_{11}$ (857.0): C 58.86, H 7.53, N 13.07; found: C 58.65, H 7.28, N 12.68.

10-[2-(2-Methoxyethoxy)ethyl]-7,8-dimethyl-3-[2-oxo-2-(1,4,7,10-tetraazacyclododec-1-yl)ethyl]-10*H*-benzo[*g*]pteridine-2,4-dione·3 CF_3COOH (9): A solution of **8** (0.25 g, 0.29 mmol) dissolved in dichloromethane (5 mL) and trifluoroacetic acid (5 mL) was stirred for 3 h under nitrogen at room temperature. The solvents were evaporated, and the remaining solid was dissolved in water (10 mL). The aqueous solution of **9** was extracted with dichloromethane (10 mL), the water was evaporated under reduced pressure, and the remaining solid was dried in vacuo to yield **9** (0.26 g, 99%) as a yellow solid. M.p. 69–70 °C; ^{1}H NMR (600 MHz, CD_3CN, TMS): δ = 2.43 (s, 3H; $ArCH_3$), 2.55 (s, 3H; $ArCH_3$), 3.19 (s, 3H; CH_3O), 3.22 (m, 8H; CH_2N), 3.26 (m, 4H; CH_2N), 3.37 (t, ^3J(H,H) = 4.7 Hz, 2H; CH_3OCH_2), 3.56 (t, ^3J(H,H) = 4.6 Hz, 2H; $CH_3OCH_2CH_2$), 3.69 (m, 2H; $CH_2NC{=}O$), 3.88 (m, 2H; $CH_2NC{=}O$), 3.91 (t, ^3J(H,H) = 5.5 Hz, 2H; OCH_2CH_2N), 4.85 (t, ^3J(H,H) = 5.5 Hz, 2H; CH_2N), 4.89 (s, 2H; $NCH_2C{=}O$), 7.84 (s, 1H; ArH[6]), 7.89 ppm (s, 1H; ArH[9]); ^{13}C NMR (150 MHz, CD_3CN): δ = 18.2 (+), 20.3 (+), 42.5 (−), 43.3 (−), 44.1 (−), 44.3 (−), 44.9 (−), 45.0 (−) 45.8 (−), 46.35 (−), 46.43 (−), 47.5 (−), 57.8 (+), 67.0 (−), 70.3 (−), 71.3 (−), 115.7 (q, CF_3), 116.9 (+), 131.1 (+), 131.9 (C_{quat}), 135.07 (C_{quat}), 135.10 (C_{quat}), 137.5 (C_{quat}), 148.5 (C_{quat}), 149.1 (C_{quat}), 155.7 (C_{quat}), 160.1 (C_{quat}), 160.4 (q, CF_3COO^-), 169.8 ppm (C_{quat}); MS (ESI, CH_3CN): *m/z* (%): 557 (100) $[M+H-3\times CF_3COOH]^+$, 279 (13) $[M+H_2^{2+}-3CF_3COOH]$, 186 (24) $[M+H_3^{3+}-3CF_3COOH]$; MS (-ESI, CH_3CN): *m/z* (%): 783 (59) $[M-CF_3COOH-H]^-$, 669 (15) $[M-2\times CF_3COOH-H]^-$, 227 (100) $[(2\times CF_3COOH-H)]^-$; elemental analysis calcd (%) for $C_{33}H_{43}F_9N_8O_{11}$ (898.8): C 44.10, H 4.82, N 12.47; found: C 43.96 H 4.97, N 12.71.

10-[2-(2-Methoxyethoxy)ethyl]-7,8-dimethyl-3-[2-oxo-2-(1,4,7,10-tetraazacyclododec-1-yl)ethyl]-10*H*-benzo[*g*]pteridine-2,4-dione zinc(II) bisperchlorate (10): Ammonium salt **9** (0.25 g, 0.28 mmol) was dissolved in water and passed trough an ion exchanger (Merck Ion exchanger III, OH^- form) to obtain its free base form. The water was evaporated under reduced pressure and the remaining solid was dried under vacuum to yield 10-[2-(2-methoxyethoxy)ethyl]-7,8-dimethyl-3-[2-oxo-2-(1,4,7,10-tetraazacyclododec-1-yl)ethyl]-10*H*-benzo[*g*]pteridine-2,4-dione (0.112 g, 72.3%), which was used without purification for the preparation of the zinc complex. ^{1}H NMR (CD_3CN): δ = 2.44 (s, 3H; $ArCH_3$), 2.53 (s, 3H; $ArCH_3$), 2.57 (m, 4H; CH_2N), 2.64 (m, 4H; CH_2N), 2.77 (m, 4H; CH_2N), 3.19 (s, 3H; CH_3O), 3.37 (m, 2H; CH_3OCH_2), 3.51 (m, 2H; $CH_2NC{=}O$), 3.56 (m, 2H; $CH_3OCH_2CH_2$), 3.59 (m, 2H; $CH_2NC{=}O$), 3.91 (t, J = 5.8 Hz, 2H; OCH_2CH_2N), 4.83 (t, J = 5.8 Hz, 2H; CH_2N), 4.96 (s, 2H; $NCH_2C{=}O$), 7.80 (s, 1H; ArH), 7.90 ppm (s, 1H; ArH); MS (ESI, CH_3CN): *m/z* (%): 557.3 (100) $[M+H]^+$; HR-MS ($C_{27}H_{41}N_8O_5$): calcd. 557.3200; found 557.3206 ± 0.0007.

A solution of zinc(II) bisperchlorate hexahydrate in acetonitrile (2 mL) was added to the solution of the free amine base of **9** (0.119 g, 0.21 mmol) in acetonitrile (3 mL) under nitrogen. The mixture was stirred for 30 min at 60 °C and after evaporation of solvents a red solid was obtained. The crude product was dissolved in hot acetone (60 °C), and after cooling impurities precipitated. The solids were filtered off and, after evaporation of the solvent from the filtrate, compound **10** (0.09 g, 51%) was obtained as a red solid. M.p. > 260 °C, decomp. at 260 °C; ^{1}H NMR (CD_3CN): δ = 2.45 (s, 3H; $ArCH_3$), 2.55 (s, 3H; $ArCH_3$), 2.72 (m, 2H; CH_2N), 2.85 (m, 2H; CH_2N), 2.95 (m, 2H; CH_2N), 3.00–3.25 (m, 6H; CH_2N), 3.15 (s, 3H; CH_3O), 3.34 (m, 2H; CH_3OCH_2), 3.53 (m, 2H; $CH_3OCH_2CH_2$), 3.71 (m, 2H; $CH_2NC{=}O$), 3.89 (t, J = 5.8 Hz, 2H; OCH_2CH_2N), 3.94 (m, 2H; $CH_2NC{=}O$), 4.88 (t, J = 5.6 Hz, 2H; CH_2N), 4.90 (s, 2H; $NCH_2C{=}O$), 7.88 (s, 1H; ArH[6]), 7.94 ppm (s, 1H; ArH[9]); ^{13}C NMR: δ = 18.2 (+), 20.2 (+), 43.4 (−), 43.5 (−), 45.2 (−), 45.9 (−), 46.0(−), 57.7 (+), 66.9 (−), 70.2 (−), 71.2 (−), 117.7 (+), 131.0 (+), 132.3 (C_{quat}), 133.0 (C_{quat}), 136.1 (C_{quat}), 139.8 (C_{quat}), 150.2 (C_{quat}), 150.7 (C_{quat}), 157.8 (C_{quat}), 161.0 (C_{quat}), 173.8 ppm (C_{quat}); UV/Vis (acetonitrile): λ_{max} (ε) = 225 (27100), 270 (28600), 345 (7400), 444 (10100); MS (ESI, CH_3CN): *m/z* (%): 310.1 (100) $[(M-2\times ClO_4^-)]^{2+}$, 557.4 (50) $[LH]^+$, 619.3 (16) $[(M-2\times ClO_4^- -H^+)]^+$, 679.4 (48) $[(M-2\times ClO_4^- +CH_3COO^-)]^+$, 719.2 (17) $[(M-ClO_4^-)]^+$; HR-MS ($C_{27}H_{39}N_8O_5Zn^+$): calcd. 619.2335; found 619.2375 ± 0.0029.

10-[2-(2-Methoxyethoxy)ethyl]-3,7,8-trimethyl-10*H*-benzo[*g*]pteridine-2,4-dione (5): A mixture of flavin **4** (0.05 g, 0.15 mmol), sodium carbonate (0.18 g, 1.7 mmol), and methyl iodide (0.78 g, 5.5 mmol) in dry DMF (3 mL) was stirred at room temperature for 45 h. Water (1 mL) was then added and the pH was adjusted to 7 with hydrochloric acid (1 M). The solution was extracted with chloroform (3×20 mL) and the organic phase was dried with sodium sulfate. After evaporation of the solvents and recrystallization from water, the pure product was obtained as yellow needles (0.027 g, 52%). M.p. 162–164 °C; ^{1}H NMR ($CDCl_3$): δ = 2.43 (s, 3H; $ArCH_3$), 2.52 (s, 3H; $ArCH_3$), 3.26 (s, 3H; CH_3O), 3.39 (m, 2H; CH_3OCH_2), 3.51 (s, 3H; CH_3N), 3.56 (m, 2H; $CH_3OCH_2CH_2$), 3.99 (t, J = 5.2 Hz, 2H; OCH_2CH_2N), 4.93 (t, J = 5.2 Hz, 2H; CH_2N), 7.74 (s, 1H; ArH), 8.03 ppm (s, 1H; ArH); ^{13}C NMR: δ = 19.5 (+), 21.4 (+), 28.7 (+), 45.3 (−), 59.0 (+), 68.1 (−), 70.8 (−), 71.7 (−), 116.8 (+), 132.1 (C_{quat}), 132.2 (+), 135.0 (C_{quat}), 135.4 (C_{quat}), 136.6 (C_{quat}), 147.4 (C_{quat}), 148.7 (C_{quat}), 156.0 (C_{quat}), 160.2 ppm (C_{quat}); MS (70 eV, EI): *m/z* (%): 358 (4) $[M]^+$, 256 (100) $[M-C_5H_{10}O_2]^+$, 199.1 (38) $[C_{11}H_9N_3O]^+$, 171 (28) $[C_{10}H_9N_3]^+$, 156 (12) $[C_{10}H_8N]_2^+$; elemental analysis calcd (%) for $C_{18}H_{22}N_4O_4$ (358.4): C 60.32, H 6.19, N 15.63; found: C 59.98, H 5.76, N 15.45.

Photooxidations: Photooxidations were performed in quartz cuvettes (d = 10 mm). Aliquot portions of stock solutions of reactants in acetonitrile or in water were added direct into the cell to achieve concentrations of flavin catalyst and benzyl alcohol of 2×10^{-4} mol L^{-1} and 2×10^{-3} mol L^{-1}, respectively. The mixture was purged with oxygen for 5 min before the reaction. The cell containing the reactants was irradiated with a lamp (500 W) through a filter transmitting only light with $\lambda > 420$ nm. The amount of hydrogen peroxide produced was determined by the sodium iodide method:[26] The sample (50 µL) was diluted with excess sodium iodide and the amount of I^{3-} formed was determined spectrophotometrically (λ_{max} = 350 nm). The amount of the reactant, 4-methoxybenzyl alcohol and the product, 4-methoxybenzaldehyde, was determined by HPLC: aliquot portions of the reaction mixture were diluted with the solution of the internal standard (naphthalene, Fluka p. a. grade) and the sample was analyzed on an Agilent 1100 HPLC System (column: Phenomenex Luna C18 column, 150 mm, 5 µl) with use of spectrophotometric detection (Agilent 1100 Diode Array Detector). The amount of the flavin catalyst was monitored by measurement of the absorbance of the reaction mixture at the maximum of the flavin absorption (λ = 444 nm). Quantum yields of 4-methoxybenzyl alcohol photooxidation were determined from the kinetics of 4-methoxybenzaldehyde formation over irradiation for 5 min with the standard actinometer potassium ferrioxalate.[27] The amount of 4-methoxybenzylaldehyde formed was monitored by HPLC as described above.

For reaction monitoring in deaerated water and acetonitrile by NMR spectroscopy, solutions were prepared directly in the NMR tube. The solution was then purged with argon for 15 min and the reaction mixture was irradiated ($\lambda > 420$ nm) for 8 h. Signals of the resulting aldehyde were correlated with signals of a standard.

Fluorescence quenching: The relative fluorescence intensities were measured on a Varian Eclipse spectrometer in acetonitrile solutions containing **10** ($c = 2\times10^{-5}$ mol L^{-1}), **4** ($c = 1\times10^{-5}$ mol L^{-1}), or **5** ($c = 1\times10^{-5}$ mol L^{-1}) and the corresponding benzyl alcohol (c = 0–2×10^{-2} mol L^{-1}) at 25 °C. Stern–Volmer plots ($I_0/I = 1+K_S[Q]$) were constructed, and constants K_S were evaluated as the slope of the dependence (in the case of **4** and **5**) or as a slope of the linear part (in the case of **10**). Quenching rate constants (k_q) were calculated from values of K_S ($K_S = k_q\cdot\tau$). Fluorescence lifetimes (τ) of flavins **10**, **4**, and **5** in acetonitrile were measured by use of a Hurricane (Spectra-Physics) laser source (λ_{ex} = 401.5 nm) and a high speed digital oscilloscope LeCroy 9360 analyzer (200 ps).

Cyclic voltammetry: Cyclic voltammetry measurements were performed with An Autolab PGSTAT 20 set-up at room temperature in acetonitrile under argon with use of a conventional undivided electrochemical cell and a platinum disc as the working electrode, platinum wire as the auxiliary electrode, and calomel as the reference electrode. Redox potentials were referenced against ferrocenium/ferrocene. In all experiments, the scan rate was 50 mV s^{-1} and Pr_4NBF_4 (tetrapropylammonium tetrafluoroborate) was used as supporting electrolyte (c = 0.1 mol L^{-1}).

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