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Aggregation Effects in Visible-Light Flavin Photocatalysts: Synthesis, Structure, and Catalytic Activity of 10-Arylflavins

Jitka Daďová,[a, b] Susanne Kümmel,[a] Christian Feldmeier,[a] Jana Cibulková,[c] Richard Pažout,[c] Jaroslav Maixner,[c] Ruth M. Gschwind,[a] Burkhard König,[a] and Radek Cibulka*[b]

Abstract: A series of 10-arylflavins (10-phenyl-, 10-(2′,6′-dimethylphenyl)-, 10-(2′,6′-diethylphenyl)-, 10-(2′,6′-diisopropylphenyl)-, 10-(2′-*tert*-butylphenyl)-, and 10-(2′,6′-dimethylphenyl)-3-methylisoalloxazine (**2a–f**)) was prepared as potentially nonaggregating flavin photocatalysts. The investigation of their structures in the crystalline phase combined with ^{1}H-DOSY NMR spectroscopic experiments in CD_3CN, CD_3CN/D_2O (1:1), and D_2O confirm the decreased ability of 10-arylflavins **2** to form aggregates relative to tetra-*O*-acetyl riboflavin (**1**). 10-Arylflavins **2a–d** do not interact by π–π interactions, which are restricted by the 10-phenyl ring oriented perpendicularly to the isoalloxazine skeleton. On the other hand, N3–H···O hydrogen bonds were detected in their crystal structures. In the structure of 10-aryl-3-methylflavin (**2f**) with a substituted N3 position, weak C–H···O bonds and weak π–π interactions were found. 10-Arylflavins **2** were tested as photoredox catalysts for the aerial oxidation of 4-methoxybenzyl alcohol to the corresponding aldehyde (model reaction), thus showing higher efficiency relative to **1**. The quantum yields of 4-methoxybenzyl alcohol oxidation reactions mediated by arylflavins **2** were higher by almost one order of magnitude relative to values in the presence of **1**.

Keywords: aggregation · flavins · noncovalent interactions · organocatalysis · oxidation · photocatalysis

Introduction

Flavins (isoalloxazines) are biologically active compounds that are responsible for redox processes in many types of enzyme, mostly in the form of flavin mononucleotide or flavin adenin dinucleotide cofactors.[1] Besides, synthetic flavin analogues are the subject of intensive research as organocatalysts of oxidation and reduction reactions.[2,3] The redox activity of flavin derivatives is dramatically enhanced by absorption of visible light; the longest wavelength absorption maximum is at around $\lambda_{max} = 450$ nm.[4] Thus, the photoexcitation of flavins enables the oxidation of substrates that cannot be oxidized thermally.[5–14] Until now, flavins have been applied to the photooxidation of benzyl alcohols,[5] benzyl amines,[6] and methylbenzenes[7] to benzaldehydes; the photooxidation of benzyl methyl ethers to methyl benzoates;[7] the photooxidation of dopamine,[8] amino acids,[9] indols,[10] unsaturated lipids and fatty acids,[11] glucose,[12] and phenols;[13] and the selective photocatalytic removal of benzylic protecting groups.[14] The photooxidation reactions mentioned are usually performed in the presence of air, thus allowing the regeneration of the flavin catalyst **Fl** from its dihydro form **Fl-H$_2$**, which is formed from flavin in the excited state **Fl*** in the presence of a substrate (quencher) by a subsequent two-electron reduction and protonation process. Therefore, only a catalytic amount of flavin is required (Scheme 1). Flavins are also known to sensitize singlet oxygen production.[15] Until now, flavin-mediated sulfoxidation reactions[16] and oxidation reactions of unsaturated lipids[17] that are proceeded by a singlet-oxygen mechanism have been reported.

In almost all studies, the photooxidation of benzyl alcohols to benzaldehydes in acetonitrile was studied as a typical procedure to elucidate the efficiency of the flavin photocatalyst. The activity of simple flavins, for example, tetra-*O*-acetyl riboflavin (**1**) and lumiflavin (see Figure 1 for the structures), in the oxidation of 4-methoxybenzyl alcohol in acetonitrile is very low, with quantum yields of up to 0.03 %.[5c,18] Several attempts to improve the efficiency of flavins have recently been reported. Substantially higher quantum yields of the oxidation of benzyl alcohol were ach-

[a] J. Daďová, S. Kümmel, C. Feldmeier, Prof. Dr. R. M. Gschwind, Prof. Dr. B. König
Institute of Organic Chemistry
University of Regensburg
Universitätsstrasse 31, 93040 Regensburg (Germany)

[b] J. Daďová, Dr. R. Cibulka
Department of Organic Chemistry
Institute of Chemical Technology, Prague
Technická 6, 166 28 Prague (Czech Republic)
Fax: (+420) 220-444-288
E-mail: cibulkar@vscht.cz

[c] J. Cibulková, Dr. R. Pažout, Dr. J. Maixner
Central Laboratories
Institute of Chemical Technology, Prague
Technická 6, 166 28 Prague (Czech Republic)

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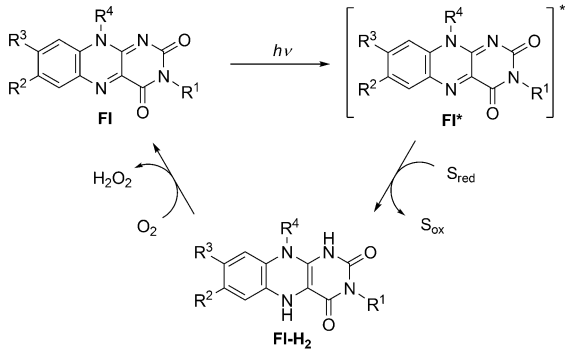


Scheme 1. Catalytic cycle for the aerobic photooxidation of a substrate **S** mediated by flavin **Fl**.

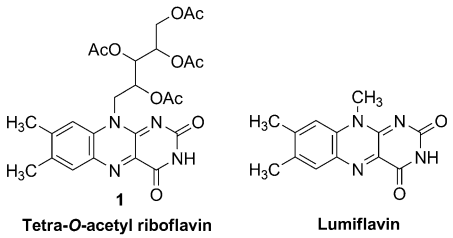
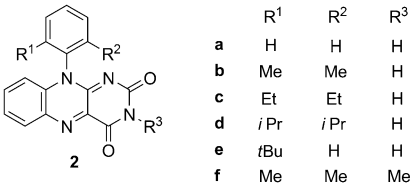


Figure 1. Structure of the flavin compounds typically used in photocatalysis.

ieved if the flavin photocatalyst was protonated or coordinated to rare-earth metal ions, with the highest value of 17% in the case of a scandium(III) complex.[5g,h,l] Also, thiourea accelerated the photooxidation of benzyl alcohol mediated by flavins and reached a high turnover number (TON) of up to 580.[5c] A remarkable improvement in the catalytic efficiency of the flavin moiety was achieved by its covalent attachment to Zn^{II}–cyclen or a β-cyclodextrin substrate-binding site.[5d,f] The reaction medium enhances the photooxidation if performed in sodium dodecyl sulfate (SDS) micelles.[5e] A positive effect of water on the rate of photooxidation reactions mediated by flavins has also been described.[5a,d,18] Immobilization of flavins on fluorinated silica gel stabilizes the chromophore.[5b]

Besides hydrogen bonding, flavins are known to interact with several molecules by π–π stacking,[19] donor–π interactions,[20] and cation or anion–π interactions.[21] These interactions are essential not only for the binding of flavin cofactors in proteins, but also to modulate their redox properties and, consequently, the reactivity of flavin moieties in biological systems.[19f,21] The effect of noncovalent interactions on the properties of flavins in artificial systems is also well documented.[19,20] There is evidence for flavin dimer formation, even in dilute solutions,[22] and such intermolecular aggregation may decrease the photocatalytic efficiency of flavins by quenching excited states or alter their redox properties.[5a] With the aim of minimizing the ability of flavins to aggregate, we prepared a series of derivatives **2b–e**, with an *ortho*-substituted phenyl ring in position 10 (Figure 2). The aryl ring should be oriented perpendicular to the flavin skeleton due to *ortho* substitution, thus making π–π interactions between flavins less possible. Compound **2a**, without substitution on the phenyl ring, and the 3-methyl derivative **2f** were prepared for comparison. The photochemical, electrochemical, and aggregation properties; crystal structures; and ability to mediate the photooxidation of 4-methoxybenzyl alcohol (model reaction) of arylflavins **2** were studied and compared with those of **1**.

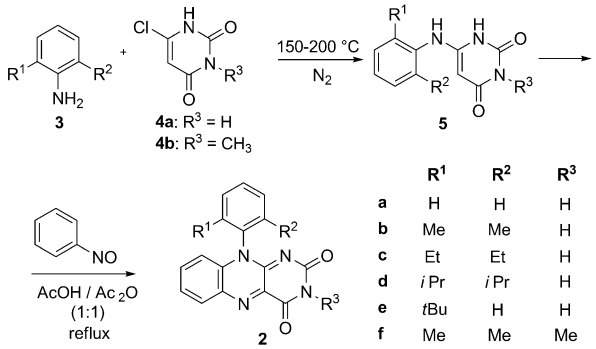


	R^1	R^2	R^3
a	H	H	H
b	Me	Me	H
c	Et	Et	H
d	*i*Pr	*i*Pr	H
e	*t*Bu	H	H
f	Me	Me	Me

Figure 2. Structure of 10-arylflavins synthesized and investigated as photocatalysts.

Results and Discussion

Synthesis: The synthesis of 10-arylisoalloxazines **2** (Scheme 2) was started by converting commercially available substituted anilines **3a–e** with 6-chlorouracil (**4a**) into 6-arylaminouracils **5a–e**. It is evident from the reaction conditions and yields (Table 1) that the substitution becomes more difficult with increasing steric hindrance of the substituents on C2 and C6 of the phenyl ring. Although the nonsubstituted phenyl derivative **5a** was obtained almost



	R^1	R^2	R^3
a	H	H	H
b	Me	Me	H
c	Et	Et	H
d	*i*Pr	*i*Pr	H
e	*t*Bu	H	H
f	Me	Me	Me

Scheme 2. Synthesis of 10-arylflavins **2**.

Table 1. Reaction conditions and yields for the preparation of 6-aminouracils **5** by the reaction of 6-chlorouracil (**4a**) with substituted anilines **3**.[a]

6-Aminouracil	*T* [°C]	Reaction time [h]	Yield [%]
5a	150	1	98
5b	180	1	74
5c	180	7	58
5d	200	24	75
5e	180	10	57

[a] A mixture of **4a** and **3** was heated in a nitrogen atmosphere (see the Supporting Information for further details).

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quantitatively, sterically hindered aminouracils were isolated only in moderate yields (i.e., **5c** and **5e**) or after a substantially longer reaction time (i.e., **5d**).

The prepared aminouracils **5a–e** were converted into the target flavins **2a–e** by reaction with nitrosobenzene in acetic acid/acetic anhydride (1:1). Although this synthetic approach was effective for the synthesis of other sterically hindered flavins,[3c,23] derivatives **2** were obtained in relatively low yields (13–25%). Unfortunately, the yield did not increase even when acetic acid and acetic anhydride in other ratios were used as the solvent. The 3-methyl derivative **2f** was prepared in an analogous process by using 6-chloro-3-methylaminouracil (**4b**; Scheme 2). Interestingly, the conversion of 6-arylamino-3-methyluracil (**5f**) into 3-methylflavin (**2f**) proceeded in a substantially higher yield relative to the formation of **2b** (44 versus 23%, respectively), which possesses a nonsubstituted N3 position.

Crystal structures: The interaction of flavin molecules in the crystal can provide information about the aggregation behavior in the solution. For this purpose, crystals for single-crystal analysis were prepared of **2a–d** and **2f**. Interestingly, of the five structures only two **2b** and **2d** exhibited one molecule in the asymmetric unit, as could be expected. Three structures **2a**, **2c**, and **2f** possessed two different molecules A and B in the asymmetric unit. A close inspection of the structures with A and B molecules showed that a significant difference between the two molecules was displayed only by **2c**, in which one ethyl group of the *ortho*-substituted phenyl ring of the molecule B was rotated around the C(phenyl)–CH_2 bond by 83.9(1)° (Figure 3c). In the structure of **2f**, molecules A and B differed only by a slightly different rotation of the phenyl ring (Table 2). In the case of the structure **2a**, no marked difference between molecules A and B was observed.

Structures of several simple flavin derivatives have already been investigated by X-ray diffraction.[24] In most cases, π-stacking interactions between the isoalloxazine moieties were recognized, which results in the packing of flavin molecules with distances of between 3.3 and 3.6 Å. In such stacked systems, flavin molecules adopt an alternating orientation, and the benzene ring of one flavin moiety overlaps with the pyrimidine ring of the adjacent one (and vice versa). Tetra-*O*-acetyl riboflavin (**1**),[24d] 3-methyl-tetra-*O*-acetyl riboflavin,[24a] 3-benzyllumiflavin,[24b] and 10-methylisoalloxazine[24e] are examples of such stacked structures in the crystal phase. As expected, no π–π interactions between flavin moieties were found in the structures of 10-arylflavins **2b–d**, even in the case of **2a** with the unsubstituted phenyl ring, in which a coplanar orientation of the phenyl and isoalloxazine subunits was still allowed. In the structures of flavins **2a–d**, the aryl ring is almost perpendicular to the mean plane of the isoalloxazine fragment, with a dihedral angle that ranges from 78.4 to 86.5°, thus preventing the stacking of flavins (see Table 2, Figure 3, and the Supporting Information). A similar value of the dihedral angle of 79.7° was reported for 10-(2-hydroxyphenyl)-3-methylisoalloxazine.[25]

The analysis of the X-ray crystallographic data showed pairs of symmetrical hydrogen N–H···O bonds between the pyrimidine rings of two adjacent molecules of flavins **2a–d** (Figure 3a–d). Additionally, a relatively short N3B–H···O12A hydrogen bond in the structure of **2c** and weak C–H···O interactions in **2a–d** contribute to the aggregation. Hydrogen bonds C16–H···O11 in **2b** (Figure 3b) and C22–H···O12 in **2d** (Figure 3d), with participation of the hydrogen atoms on the (alkyl)phenyl ring on one hand, and hydrogen bond C7B–H···O11B in **2a** (Figure 3a), with participation of the hydrogen atoms on the isoalloxazine skeleton on the other hand, can be given as examples (see the Supporting Information for all the hydrogen-bonding data). In contrast to flavins with a free N3–H bond (**2a–d**), compound **2f** cannot form N-H···O bonds, and thus relatively weak C–H···O interactions dominate in the crystal structure of **2f** (Figure 3e). Methyl groups on both the N3 atom and the aryl ring participate in these C–H···O bonds. However, despite the presence of the *ortho*,*ortho*-disubstituted phenyl ring with perpendicular orientation toward the isoalloxazine skeleton (Table 2), little overlap of the flavin subunits that results in a weak π–π interaction was found in the structure of **2f** (Figure 3f). The distance between the neighboring planes in the stack is about 3.5 Å.

The investigation of the structure in the crystalline phase confirms that 10-arylflavins **2** have no structural prerequisites to interact by mean of strong π–π interactions and to form stacks in a similar manner to simple flavin molecules.[24] One could speculate about the situation in solution due to the conformational flexibility of the molecules. Flavin **2a** may show rotation of the phenyl ring; however, this behavior is strongly limited by the *ortho* substituents in **2b–f**. Therefore, only partial overlap of the isoalloxazine skeletons (e.g., by one ring) that results in a weak π–π interaction could be expected in solution. As was shown in flavoenzyme models, the binding constants based on the overlap of one or three rings of the flavin skeleton with an aromatic compound can differ by a factor of 30.[19g]

Aggregation properties determined by ^{1}H-DOSY NMR spectroscopy: ^{1}H-DOSY NMR experiments[26] were used to measure the diffusion coefficients of **1** and arylflavins **2** in CD_3CN, D_2O, and CD_3CN/D_2O (1:1). The resulting aggregation numbers calculated from the experimental diffusion coefficients (see the Experimental Section and Supporting Information) are presented in Table 3. A significant aggregation for **1** was detected in CD_3CN, with an average aggregation number of 3.0, which decreased upon the addition of water down to monomers in pure D_2O. Next, the aggregation trends for arylflavins **2a–f** were investigated. For all the compounds, a significantly decreased aggregation number was found in CD_3CN relative to **1**. Again, the addition of water led to disaggregation for arylflavins **2a–f**. These data show that the basic idea to decrease π–π interactions in the aggregates by the introduction of an aryl ring with sterically demanding substituents works. However, there was no direct correlation between the steric demand of the substitu-

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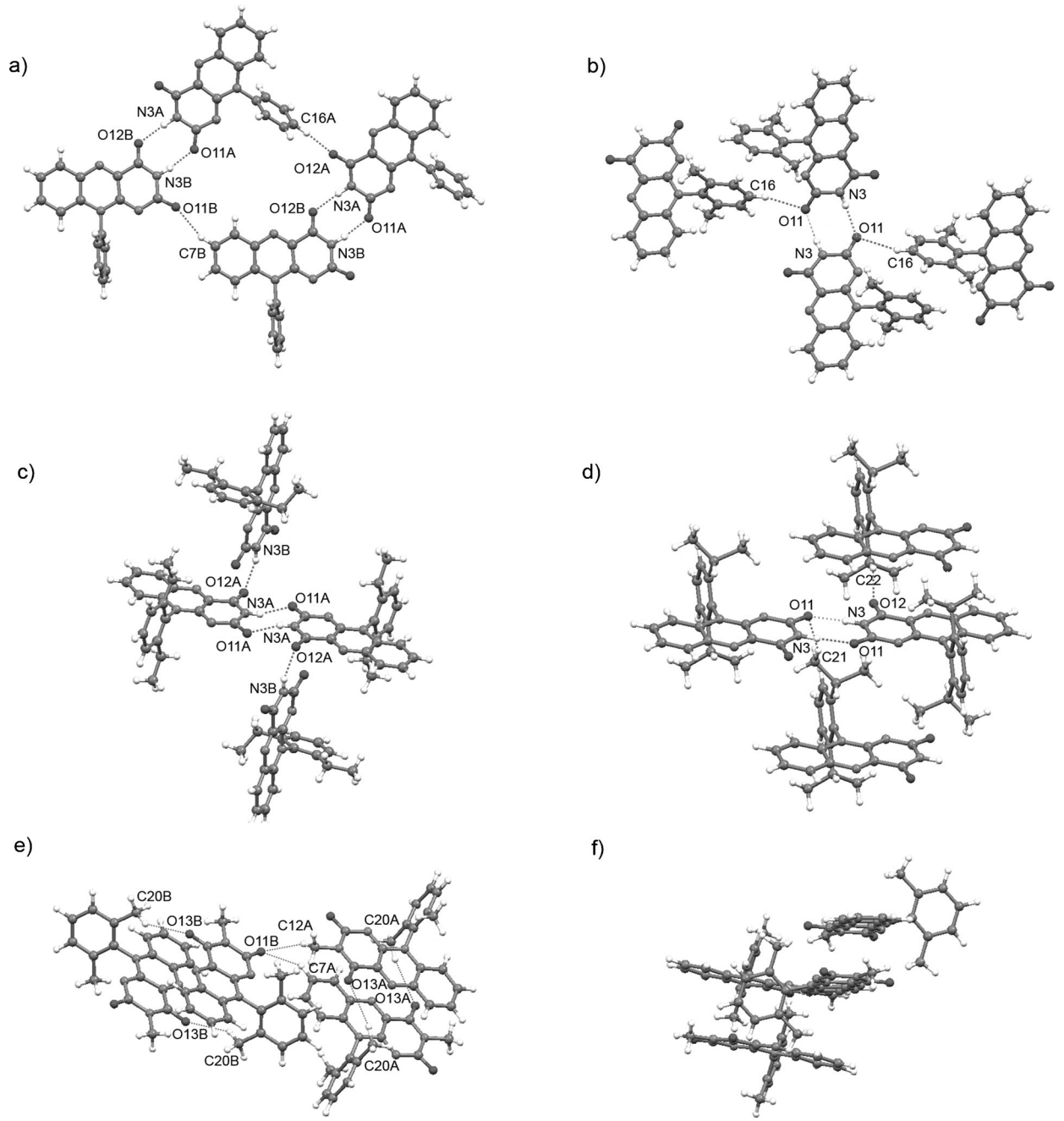

Figure 3. Hydrogen bonding in the crystal structures of 10-arylflavins a) **2a**, b) **2b**, c) **2c**, d) **2d**, and e) **2f** and f) a fragment that shows π stacking of the molecules **2f**. The hydrogen bonds are shown as dashed lines, and the non-hydrogen atoms that participate in the hydrogen bonds are labeled. See the Supporting Information for a colour version, hydrogen-bonding data, and more images.

Table 2. Dihedral angles between the aryl and isoalloxazine planes in the crystal structures.

Flavin	Angle [°]
2a	79.73(5),[a] 78.43(4)[b]
2b	83.25(4)
2c	86.48(4),[a] 83.48(4)[b]
2d	85.69(5)
2f	79.49(5),[a] 82.02(5)[b]

[a] Molecule A. [b] Molecule B.

ents in **2a–f** and the aggregation number detected experimentally. For example, **2c** shows decreased aggregation relative to **2b**, as expected for ethyl groups relative to methyl groups as substituents; however, a further increase in the steric demand in **2d** and **2e** did not lead to decreased aggregation numbers. This finding suggests that not only π–π interactions between the isoalloxazine moieties contribute to the aggregation, but also additional stabilizing dispersion forces between the bulkier substituents[27] and other nonco-

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Table 3. Aggregation numbers of **1** and 10-arylflavins **2** in different solvents.[a]

Flavin	Aggregation number		
	CD_3CN	CD_3CN/D_2O (1:1)	D_2O
1	3.0	1.7	1.0
2a	2.4	1.2	1.0
2b	2.6	1.4	1.0
2c	1.9	1.0	1.0
2d	2.1	1.2	1.0
2e	2.2	1.0	1.0
2f	2.4	1.3	1.0

[a] Conditions: $T=300$ K, $c=5\times10^{-3}$ mol L^{-1} of flavins **1** and **2** in solution with CD_3CN and CD_3CN/D_2O (1:1) or a saturated solution in D_2O.

valent interactions play an important role. Interestingly, analysis of the crystal structures of **2a–d** revealed N–H···O hydrogen bonding as the dominant noncovalent interaction for these arylflavins and not π–π interactions, as found for **1**. In the 3-methyl derivate **2f**, hydrogen bonding through the N3–H bond is blocked. However, the diffusion measurements showed only a slightly decreased aggregation number relative to **2b**. This outcome is in accordance with the crystal structure of **2f**, which shows π–π interactions again besides weaker C–H···O interactions. The solvent-dependent disaggregation of arylflavins **2a–e** going from CD_3CN to CD_3CN/D_2O (1:1) and D_2O correlates with the relative hydrogen-bond acceptor properties of these solvents in terms of better solute/solvent interactions toward pure D_2O.[28] Interestingly, the aggregates driven by π–π-interactions show a similar solvent dependence, thus demonstrating that the solvent dependence in flavins cannot be used as an indicator of the intermolecular interaction mode. Thus, the combination of aggregation numbers and crystal-structure analysis reveals that both π–π interactions and hydrogen bonding play a decisive role in the aggregation of the flavins, and their relative contribution can be tuned by the structure of the synthesized flavins.

Spectral and electrochemical properties: The spectral and electrochemical properties of the newly prepared 10-arylflavins **2** in acetonitrile were studied and compared to those of **1** (see Table 4 and the Supporting Information). The aryl substituent in position 10 of the isoalloxazine causes a small blue shift of the absorption maxima and a decrease in the absorption intensity in the UV/Vis spectra. Substitution at the N3 position of the 10-arylisoalloxazine ring effects the position of the absorption maxima more significantly (cf. flavins **2b** and **2f**), than it was observed in the case of lumiflavin and 10-methylisoalloxazine.[29] All flavins **2** show intensive fluorescence with a maximum at around $\lambda_{max}=500$ nm. A small effect of the aryl substitution on the fluorescence maxima was only observed in the case of **2a**, which bears a nonsubstituted phenyl ring. However, the fluorescence quantum yield of **2a** is significantly decreased by half relative to **1** and **2b–d**. Similarly, substitution at N3 decreases the fluorescence quantum yield of arylflavins, which corresponds to the observed effect of N3 substitution in **1**[24a,30] and 10-methylisoalloxazine.[29b] On the other hand, the fluorescence quantum yields reported for lumiflavin and 3-methyllumiflavin are almost the same.[29a]

Table 4. Spectroscopic data for flavins **1** and **2** in acetonitrile.

Flavin	λ_2 [nm] (ε [mol^{-1} dm^3 cm^{-1}])[a]		λ_1 [nm] (ε [mol^{-1} dm^3 cm^{-1}])[a]		λ_F [nm][b]	Φ_F[c]
1	343	(8500)	440	(12000)	505	0.499
2a	335	(6200)	436	(8900)	517	0.244
2b	330	(7000)	437	(10000)	498	0.447
2c	331	(7000)	434	(10000)	500	0.537
2d	330	(6200)	436	(8900)	501	0.434
2e	332	(7000)	437	(9900)	502	0.328
2f	321	(5500)	427	(6500)	498	0.282

[a] λ_1 and λ_2 are the positions of the two lowest-energy bands in the absorption spectra. [b] The maximum of the fluorescence emission spectrum, $\lambda_{ex}=\lambda_1$. [c] The fluorescence quantum yield determined with quinidine sulfate as a standard.

The reduction potentials of the synthesized flavin derivatives in acetonitrile that correspond to one-electron reduction (Fl→Fl$^{\bullet-}$)[30] were determined by cyclic voltammetry (CV) relative to ferrocene/ferrocenium. Moreover, the change in the Gibbs free energy ΔG_{ET} of the electron transfer from the substrate 4-methoxybenzyl alcohol to the excited flavins in the singlet state (Table 5) were calculated from the observed reduction potentials by using the Rehm–Weller equation (1):[31]

$$\Delta G_{ET} = 96.4(E^{ox}{}_{1/2} - E^{red}{}_{1/2}) - e^2/\varepsilon a - E^{0-0} \quad (1)$$

where $E^{ox}{}_{1/2}$ and $E^{red}{}_{1/2}$ are the oxidation potentials of the substrate ($E^{ox}{}_{1/2}=+1.19$ V for 4-methoxybenzyl alcohol)[5d] and the reduction potential of the flavin (Table 5); $e^2/\varepsilon a$ is the Coulomb term (5.4 kJ mol^{-1});[30] E^{0-0} is the flavin excitation energy (given in kJ mol^{-1}), which was estimated as the average of absorption (hc/λ_1) and emission (hc/λ_F) energies with λ_1 and λ_F values derived from the flavin absorption and fluorescence spectra (Table 4); h is the Planck constant (6.63×10^{-34} m^2 kg s^{-1}); and c is the velocity of light (2.99×10^8 m s^{-1}). The redox potential of arylflavins **2** shifts to more positive values, but by only 60 mV relative to **1**, which did not seem to be enough to influence the oxidation power of the flavin significantly. According to Gibbs free energy

Table 5. Redox potentials of flavins **1** and **2**, estimated free-energy changes ΔG_{ET}, and Stern–Volmer K_S constants for the electron transfer from 4-methoxybenzyl alcohol to flavins **1** and **2** in acetonitrile.

Flavin	$E^{red}{}_{1/2}$ [V][a]	ΔG_{ET} [kJ mol^{-1}][b]	K_S [mol^{-1} dm^3]
1	−1.18	−42	26
2a	−1.12	−46	25
2b	−1.11	−51	42
2c	−1.10	−52	44
2d	−1.11	−51	35
2e	−1.10	−51	36
2f	−1.11	−53	33

[a] Values obtained in acetonitrile at a scan rate of 50 mV s^{-1} in solutions of the flavins (1×10^{-3} mol L^{-1}) with Bu_4NPF_6 (1×10^{-2} mol L^{-1}) at 20 °C versus ferrocene/ferrocenium. [b] Free-energy changes calculated from Equation (1) using $E^{ox}{}_{1/2}=1.19$ V for 4-methoxybenzyl alcohol versus ferrocene/ferrocenium.[5d]

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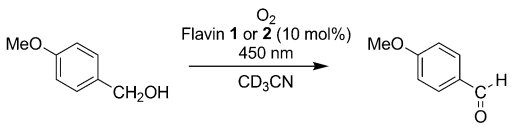
changes, electron transfer between 4-methoxybenzyl alcohol and flavins **1** and **2** in their singlet excited state is exergonic, and thus favorable ($\Delta G_{ET} < 0$). The ΔG_{ET} values are less negative for **1** and 10-phenylisoalloxazine (**2a**) by about 10 kJ mol^{-1} relative to **2b–f**.

Fluorescence quenching for the newly synthesized derivatives **2** with 4-methoxybenzyl alcohol was studied in acetonitrile. Stern–Volmer plots constructed from the results are linear in all the cases (see the Supporting Information). The values of Stern–Volmer constants K_S ($K_S = k_Q \tau_F$, where k_Q is the apparent rate constant and τ_F is the fluorescence lifetime) were calculated as the slope of Stern–Volmer dependence ($I_0/I = 1 + K_S[Q]$), that is, as the slope of the ratio of the fluorescence intensities I_0/I in the absence and presence of 4-methoxybenzyl alcohol (quencher Q) plotted against concentration $[Q]$. Interestingly, for almost all the newly prepared flavins bearing substituted phenyl rings **2b–f**, higher quenching K_S constants were measured relative to **1**. Only the value for 10-phenylisoalloxazine (**2a**) is equal to that of **1**. The observed decreased values of Stern–Volmer K_S constants for **1** and **2a** probably result from the decreased rate of electron transfer k_Q, which corresponds to the decreased Gibbs free energy changes ΔG_{ET} (Table 5).

Photooxidation of 4-methoxybenzyl alcohol: The ability of the prepared flavins **2** to mediate the photooxidation of 4-methoxybenzyl alcohol with oxygen to the corresponding aldehyde was investigated under standard conditions, namely, 10 mol% of photocatalyst in deuterated acetonitrile at 25 °C under the atmospheric pressure of air (Scheme 3). A high-



Scheme 3. Model photooxidation reaction.

power light-emitting diode was used for the irradiation of the reaction mixture. A comparison of the efficiencies of flavins in the photooxidation reactions was made by determining 1) conversion after 90 minutes determined by ^{1}H NMR spectroscopic analysis of the reaction mixture and 2) quantum yield of the photooxidation reactions determined independently. Importantly, the oxidation reaction does not proceed in the absence of flavin or light.

With **1** as a photocatalyst, only 5% conversion was achieved after 90 minutes of irradiation (Table 6, entry 1). The use of **2a** without substitution on the phenyl ring led to only a small improvement of the conversion (Table 6, entry 2). On the other hand, the introduction of an phenyl ring with substituents in *ortho* positions resulted in a substantial increase in flavin efficiency to mediate photooxidation, thus reaching conversions of up to 37% after 90 minutes of irradiation in the presence of **2b** (Table 6, entry 3). The character of the alkyl substituents on the aryl ring seems to be important for the efficiency of the flavin photocatalysts. The diethyl derivative **2c** showed nearly the same activity as **2b** (compare entries 3 and 4 in Table 6), whereas the activity of **2d** and **2e** with branched isopropyl and *tert*-butyl substituents is slightly decreased (Table 6, entries 5 and 6). Interestingly, the alkylation of the N3 atom also decreases the efficiency of the flavin chromophore in the photooxidation reactions (Table 6, entry 7). The conversion of the photooxidation reactions in the presence of **2b–f** are relatively high after 1.5 hours of irradiation, but they are not remarkably increased during the next irradiation period. This behavior is caused by degradation of the flavin photocatalysts during photooxidation reactions, which was evidenced from bleaching of the reaction mixtures (see Table 6 and the Supporting Information). Nevertheless, the photostability is not the most important factor that influences the activity of flavin photocatalysts. The least stable flavin **2c** showed relatively high efficiency. Interestingly, all the synthesized catalysts **2** are less photostable than flavin **1**.

Table 6. Photooxidation of 4-methoxybenzyl alcohol to 4-methoxybenzaldehyde in CD_3CN catalyzed by **1** and 10-arylflavins **2a–f**.

Entry	Flavin	Conversion [%][a]	Relative absorbance [%][b]	Quantum yield[c] Φ [%] of aldehyde formation
1	**1**	5	94	0.0034 (0.0041)[d]
2	**2a**	9	74	0.0045 (0.0042)[d]
3	**2b**	37	83	0.0204 (0.0210)[d]
4	**2c**	36	27	0.0179 (0.0149)[d]
5	**2d**	29	72	0.0126 (0.0125)[d]
6	**2e**	28	56	0.0102 (0.0086)[d]
7	**2f**	25	87	0.0118 (0.0113)[d]

[a] After irradiation for 90 min. Conditions: $c_{alcohol} = 4 \times 10^{-3}$ mol L^{-1}, $c_{flavin} = 4 \times 10^{-4}$ mol L^{-1}, irradiation with 1 W LED ($\lambda_{max} = 450$ nm), $T = 25$ °C, monitoring by ^{1}H NMR. [b] Relative absorbance of the reaction mixture at $\lambda = 443$ nm after irradiation for 60 min relative to the absorbance at the beginning of the experiment. [c] Determined by independent experiments with monitoring by GC. [d] Determined in CH_3CN.

The results of quantum-yield measurements are in accordance with the observed conversions (Table 6). The introduction of disubstituted aryl rings at position 10 of the isoalloxazine ring causes a substantial increase in the quantum yield of the oxidation of 4-methoxybenzyl alcohol, which is, in the case of **2b**, by almost one order of magnitude higher than the photooxidation in the presence of **1**. However, the increase in the quantum yield of the flavin photocatalyst is approximately half with bulky isopropyl or *tert*-butyl substituents or if the N3 position of isoalloxazine is substituted by a methyl group. As expected, the quantum yields of the oxidation reactions are not affected by deuteration of the solvent, thus indicating that a singlet-oxygen pathway is not involved.[32]

One could speculate that the lower efficiency of **2a** relative to **2b–f** is a result of its smaller oxidation power, but the differences in reduction potentials and in estimated ΔG_{ET} values are not sufficient to explain the observed significant differences in reactivity. The low activity of **2a** can also be attributed to the possible free rotation of the non-

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substituted aryl ring, thus allowing its coplanar arrangement relative to the isoalloxazine plane. This effect may increase the ability of **2a** to aggregate in solution with flavins or substrates, thus supporting fast unproductive charge recombination.[5a] Interestingly, the N3–H···O hydrogen bonds that dominate among the intermolecular interactions of flavins **2b–e** seem to have no negative effect on the catalytic activity of flavin photocatalysts, as evidenced by the comparison of **2b** and **2f** (compare entries 3 and 7 in Table 6).

Significantly enhanced quantum yields (by a factor of 80) were reported for the oxidation of 4-methoxybenzyl alcohol catalyzed by **1** by changing the solvent from pure acetonitrile to acetonitrile/water (1:1).[5a,18] In the case of arylflavin **2b**, the effect of water content on the quantum yield is even higher and a factor of 220 was reached (Table 7). Consequently, quantitative conversion was observed after only 15 minutes of photooxidation catalyzed by **2b**, whereas only 37% conversion was achieved in pure CD_3CN after 90 minutes (compare Table 7 with Table 6, entry 3). Unfortunately, the decomposition of **2b** was also relatively fast in CD_3CN/D_2O (1:1; see Table 7 and the Supporting Information).

Table 7. Photooxidation of 4-methoxybenzyl alcohol to 4-methoxybenzaldehyde in CD_3CN/D_2O (1:1) catalyzed by **1** and 10-arylflavin **2b**.

Flavin	Conversion after irradiation [%][a]		Relative absorbance [%][b]	Φ/Φ_{CD_3CN}[c]
	5 min	15 min		
1	17	51	94	80
2b	58	quant.	49	220

[a] Conditions: $c_{alcohol} = 4\times10^{-3}$ mol L^{-1}, $c_{flavin} = 4\times10^{-4}$ mol L^{-1}, irradiation with 1 W LED ($\lambda_{max} = 450$ nm), $T = 25$ °C, monitoring by ^{1}H NMR. [b] Relative absorbance of the reaction mixture at $\lambda = 443$ nm after irradiation for 10 min relative to the absorbance at the beginning of the experiment. [c] Relative values of the quantum yields in CD_3CN/D_2O (1:1) relative to the quantum yields in pure CD_3CN (Table 6).

Conclusion

10-Arylisoalloxazines **2a–f** were prepared as potentially nonaggregating flavin photocatalysts by condensation of the appropriately substituted aminouracils **5a–f** with nitrosobenzene. The investigation of their structures in the crystalline phase confirms that 10-arylflavins **2** have no structural prerequisites to interact by means of strong π–π interactions and to form stacks in a similar manner to simple flavin molecules, which is caused by steric hindrance of the substituted phenyl ring oriented perpendicularly to the flavin skeleton. X-ray diffraction studies also revealed that N–H···O hydrogen bonding dominates in the crystals of **2a–d**. Blocking the N3 position with a methyl group in **2f** inhibits the formation of N–H···O bonds; instead, C–H···O hydrogen bonds and weak π–π interactions shape the structure of the molecules in the solid state. The significantly lower tendency of flavins **2a–f** to aggregate in acetonitrile was confirmed by ^{1}H-DOSY NMR spectroscopic experiments. Nevertheless, it was shown that there is no direct correlation between the steric demand of the substituents in **2a–f** and the aggregation numbers, which is probably due to the contributions of other noncovalent interactions; for example, the N–H···O hydrogen bonds in the case of **2a–e** or dispersion forces between the bulkier substituents in the case of **2d** and **2e**.

Flavins **2b–f** are far more effective photocatalysts for the photooxidation of 4-methoxybenzyl alcohol than tetra-*O*-acetyl riboflavin (**1**). The observed quantum yield of this oxidation in the presence of **2b** (the best photocatalyst among 10-arylflavins **2**) exceeds that of **1** by almost one order of magnitude. Unfortunately, the increased reactivity of **2** is accompanied by their lower photostability. Although the conversions of the photooxidation reactions of 4-methoxybenzyl alcohol in acetonitrile catalyzed by flavins **2b–f** are not quantitative, they are among the most active flavins tested so far in the photooxidation reactions of benzyl alcohols. The efficiency of flavins **2** can be significantly enhanced by water as reported for **1**.[5a,18]

The results show that the efficiency of a flavin photocatalyst can be altered and improved by changing the structural elements that influence aggregation properties. However, there is no simple correlation as to how intermolecular interactions affect the ability of flavins to mediate the photooxidation of 4-methoxybenzyl alcohol. Although π–π interactions decrease the activity of flavin photocatalysts, the effect of hydrogen bonding seems to be positive. Therefore π–π interactions and hydrogen bonding should both be taken into account in the design of the structure of new flavins for photocatalysis. Additionally, photophysical properties (e.g., the quantum yields of singlet and triplet flavin excited-state formation) are influenced by substitution.

Experimental Section

Materials and methods: NMR spectra were recorded on a Varian Mercury Plus 300 (299.97 and 75.44 MHz for ^{1}H and ^{13}C, respectively), Bruker Avance 300 (300.13 and 75.03 MHz for ^{1}H and ^{13}C, respectively), Bruker Avance 400 (400.13 and 100.03 MHz for ^{1}H and ^{13}C, respectively), and Bruker Avance 600 (600.13 and 150.03 MHz for ^{1}H and ^{13}C, respectively) spectrometers. Chemical shifts δ are given in ppm with the residual solvent or tetramethylsilane (TMS) as an internal standard. Coupling constants are reported in Hz. UV/Vis spectra were recorded on a Varian Cary 50 spectrophotometer and fluorescence spectra on a Varian Cary Eclipse fluorescence spectrophotometer. TLC analyses were carried out on DC Alufolien Kieselgel 60 F_{254} and on DC Silicagel 60 RP-18 F_{254}s (Merck). Preparative column-chromatography separations were performed on silica gel Kieselgel 60 0.040–0.063 mm (Merck). Melting points were measured on a Boetius melting point apparatus or SRS MPA100 OptiMelt and are uncorrected. Elemental analyses (C, H, N) were performed on a Perkin–Elmer 240 analyzer. MS spectra were recorded on a ThermoQuest Finnigran TSQ 7000 mass spectrometer in tandem with a Janeiro LC system. HPLC analyses were carried out on an Ingos HPLC System (column: Phenomenex Luna 5u Silica, 150×4.6 mm) with a UV/Vis spectrophotometric detector. The starting materials and reagents were purchased from Sigma–Aldrich, Eurorad (deuterated solvents: $CDCl_3$, [D_6]DMSO, CD_3CN), and Lach-Ner (acetonitrile, propan-2-ol, and *n*-heptane for HPLC). The solvents were purified and dried by using standard procedures.[34]

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Tetra-*O*-acetyl riboflavin (**1**),[35] 6-chlorouracil (**4a**),[36,37] 6-chloro-3-methyluracil,[3c] and nitrosobenzene[38] were prepared according to the reported procedures. The experimental details about the synthesis and characterization of 6-aminouracils **5a–f** are provided in the Supporting Information.

Synthesis of 10-arylisoalloxazines 2a–f: Nitrosobenzene and the substituted 6-arylaminouracil **5** were dissolved in acetic acid/acetic anhydride (1:1, 10 mL). The reaction mixture was heated under reflux and stirred for 1.5 h (monitoring by TLC analysis with dichloromethane/methanol (10:1) as the mobile phase). The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography with dichloromethane/methanol as the eluent (10:1 for **2a–c** and **2f**; 8:1 for **2d** and **2e**) or/and by recrystallization from ethanol. The resulting isoalloxazine derivative was dried in vacuo.

10-Phenylisoalloxazine (2a): Following the general procedure, aminouracil **5a** (0.68 g, 3.35 mmol) and nitrosobenzene (1.00 g, 10.4 mmol) were heated to reflux to yield 10-phenylisoalloxazine (**2a**) as a green-yellow powder (0.32 g, 33%). M.p. 215°C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25°C, TMS): δ = 6.75 (dd, J(H,H) = 8.5, 0.8 Hz, 1H; Ar-*H*), 7.44 (dd, J-(H,H) = 5.2, 3.2 Hz, 2H; Ar-*H*), 7.85–7.54 (m, 5H; Ar-*H*), 8.19 (dd, J-(H,H) = 8.1, 1.3 Hz, 1H; Ar-*H*), 11.43 ppm (s, 1H; N*H*); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25°C, TMS): δ = 116.71, 125.93, 127.78, 129.75, 130.26, 131.33, 134.00, 134.69, 136.05, 139.46, 151.68, 155.46, 159.47 ppm; UV/Vis (CH$_3$CN): λ_{max} (ε) = 335 (6200), 436 nm (8900 mol^{-1} dm^3 cm^{-1}); MS (ESI): m/z (%): 291 (100) [M+H]$^+$; 581 (32) [2M+H]$^+$; HRMS (ESI): m/z calcd for $C_{16}H_{10}N_4O_2$ [M+H]$^+$: 291.08765; found: 291.08764; elemental analysis calcd (%) for $C_{16}H_{10}N_4O_2$: C 66.20, H 3.47, N 19.30; found: C 66.24, H 3.15, N 18.86.

10-(2′,6′-Dimethylphenyl)isoalloxazine (2b): Following the general procedure, aminouracil **5b** (360 mg, 1.56 mmol) and nitrosobenzene (500 mg, 4.67 mmol) were heated to reflux to yield 10-(2′,6′-dimethylphenyl)isoalloxazine (**2b**). The pure product was obtained after recrystallization from ethanol as an orange powder (115 mg, 23%). M.p. 350°C (decomp); ^{1}H NMR (400 MHz, CDCl$_3$, 25°C, TMS): δ = 1.93 (s, 6H; CH$_3$), 6.80 (dd, J(H,H) = 8.5, 1.0 Hz, 1H; Ar-*H*), 7.29 (d, J(H,H) = 7.7 Hz, 2H; Ar-*H*), 7.40 (dd, J(H,H) = 8.1, 7.1 Hz, 1H; Ar-*H*), 7.67–7.57 (m, 1H; Ar-*H*), 7.71 (ddd, J(H,H) = 8.6, 7.2, 1.6 Hz, 1H; Ar-*H*), 8.38 (dd, J(H,H) = 8.1, 1.5 Hz, 1H; Ar-*H*), 8.83 ppm (s, 1H; N*H*); ^{13}C NMR (100 MHz, CDCl$_3$, 25°C, TMS): δ = 17.81, 116.19, 127.26, 129.79, 130.57, 133.09, 133.58, 134.38, 135.98, 136.47, 138.64, 150.46, 155.15, 159.18 ppm; UV/Vis (CH$_3$CN): λ_{max} (ε) = 330 (7000), 437 nm (10000 mol^{-1} dm^3 cm^{-1}); MS (ESI): m/z (%): 319 (100) [M+H]$^+$; 637 (82) [2M+H]$^+$; HRMS (ESI): m/z calcd for $C_{18}H_{14}N_4O_2$ [M+Na]$^+$: 341.10090; found: 341.10087; elemental analysis calcd (%) for $C_{18}H_{14}N_4O_2$: C 67.91, H 4.43, N 17.60; found: C 67.91, H 4.29, N 17.72.

10-(2′,6′-Diethylphenyl)isoalloxazine (2c): Following the general procedure, aminouracil **5c** (405 mg, 1.56 mmol) and nitrosobenzene (500 mg, 4.67 mmol) were heated to reflux to yield 10-(2′,6′-diethylphenyl)isoalloxazine (**2c**). The pure product was obtained after recrystallization from ethanol as an orange powder (110 mg, 20%). M.p. 350°C (decomp); ^{1}H NMR (400 MHz, CDCl$_3$, 25°C, TMS): δ = 1.06 (t, J(H,H) = 7.6 Hz, 6H; CH$_3$), 2.07 (dq, J(H,H) = 15.1, 7.5 Hz, 2H; CH$_2$), 2.24 (dq, J(H,H) = 15.2, 7.6 Hz, 2H; CH$_2$), 6.78 (dd, J(H,H) = 8.5, 1.1 Hz, 1H; Ar-*H*), 7.36 (d, J(H,H) = 7.7 Hz, 2H; Ar-*H*), 7.52 (t, J(H,H) = 7.7 Hz, 1H; Ar-*H*), 7.65–7.59 (m, 1H; Ar-*H*), 7.69 (ddd, J(H,H) = 8.6, 7.3, 1.5 Hz, 1H; Ar-*H*), 8.37 (dd, J(H,H) = 8.1, 1.5 Hz, 1H; Ar-*H*), 8.96 ppm (s, 1H; N*H*); ^{13}C NMR (100 MHz, CDCl$_3$, 25°C, TMS): δ = 13.41, 23.85, 116.76, 127.21, 127.46, 130.87, 132.55, 132.97, 133.84, 135.91, 136.17, 138.59, 139.49, 151.05, 155.14, 159.24 ppm; UV/Vis (CH$_3$CN): λ_{max} (ε) = 331 (7000), 434 nm (10100 mol^{-1} dm^3 cm^{-1}); MS (ESI): m/z (%): 347 (100) [M+H]$^+$; 693 (70) [2M+H]$^+$; HRMS (ESI): m/z calcd for $C_{20}H_{18}N_4O_2$ [M+Na]$^+$: 369.13220; found: 369.13216; elemental analysis calcd (%) for $C_{20}H_{18}N_4O_2$: C 69.35, H 5.24, N 16.17; found: C 69.20, H 5.20, N 16.55.

10-(2′,6′-Diisopropylphenyl)isoalloxazine (2d): Following the general procedure, aminouracil **5d** (200 mg, 0.70 mmol) and nitrosobenzene (224 mg, 2.09 mmol) were reacted to yield 10-(2′,6′-diisopropylphenyl)isoalloxazine (**2d**). The pure product was obtained after recrystallization from ethanol as an orange powder (50 mg, 19%). M.p. 350°C (decomp); ^{1}H NMR (400 MHz, CDCl$_3$, 25°C, TMS): δ = 0.97 (d, J(H,H) = 6.8 Hz, 6H; CH$_3$), 1.15 (d, J(H,H) = 6.8 Hz, 6H; CH$_3$), 2.16 (m, 2H; CH), 6.82 (dd, J-(H,H) = 8.5, 1.0 Hz, 1H; Ar-*H*), 7.40 (d, J(H,H) = 7.8 Hz, 2H; Ar-*H*), 7.75–7.50 (m, 3H; Ar-*H*), 8.37 (dd, J(H,H) = 8.1, 1.3 Hz, 1H; Ar-*H*), 8.79 ppm (s, 1H; N*H*); ^{13}C NMR (100 MHz, CDCl$_3$, 25°C, TMS): δ = 23.84, 24.09, 29.18, 117.20, 125.54, 127.22, 130.65, 131.34, 132.97, 134.44, 135.87, 138.47, 144.52 ppm; UV/Vis (CH$_3$CN): λ_{max} (ε) = 330 (6200), 436 nm (8900 mol^{-1} dm^3 cm^{-1}); MS (ESI): m/z (%): 375 (100) [M+H]$^+$; 749 (24) [2M+H]$^+$; HRMS (ESI): m/z calcd for $C_{22}H_{22}N_4O_2$ [M+Na]$^+$: 397.16350; found: 397.16345; elemental analysis calcd (%) for $C_{22}H_{22}N_4O_2$: C 69.57, H 5.92, N 14.96; found: C 69.86, H 6.06, N 15.25.

10-(2′-*tert*-Butylphenyl)isoalloxazine (2e): Following the general procedure, aminouracil **5e** (390 mg, 1.50 mmol) and nitrosobenzene (483 mg, 4.50 mmol) were heated to reflux to yield 10-(2′-*tert*-butylphenyl)isoalloxazine (**2e**). The pure product was obtained after recrystallization from ethanol as an orange powder (65 mg, 13%). M.p. 300°C (decomp); ^{1}H NMR (400 MHz, CDCl$_3$, 25°C, TMS): δ = 1.12 (s, 9H; CH$_3$), 6.83 (dd, J(H,H) = 8.6 and 0.9 Hz, 1H; Ar-*H*), 6.91 (dd, J(H,H) = 7.9 and 1.4 Hz, 1H; Ar-*H*), 7.42 (m, 1H; Ar-*H*), 7.58–7.51 (m, 1H; Ar-*H*), 7.61 (m, 1H; Ar-*H*), 7.71 (m, 1H; Ar-*H*), 7.76 (dd, J(H,H) = 8.2 and 1.3 Hz, 1H; Ar-*H*), 8.34 (dd, J(H,H) = 8.2 and 1.3 Hz, 1H; Ar-*H*), 8.80 ppm (s, 1H; N*H*); ^{13}C NMR (100 MHz, CDCl$_3$, 25°C, TMS): δ = 31.75, 36.70, 118.24, 127.03, 128.73, 129.34, 130.76, 131.15, 132.81, 135.49, 135.62, 135.77, 138.16, 146.29, 152.66, 154.80, 159.11 ppm; UV/Vis (CH$_3$CN): λ_{max} (ε) = 332 (7000), 437 nm (9900 mol^{-1} dm^3 cm^{-1}); MS (ESI): m/z (%): 347 (100) [M+H]$^+$; 693 (60) [2M+H]$^+$; HRMS (ESI): m/z calcd for $C_{20}H_{18}N_4O_2$ [M+Na]$^+$: 369.13220; found: 369.13213; elemental analysis calcd (%) for $C_{20}H_{18}N_4O_2$: calcd C 69.35, H 5.24, N 16.17; found: C 68.93, H 5.62, N 16.42.

10-(2′,6′-Dimethylphenyl)-3-methylisoalloxazine (2f): Following the general procedure, aminouracil **5f** (100 mg, 0.41 mmol) and nitrosobenzene (200 mg, 1.87 mmol) were reacted to yield isoalloxazine **2f**. The pure product was obtained after recrystallization from ethanol as an orange powder (60 mg, 44%). M.p. 350°C (decomp); ^{1}H NMR (400 MHz, CDCl$_3$, 25°C, TMS): δ = 1.92 (s, 6H; CH$_3$), 3.52 (s, 3H; CH$_3$), 6.86–6.73 (m, 1H; Ar-*H*), 7.30 (d, J(H,H) = 7.6 Hz, 2H; Ar-*H*), 7.40 (d, J(H,H) = 7.4 Hz, 1H; Ar-*H*), 7.64–7.56 (m, 1H; Ar-*H*), 7.68 (dd, J(H,H) = 8.5 and 1.4 Hz, 1H; Ar-*H*), 8.39 ppm (dd, J(H,H) = 8.1 and 1.4 Hz, 1H; Ar-*H*); ^{13}C NMR (100 MHz, CDCl$_3$, 25°C, TMS): δ = 17.66, 28.87, 115.84, 126.79, 129.60, 130.38, 132.81, 132.85, 133.30, 134.42, 135.87, 135.94, 137.93, 148.73, 155.81, 159.70 ppm; UV/Vis (CH$_3$CN): λ_{max} (ε) = 321 (5500), 427 nm (6500 mol^{-1} dm^3 cm^{-1}); MS (ESI): m/z (%): 333 (100) [M+H]$^+$; 665 (86) [2M+H]$^+$; HRMS (ESI): m/z calcd for $C_{19}H_{16}N_4O_2$ [M+H]$^+$: 333.13460; found: 333.13457; elemental analysis calcd (%) for $C_{19}H_{16}N_4O_2$: C 69.35, H 5.24, N 16.17; found: C 69.20, H 5.20, N 16.55.

X-ray diffraction studies: Single crystals of **2a**, **2b**, **2d**, and **2f** suitable for X-ray analysis were prepared by slow evaporation of the solvent from solutions of **2a** (2.6 mg, 0.009 mmol), **2b** (1.6 mg, 0.005 mmol), **2d** (4.4 mg, 0.012 mmol), and **2f** (1.0 mg, 0.003 mmol) in ethanol (1.46, 1.00, 0.50, and 0.20 mL, respectively). A single crystal of **2c** was prepared by slow cooling of a solution of **2c** (3.2 mg, 0.009 mmol) in ethanol (0.50 mL) from 60°C to ambient temperature.

X-ray diffraction data for yellow-to-ruby crystals of flavin derivatives **2a–d** and **2f** were measured at 170 K on a four-circle CCD diffractometer Gemini of Oxford Diffraction Ltd. with graphite monochromated $Cu_{K\alpha}$ radiation (λ = 1.5418 Å). Data reduction including empirical absorption correction by using spherical harmonics were performed with CrysAlisPro[39] (Oxford Diffraction). The crystal structure was solved by the charge-flipping method using the program Superflip[40] and refined with the Jana2006 program package[41] by full-matrix least-squares technique on *F*. The non-hydrogen atoms were refined anisotropically and the hydrogen atoms were positioned geometrically and refined by using the riding model. The molecular-structure plots were prepared by using ORTEP III,[42] and the intermolecular interactions were viewed in Mercury.[43] Selected data for **2a–d** and **2f** are collected in the Supporting Information.

CCDC-887842 (**2c**), CCDC-887843 (**2a**), CCDC-887844 (**2b**), CCDC-887845 (**2d**), and CCDC-887846 (**2f**) contain the supplementary crystal-

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lographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

^{1}H-DOSY NMR: The ^{1}H-DOSY NMR spectroscopic measurements were conducted on a Bruker Avance 600 spectrometer (600.13 Hz) equipped with a triple-resonance broadband inverse (TBI) ^{31}P/^{13}C selective probe. Temperature stability was ensured by a BVT 3000 unit. The data were processed and evaluated with Bruker Topspin 2.1 with the software package t1/t2. The measurements were conducted at 300 K with solutions of $c_{flavin}=5\times10^{-3}$ mol L^{-1} in CD_3CN and CD_3CN/D_2O (1:1) and saturated solutions in D_2O ($c_{flavin}=<5\times10^{-3}$ mol L^{-1}). The aggregation numbers are based on diffusion coefficients measured by ^{1}H-DOSY NMR experiments by using a convection-compensating pulse sequence developed by Jerschow and Müller.[44] Diffusion coefficients of TMS served as a viscosity reference. By assuming a spherical shape of the molecules and considering a microfriction factor, calculation of the hydrodynamic volumes from experimental diffusion coefficients was carried out according to the reported procedure.[26,45] The comparison of this experimental determined hydrodynamic volumes with theoretical volumes calculated according to Zhao et al.[46] show that all the experimental hydrodynamic volumes for the flavins in water are smaller than the theoretically expected values with a factor of 0.7–0.8. This factor is in accordance with previous studies on experimental diffusion coefficients of aromatic systems[47,48] and shows that the flavins appear as monomers in D_2O. The aggregation numbers were calculated as the ratio between the experimentally determined hydrodynamic volumes of the flavins in the respective solvent and the experimentally determined hydrodynamic volumes of their monomers in D_2O. An experimental hydrodynamic volume of flavin **2f** in D_2O was not accessible due to its poor solubility. Therefore, this value was calculated by adding the theoretical volume of a methyl group[46] to the experimental hydrodynamic volume of flavin **2b** (see the Supporting Information for data).

Cyclic voltammetry: Cyclic-voltammetry measurements were carried out on an Autolab PGSTAT 302N setup at 20 °C in acetonitrile and acetonitrile/water (1:1) solutions containing flavin ($c=1\times10^{-3}$ mol L^{-1}) in an argon atmosphere with the use of a conventional undivided electrochemical cell, a glassy carbon working electrode, platinum wire as the counter electrode, and silver wire as the reference electrode. The redox potentials were referenced against ferrocenium/ferrocene. In all the experiments, the scan rate was 50 mV s^{-1} and tetrabutylammonium tetrafluoroborate was the supporting electrolyte ($c=0.1$ mol L^{-1}).

Fluorescence quantum yields and quenching: The relative fluorescence intensities were measured on a Varian Eclipse spectrometer ($\lambda_{ex}=427$–440 nm, according to the flavin derivative). Fluorescence quantum yields Φ_F of flavins **1** and **2a–f** were determined by a standard procedure at $c=3\times10^{-6}$ mol L^{-1} in acetonitrile and ethanol with quinidine sulfate ($c=1\times10^{-7}$ mol L^{-1}) in sulfuric acid (0.5 mol L^{-1}) as a standard.[49] Fluorescence quenching by 4-methoxybenzyl alcohol was measured in acetonitrile and ethanolic solutions containing **1** or **2a–f** ($c=3\times10^{-6}$ mol L^{-1}) and 4-methoxybenzyl alcohol ($c=0$–9×10^{-3} mol L^{-1}) at 25 °C. Stern–Volmer plots ($I_0/I=1+K_S[Q]$) were constructed, and the constant K_S was evaluated as the slope of the dependence by using Origin 6.1 software.[50]

Photooxidation reactions: The photooxidation of 4-methoxybenzyl alcohol (MBA; $c_{MBA}=4\times10^{-3}$ mol L^{-1}, $c_{flavin}=4\times10^{-4}$ mol L^{-1}) was performed in quartz cuvettes ($d=1$ cm). Deuterated acetonitrile or CD_3CN/D_2O (1:1) was used as the solvent. The mixture was purged with oxygen for 2 min before the reaction was started. The reaction mixture was stirred, tempered to 25 °C, and irradiated with a diode (LED Luxeon Star; 1 W, 220 mW, 350 mA, 2.8–4 V, 440–460 nm, $\Delta\lambda_{1/2}=20$ nm). The conversion was monitored by ^{1}H NMR spectroscopic analysis by using the ratio of integral intensities of the Ar-H signals. The quantum yields of the photooxidation reactions were measured with a simple apparatus based on the absorption of light from an LED focused with a lens in a common quartz cuvette and measured by a calibrated solar cell as described before.[18] The concentration of the 4-methoxybenzyl alcohol was $c=4\times10^{-3}$ mol L^{-1} with 10 mol % of the flavin catalyst in acetonitrile, deuterated acetonitrile, or CD_3CN/D_2O (1:1). The yield of 4-methoxybenzaldehyde was determined after 20, 30, 60, 120, 180, and 240 min by mean of GC analysis with chlorobenzene as an internal standard, and the quantum yield was determined as an average from all these measurements.

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