Chemical Photocatalysis with Flavins

New Applications

and

Catalyst Improvement

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Für meine liebe Familie
Und in Gedenken an meinen Vater
Prof. Dr. Hans Martin Kümmel († 1986)

"When you realize the value of all life,
You dwell less on what is past and
Concentrate more on the preservation of the future."
Dian Fossey

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1. Flavin photocatalysis‡

1.1. Introduction

Photocatalysis is a very common principle in nature: All plants and animals are depending on sunlight and use it by means of photoreceptors. One of the most prominent example of photoreceptor dyes is riboflavin (RF), also known as vitamin B_2, which takes part in biochemical redox reactions as coenzyme.[1] Besides their role as photoreceptor dyes[2] the photoactivity of flavins is crucial for some other natural processes, e.g. the light generation by bacterial luciferase,[3] and DNA repair by photolyase.[4]

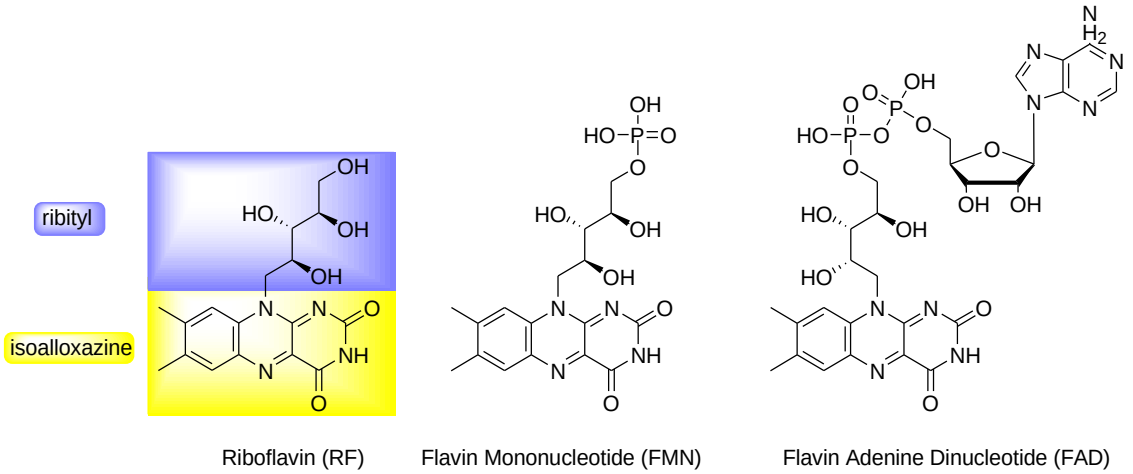
Riboflavin and its derivatives are yellow compounds and hence they can absorb visible light with a maximum absorption in the blue range. Upon excitation with blue light of 440 nm their redox power is dramatically increased by up to 2.48 eV (E_{00} of RF).[5] This value represents the maximal (theoretical) energy of light which could be utilized in photocatalysis by flavins. Flavoenzyme models have been studied extensively including investigations of redox potential changes,[1, 6] photolyase[7] and luciferase models.[8] However, the use of flavins in chemical photocatalysis was still less investigated. In this chapter we will give an overview how these photophysical redox properties can be used in synthetic applications with flavins as photocatalysts. Due to the large amount of available literature, particularly from biochemical studies, the overview cannot be comprehensive. We principally discuss typical examples, including some light-independent redox reaction, to illustrate the potential of flavin photocatalysis.

Riboflavin was first described in 1879 as bright yellow pigment isolated from cow milk and named lactochrome[9] and found afterwards several times from different sources.[1] In 1934 *Kuhn et al.* developed the first synthesis and confirmed the molecular structure (see Scheme 1.1).[10]

The name riboflavin was given due to the ribityl side chain (blue in Scheme 1.1) and the bright yellow color (lat.: *flavus* - yellow) which is caused by the isoalloxazine unit (yellow in Scheme 1.1). In nature it is mainly found as flavin adenine dinucleotide (FAD) or flavin adenine mononucleotide (FMN, riboflavin-5'-phosphate, see Scheme 1.1) and today hundreds of flavoprotein enzymes containing predominantly non-covalently bound FAD or FMN are known.[1]

‡ This chapter was written by S.K. (R.C. contributed section 1.4 and 1.5.) as a contribution of our group to a summary of chemical photocatalysis in the framework of the DFG Graduate School "Chemical Photocatalysis" 1626 and will be published in a book in 2013.

S. Kümmel, R. Cibulka, B. König, In: Chemical Photocatalysis: Flavin Photocatalysis (Editor: B. König), de Gruyter, Berlin 2013.



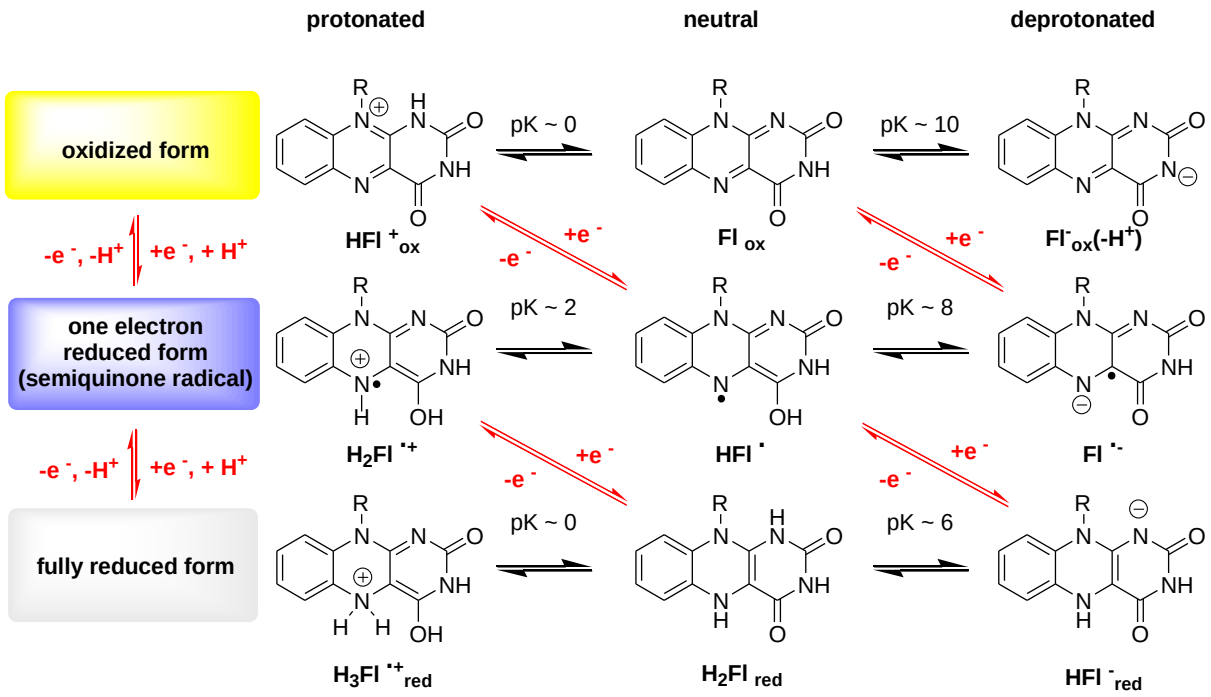
Scheme 1.1: The most important flavins in nature: Riboflavin (RF, also known as vitamin B_2, lactochrome, lactoflavin or ovoflavin), flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD).

Speaking of flavoproteins the most important domains are the LOV (light, oxygen and voltage) and the BLUF (blue-light using FAD) domains. LOV1 and LOV2 are found in the family of phototropins which undergo autophosphorylation upon blue light irradiation.[11] The BLUF domain was first discovered in a bacterium called *Rhodobacter sphaeroides* and was shown to control photosynthesis gene expression depending on blue light and oxygen.[12]

Originally, the term flavin was used for 7,8-dimethyl-10-alkylisoalloxazines; later, all isoalloxazine derivatives have been called flavins. In this chapter we use the term for all 10-substituted isoalloxazines in general.

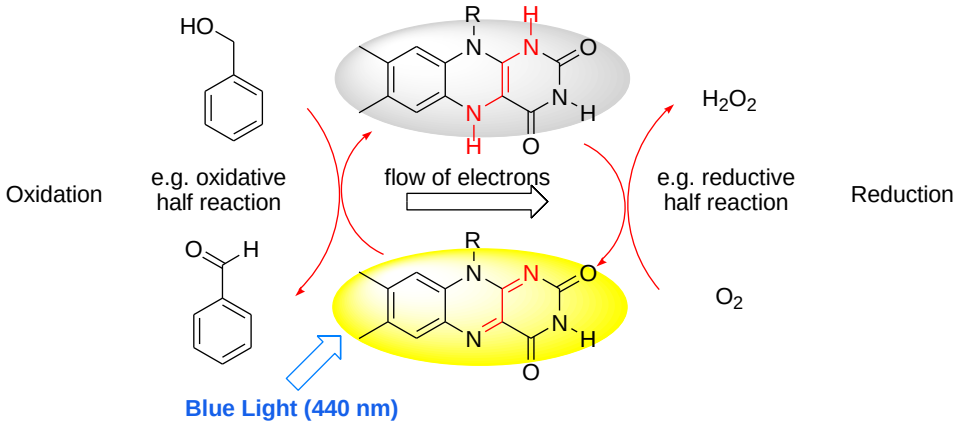
1.2. General Properties

Flavins can exist in three redox states: Oxidized, one-electron reduced (as semiquinone) or twofold reduced by two electrons, and each of these redox states has three different protonation states (see Scheme 1.2). The redox properties of flavins, their absorption and the reactivity change with substitution, non-covalent interactions, such as hydrogen bonds, and the nature of the surrounding protein.[13] It is well known from electrochemical studies that in water and in protic organic solvents flavins are reduced reversibly by a two-electron process; the reduction potential of riboflavin (RF) is about -0.507 V (*vs.* ferrocene/ferrocenium (Fc/Fc^+)) in water.[14] In aprotic media, two consecutive one-electron reductions are observed. The reduction potentials of riboflavin tetraacetate (RFTA), -1.18 V and -1.87 V (*vs.* Fc/Fc^+) measured in acetonitrile, can be given as an example.[15]



Scheme 1.2: Different redox and protonation states of flavins (10-substituted isoalloxazines).[16]

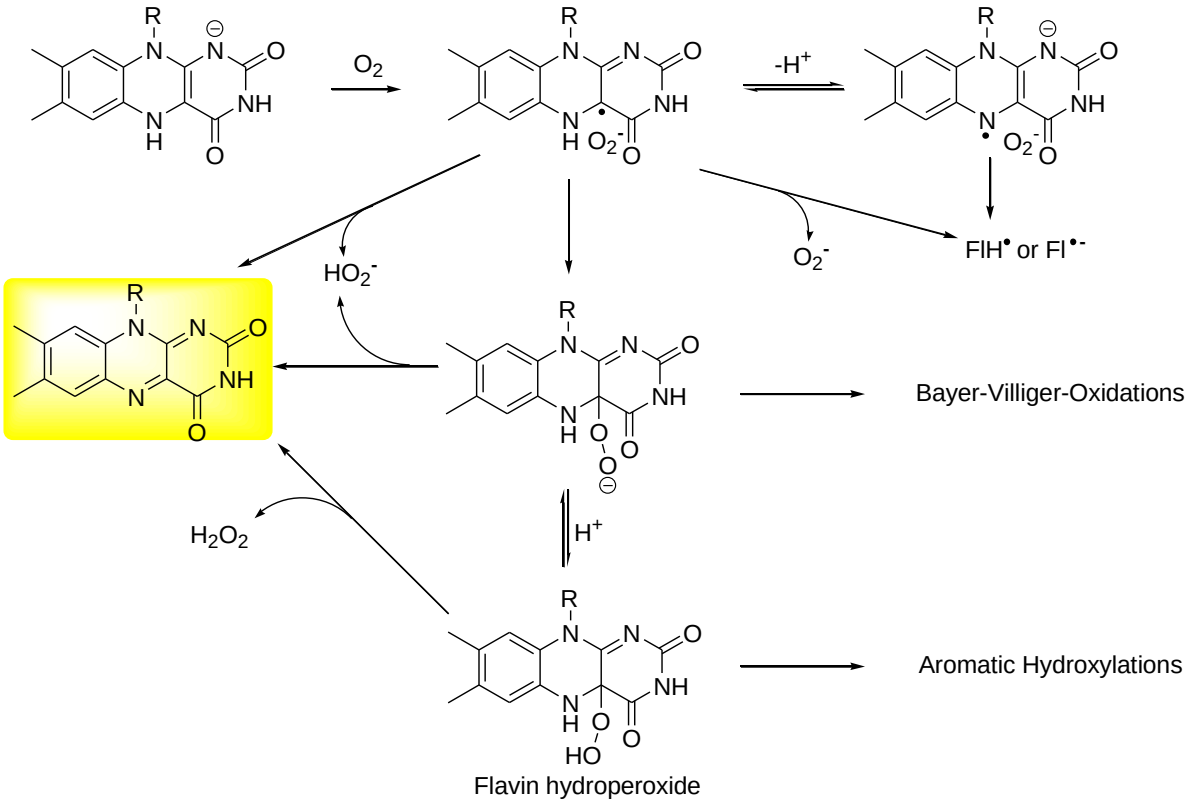
The photocatalytic cycle in flavin photocatalysis starts with irradiation of the oxidized form of flavin (Fl_{ox}) with blue light exciting it into the singlet state ($^1Fl^*$). Then intersystem crossing (ISC) to the triplet state ($^3Fl^*$) occurs rapidly in a few nanoseconds (13.5 ns for RF,[17] 23.8 ns for RFTA[18]). The triplet state is the active species and key intermediate in catalysis.[19] It can then be reduced by an appropriate substrate to the radical anion ($Fl^{\bullet -}$) which is subsequently protonated (pK_a value of 8.3)[20] and further reduced to the flavohydroquinone anion (HFl^-_{red}). The different redox states are easily distinguished by UV/Vis spectroscopy.[13]



Scheme 1.3: Catalytic cycle of flavin redox reactions: In the example of benzyl alcohol oxidation, air is used for the dark reoxidation of the catalyst.

In principle the flavin redox cycle can be used for reductions as well as for oxidations (see Scheme 1.3). For the reduction of substrates (right side) a sacrificial electron donor (e.g. typically triethylamine, EDTA or triethanol amine)[21] is needed while for oxidations, oxygen from the air is sufficient to reoxidize the flavin.[16]

The mechanism of the reoxidation by oxygen in catalytic oxidations was thoroughly investigated by Bruice *et al*. in 1979.[22] By this reaction the flavin cofactor in flavoenzymes is reoxidized and used either in an oxidative half-reaction or to generate flavin hydroperoxide, which oxygenates various substrates in flavin-dependent monooxygenases. Massey summarized the "Chemical and Biological Versatility of Riboflavin" in 2000 and described the possible reactions of the reduced flavin with oxygen (see Scheme 1.4).[23] The process converts the reduced form of the flavin back to the oxidized form and activates oxygen for subsequent reactions.



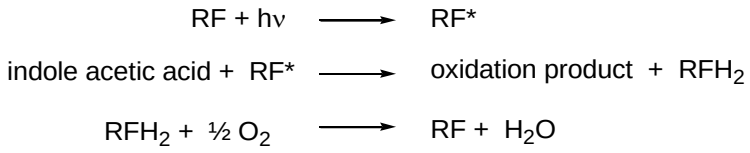
Scheme 1.4: Reactions of reduced flavins with oxygen, the terminal oxidant in catalytic photooxidations.[23]

The oxidized form of the flavin (yellow, on the right in Scheme 1.4) is used in oxidation reactions when irradiated with blue light. The redox energy of the excited state can be estimated by the Rehm-Weller equation,[24] which shows that the potential is sufficient to activate substrates with low chemical reactivity, i.e. substrates with an oxidation potential below 1.9 V (vs. Fc/Fc^+).[25] In the next section we will discuss examples along the history of flavin chemistry.

1.3. Early Examples of Flavin Photocatalysis

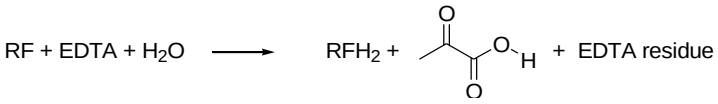
The first mechanistic investigations of the biochemical function of flavins as a coenzyme in dehydrogenases were reported in the 1930s by several groups.[26] In 1939 Lipmann discussed the use of flavins in biochemistry as autoxidizable compounds for the catalysis of pyruvic acid oxidation *via* thiamine (vitamin B_1) oxidation.[27] This certainly inspired its use as catalyst in chemical reactions.

The use of riboflavin as a photosensitizer in chemical applications was first mentioned in literature in 1948 for the oxidation of ascorbic acid by light[25] and the riboflavin-sensitized photooxidation of indole-acetic acid investigated by Galston in 1949 (see Scheme 1.5).[28] In these early days of flavin catalysis the side product of flavin reoxidation was thought to be water, instead of hydrogen peroxide.



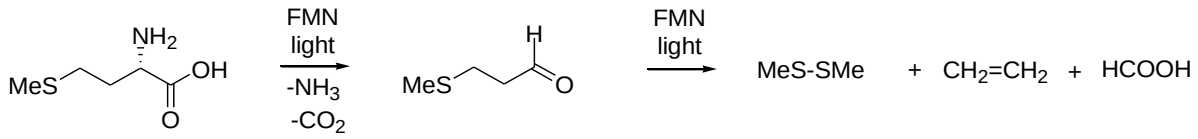
Scheme 1.5: One of the first reported chemical reactions with flavins: The oxidation of indole-acetic acid by riboflavin (RF).[28]

Flavin-catalyzed photoreactions and their mechanisms have been intensively studied since then; most of the reports describe reactions with amino acids and amines.[29] Frisell *et al*. reported the oxidation of primary, secondary and tertiary amines and amino acids. The best results were obtained for tertiary amines such as EDTA, trimethylamine, dimethylglycine, but also with sarcosine and *N*-ethylglycine. Riboflavin was reported to be a better photocatalyst than FMN and FAD.[29a] Enns and Burgess described a stoichiometric reaction of riboflavin with methionine or EDTA under anaerobic conditions (see Scheme 1.6) and could recover the riboflavin completely after oxidation with air.[29b] The first step of the mechanism of oxidation by flavins was discussed by several authors to be either hydride transfer[30] or one-electron radical mechanism.[29d, e, 31]



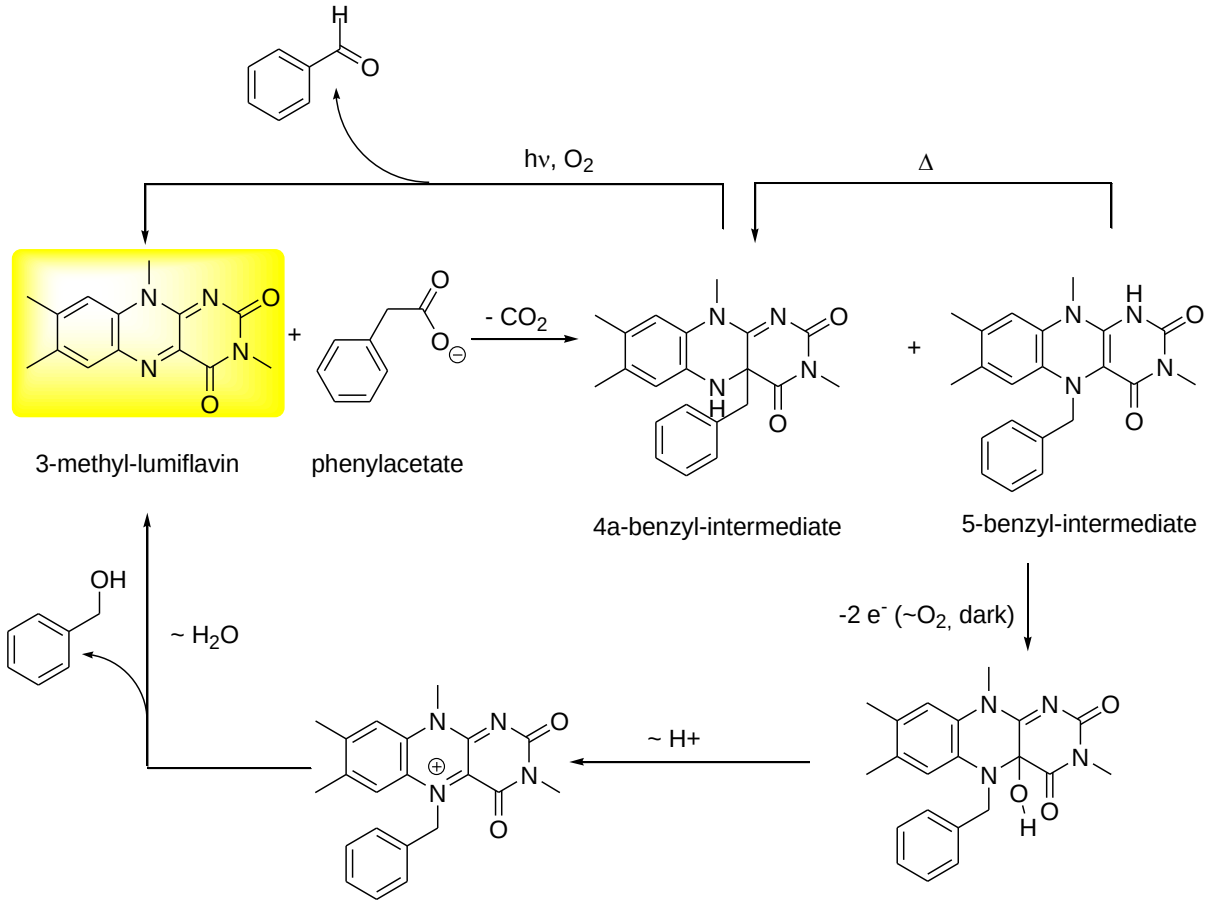
Scheme 1.6: Stoichiometric reaction of EDTA and RF under anaerobic conditions.[29b]

Later, methionine was reported to be oxidized to carbon dioxide, formic acid, ethylene, methyl disulfide and ammonia in the presence of FMN and light in aqueous solution under anaerobic conditions. Methional was suggested as the first intermediate of this transformation (Scheme 1.7).[32]



Scheme 1.7: Stoichiometric photooxidation of methionine with flavin under anaerobic conditions.

In 1967 the debate about different mechanisms for different substrates was initiated by the results of Hemmerich, Massey *et al*. regarding the photo-induced decarboxylation of phenylacetate.[33]



Scheme 1.8: Mechanistic investigations on flavin catalyzed oxidations. The phenylacetate is oxidized followed by decarboxylation and subsequently added to the flavin core. This is possible in two positions, 5 and 4a. The 4a-benzyl intermediate is thermally stable, but photolabile. It leads to an oxidized product (benzaldehyde in this case) while the 5-benzyl intermediate leads to benzyl alcohol formation *via* the purple oxidized 5-benzylflavinium cation.[33-34]

They described the mechanism of the photodecarboxylation of phenylacetate, which results as a first step in a quantitative photoalkylation of the flavin (see Scheme 1.8). The structure shows the properties of leucoflavin derivatives. Depending on the conditions, the benzyl residue can either add to position 5 (nitrogen atom) or the bridge position 4a (carbon atom). Upon heating the benzyl residue migrates from N(5) to C(4a).

The flavinium salt (substituted in 5-position) is able to transfer the benzyl group to the solvent, i.e. water, to yield benzyl alcohol and the flavin starting material. The 4a-isomer decomposes under air atmosphere and irradiation to give benzaldehyde and the flavin starting material. It is not oxidized in the dark or in the absence of oxygen.[33b]

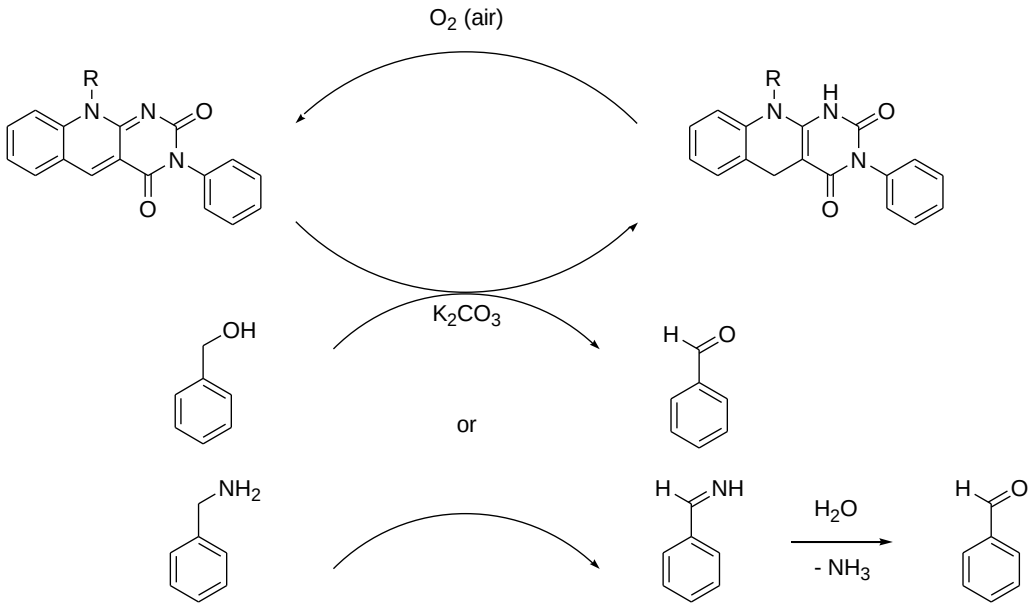
Hemmerich *et al*. compared the mechanism of oxidative photodecarboxylation of phenylacetic acids (i.e. group transfer) with the mechanism of "hydride"-transfer analyzing the spectra during the reaction.[34] They hypothesized that the latter mechanism might be also just a rapid sequence of group transfers. They found that for low pH values (< 7), high temperature (> 40 °C), with isoflavins (6-substituted flavins)[35] or with sterically demanding substrates the formation of 4a-benzyl-dihydroflavins is favored while at low temperature (< 40 °C) and pH > 7 the *N*5-substituted dihydroflavin is found, correspondingly. Then a dark rearrangement of the *N*-substituted intermediate occurs, promoted by heat or acid leading to an equimolar mixture of both types of substitution. In the absence of light no reoxidized flavin can be found even in the presence of air. When irradiated again, the 4a-substituted reduced flavin is oxidized rapidly by air, while the 5-substituted derivative yields another product *via* a pathway involving a dark green radical as intermediate. This product can be hydrolyzed (under acidic conditions) to the oxidized flavin.[34]

Several other studies investigated the flavin reduction by carboxylic acids.[29e, 36] Penzer and Radda studied the photoreduction of flavins by amines and amino acids using the example of EDTA and DL-phenylglycine.[29e] They confirmed the better reactivity of FMN compared to FAD (reported by Frisell *et al*.)[29a] and found that the reaction with phenylglycine produces equimolar amounts of benzaldehyde, carbon dioxide and reduced flavin, but they observed differences in comparison with the reaction of phenylacetic acid. They proposed "that the first step is a one-electron process between the amino acid and the excited flavin. This is probably not the case for the reaction between excited flavins and phenylacetic acid"[29e] The flavin was not fully recovered after this decarboxylation reaction by air which might be due to the different mechanism (like Hemmerich *et al*,[33, 37] see Scheme 1.8). Carr and Weatherby reported the photooxidation of dihydrophtalates to benzoic acid or methylbenzoate.[38] They propose also a mechanism with intermediate adducts.

These first examples for a chemical use of flavins were all done with the intention to gain insight in the biochemistry of flavoenzymes and not to be applied in synthesis.

1.4. Flavin Photocatalysis in Synthesis Application

In 1980 Yoneda *et al*. used 5-deazaflavin derivatives and analogues for the oxidation of alcohols and amines in the dark.[39]



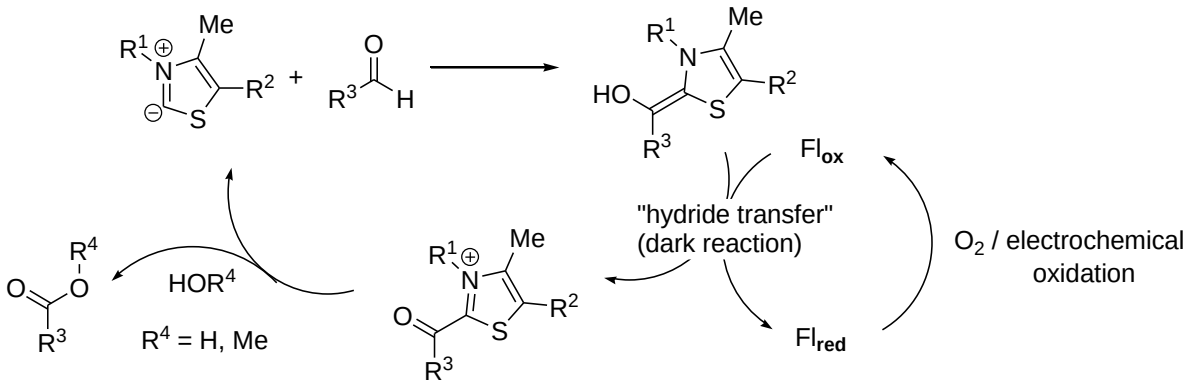
Scheme 1.9: Synthetic application: Oxidation of benzyl alcohol or benzyl amine by 5-deaza-flavins.[39a]

Later, Fukuzumi *et al*. reported the efficient and substrate-selective photocatalytic oxidation of benzyl alcohol derivatives by oxygen using 3-methyl-10-phenylisoalloxazine and 10-phenyl-5-deazaflavine coordinated to Mg^{2+} and Zn^{2+} ions and protonated riboflavin tetraacetate.[40] Ever since, the photooxidation of substituted benzyl alcohol has became the most intensively studied photocatalytic reaction mediated by flavins (Scheme 1.3).

In 1995 D'Souza *et al*. presented molecular orbital calculations on this photooxidation of substituted benzyl alcohol by riboflavin.[41] They conclude that N(1) of the flavin is preferentially protonated in the ground state and the excited states. The LUMO of the isoalloxazine is lowered by this protonation and hence the electron acceptance and therefore the oxidizing ability of the flavin are increased. The excitation results in energetically lowered corresponding SOMOs and the oxidation ability is significantly enhanced.[41] Interestingly, protonated flavin analogues were found to be efficient photocatalysts for the oxidation of benzyl alcohols with oxidation potentials around 1.9 V *vs*. SCE (4-alkyl or 4-chloro substituted benzaldehydes) while no photooxidation has been observed in the case of benzyl alcohols with strongly withdrawing (NO_2 and CN) or electron-donating (OH or OMe) substituents.[42]

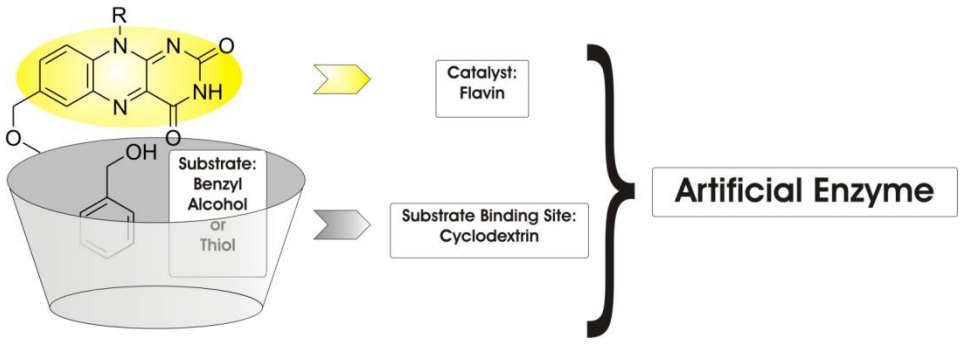
The effect of various metal ions on the oxidation power of photoexcited flavins has been studied by Fukuzumi in more detail.[43] It was shown that the effect of rare earth metal ions (Sc^{3+}, Lu^{3+} and La^{3+}) is more pronounced in comparison with the effect of magnesium or zinc ions. The metal ions interact with one or both carbonyl groups of riboflavin tetraacetate and this coordination shifts the reduction potential of the singlet excited state ($^1Fl^*$) positively by 390 mV for Mg^{2+} and even by 780 mV for Sc^{3+} which causes an increase of the chemical quantum yield of up to 0.17 for the oxidation of 4-chlorbenzyl alcohol with the Sc^{3+} complex. The photooxidation proceeds *via* electron transfer from the benzyl alcohol to the singlet excited state of the flavin-metal ion complex[40b, 43] thus differing from the mechanism dominating when a non-metal-ion-coordinated flavin is used as photocatalyst.

In 1997 Diederich *et al*. investigated a model system for pyruvate decarboxylase and reported a cooperative catalysis using a flavo-thiazolio-cyclophane as catalyst for the preparative electro-oxidation of aromatic aldehydes to methyl esters or acids (Scheme 1.10).[44]



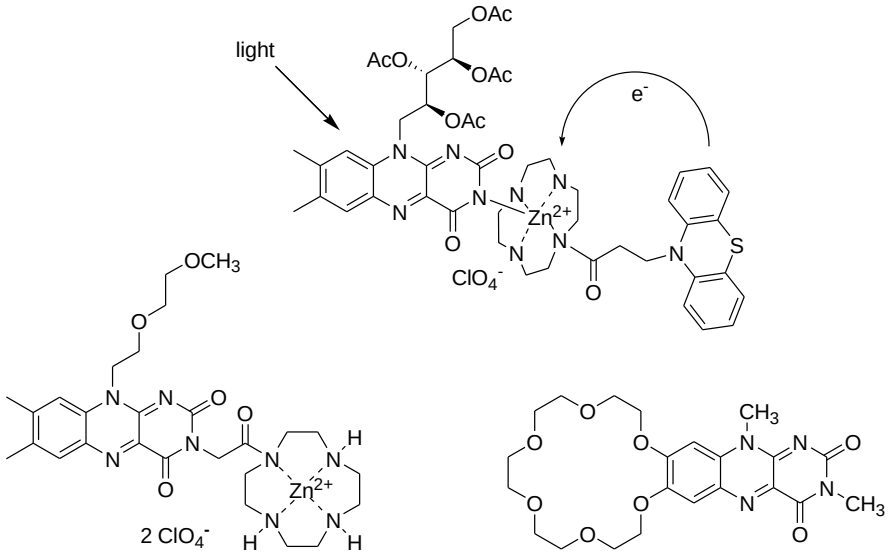
Scheme 1.10: Principle of cooperative catalysis: Oxidation of aldehydes to acids with the help of a thiazolium ylide, Diederich *et al*. synthesized a flavo-thiazolio-cyclophane as catalyst for this reaction.[44]

Many attempts have been made to mimic the biologic properties of flavoenzymes obtaining better catalyst activities in chemical applications and understanding the enzyme catalysis. In 2003 D'Souza used modified cyclodextrins with flavin moieties as artificial enzymes (Scheme 1.11). The oxidation of thiols and benzyl alcohols turned out to be much better than with free riboflavin.[45] The photooxidation of benzyl alcohols showed a turnover number (TON) of 103, demonstrating an efficient recycling of the flavin-substituted cyclodextrin. Under the same conditions with riboflavin as catalyst a TON of only 6 could be obtained.[45]



Scheme 1.11: Artificial enzyme catalyzing the oxidation of benzyl alcohols or thiols more effective than riboflavin.[45]

Another attempt to design a supramolecular sensitizer containing a photoactive flavin unit used a zinc(II)-cyclen binding site. The assembly of a riboflavin-phenothiazine dyad based on a coordinative bond allowed an efficient intramolecular electron transfer between the electron-rich phenothiazine and the excited flavin (Scheme 1.12), as well as the catalytic reductive photocleavage of thymine cyclobutane dimers.[15] The presence of the zinc(II)-cyclen unit covalently bound to the flavin increases also the efficiency of aerial *p*-methoxybenzyl alcohol photooxidation significantly; the quantum yield was shown to be 30 times higher if the flavin-zinc(II)-complex (Scheme 1.12) was used instead of the simple flavin sensitizer. The complex is water soluble and allows the photooxidation in an aqueous medium reaching a quantum yield of $\Phi = 0.4$.[46]



Scheme 1.12: Supramolecular flavin catalysts: A zinc(II)-cyclen and a crown ether were used as binding sites.

The double effect of the metal ion binding site has been shown in the light mediated oxidative decarboxylation of mandelate salts by flavin possessing a crown ether moiety (Scheme 1.12). It was found that potassium mandelate having a cation with strong affinity to the 18-crown-6-ether host is

oxidized 110 times faster and with substantially higher quantum yield in comparison to the corresponding ammonium salt.[47]

The riboflavin tetraacetate photosensitized oxidation of substituted benzyl alcohols proceeds more efficiently in micelles of sodium dodecyl sulfate (SDS) than in acetonitrile solutions. The micelle-enhancing effect was attributed to the incorporation of a lipophilic flavin into an SDS micelle where the small volume of the micellar interior, the less polar medium and the negative charge of the micellar surface favors an electron transfer.[48]

In 2008 König *et al*. described the thiourea-enhanced flavin photooxidation of benzyl alcohol in acetonitrile solution. They report TONs up to 580 with their system; the presence of thiourea, either covalently bound to a flavin derivative or added stoichiometrically, led to a significant increase in the quantum yield of up to 30-fold.[49] They investigated the system further and discovered that the reaction works even better in aqueous solution where an addition of thiourea is not necessary.[50] A turnover frequency (TOF) of more than 800 h^{-1} and a TON of up to 68,800 were observed. The reaction worked also with heterogeneous photocatalysts with flavins being immobilized on solid supports, such as fluorous silica gel, reversed phase silica gel or PE pellets, see Fig. 1.1. The catalytic activity decreased by a factor of 8–20 for the immobilization on silica gel and by a factor of 50 for the catalyst entrapment in polyethylene pellets compared to the reaction in homogeneous solution.

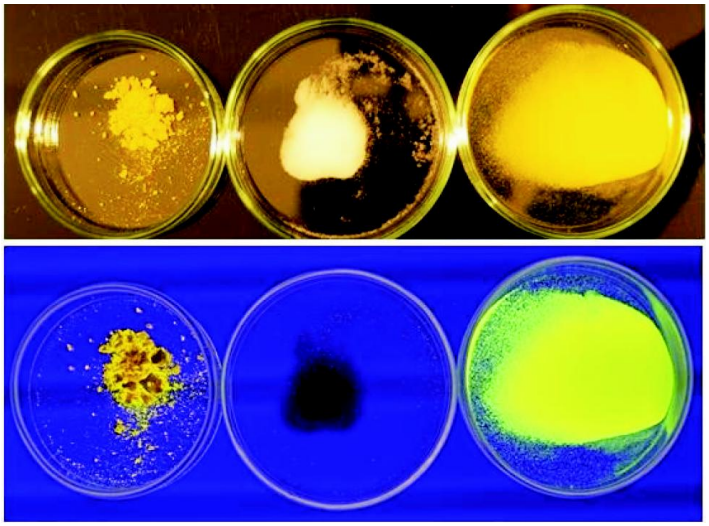
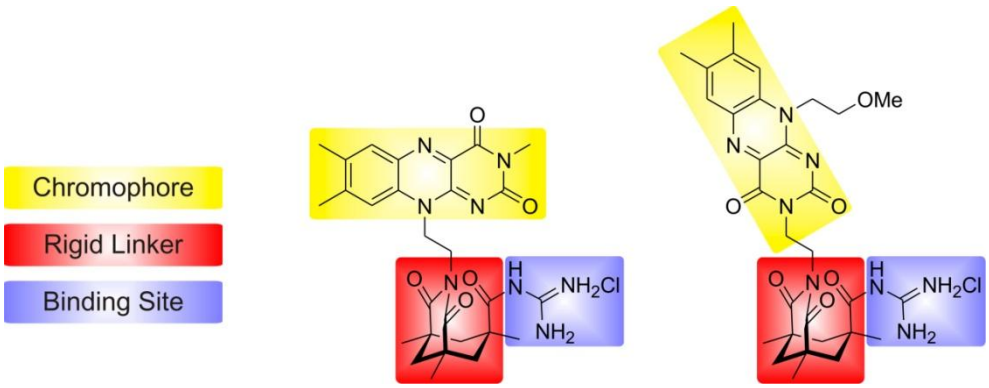


Fig. 1.1: Immobilization of flavin catalysts on silica gel: *Top*: Normal light irradiation; *bottom*: UV blue light irradiation. *Left*: solid riboflavin tetraacetate, *middle*: non-modified silica gel, *right*: immobilized catalyst.

König *et al.* prepared new flavin derivatives with an acyl guanidinium group linked to the chromophore *via* a rigid Kemp's acid spacer (Scheme 1.13).[51] This group was supposed to bind

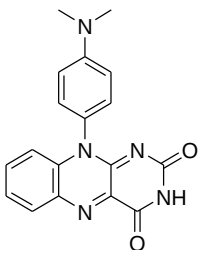
oxoanions, such as phosphates, *via* hydrogen bonds and was intended to position substrates in close proximity to the chromophore.



Scheme 1.13: Flavin photocatalysts with guanidinium binding sites and Kemp's acid as rigid linker.

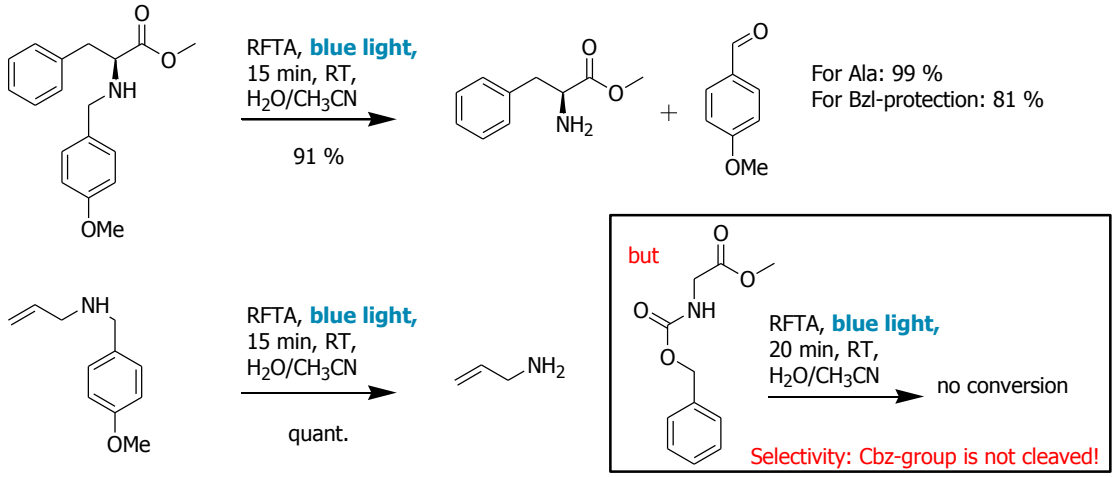
However, the expected benefit of the binding site for the photocatalytic activity was not observed as revealed by oxidative and reductive photocatalytic reactions. The performance in terms of TON and TOF decreased compared to riboflavin tetraacetate. Later, mechanistic studies of Riedle and Dick *et al.* rationalized this observation:[19] In the case of riboflavin tetraacetate the excited flavin has sufficient time in diffusion controlled reactions to reach the triplet state before colliding with a substrate molecule. It was shown, that only electron transfer from the triplet state leads to product formation. If the substrate is positioned already very close to the flavin by the substrate binding site, the electron transfer reaction occurs to the flavin singlet state, which will not give the oxidation product due to very rapid back electron transfer to the benzyl alcohol.

In 2010 Fukuzumi *et al*. reported an efficient intramolecular photo-induced electron transfer of flavin derivative DMA-Fl having an electron donor attached in 10-position (see Scheme 1.14). They observed extremely small reorganization energies for electron self-exchange between DMA-Fl/DMA-Fl$^{\bullet-}$ resulting in a very long-lived charge-separation state (2.1 ms), which can do both: oxidize electron donors (E_{ox} < 0.94 V *vs.* SCE) and reduce electron acceptors (E_{red}< -0.83 V *vs.* SCE).[52]



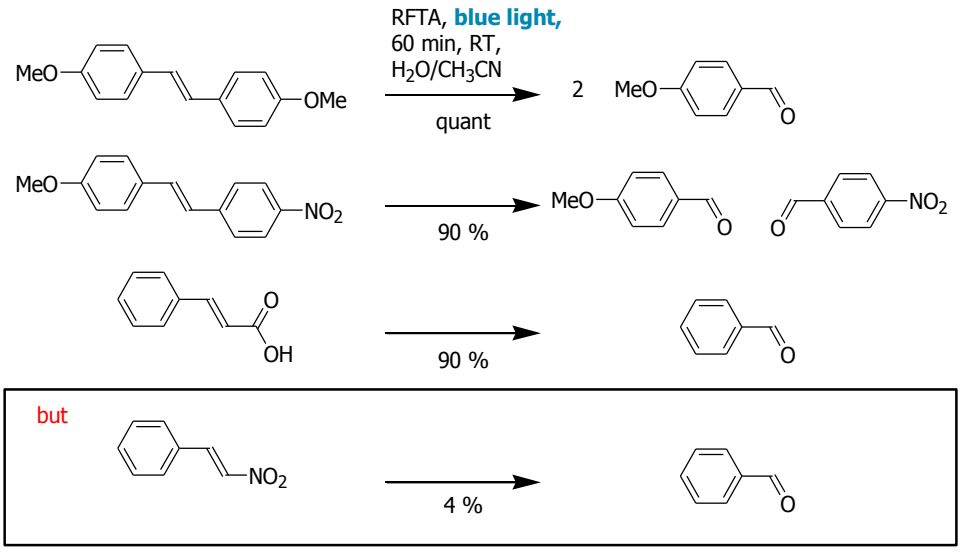
Scheme 1.14: Structure of 10-(4-dimethylamino-phenyl)-isoalloxazine - a flavin derivative that is able to do intra-molecular charge transfer upon irradiation with light generating a very long-lived charge-separation state.

In the same year several new applications of flavin photocatalysis with riboflavin tetraacetate (RFTA) were reported by König *et al*., for example the oxidation and deprotection of primary benzyl amines (see Scheme 1.15).[53]



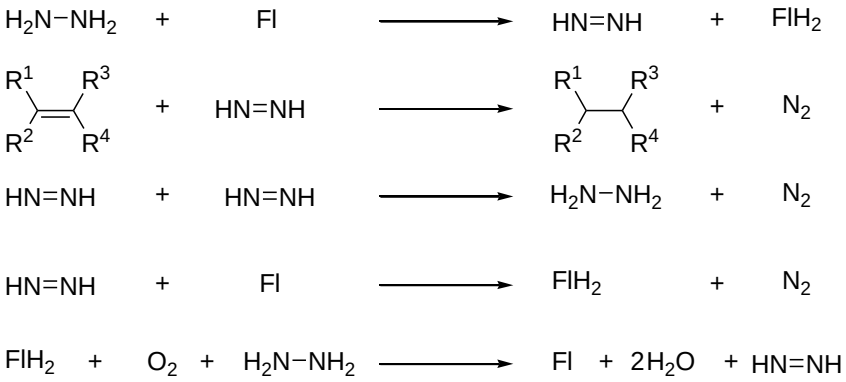
Scheme 1.15: Deprotection of benzyl protecting groups with flavin photocatalysis.

They reported the functionalization of toluene derivatives, the cleavage of styrenes and stilbenes (see Scheme 1.16) and the direct oxidation of benzyl ethers to esters or benzyl amides to the corresponding imides.[54] These studies expand the possibilities of flavin applications significantly and show that not only benzyl alcohols are suitable substrates for flavin photooxidation. The details of the mechanism and kinetics of these oxidation reactions have been investigated by Riedle, Dick, König *et al*. in 2011 by transient absorption studies in the range of sub-pico to microseconds.[19]



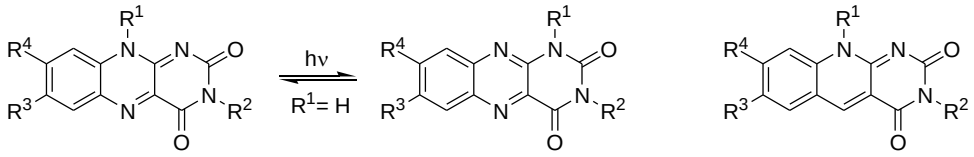
Scheme 1.16: Cleavage of styrenes and stilbenes mediated by riboflavin tetraacetate (RFTA) and blue light.

Almost all applications of flavins as catalysts and photocatalysts in synthetic applications have been focused on oxidations. In 2010 Naota, Imada *et al.* used several flavins as organocatalysts for the aerobic hydrogenation of olefins *via in situ* generation of diimide from hydrazine producing water and nitrogen gas as the only waste products (Scheme 1.17).[55] The reaction does not require irradiation.



Scheme 1.17: Indirect reductive use of flavins (Fl): Hydrogenation of olefins *via* imide generation from hydrazine. The reduced flavin (FlH_2) is re-oxidized by oxygen.

1.5. Flavin-related compounds in photocatalysis



Flavins (isoalloxazines) | Alloxazines | Deazaflavins

Riboflavin (RF):
R^1=ribityl, R^2=H, R^3=R^4=CH_3
Riboflavin tetraacetate (RFTA):
R^1=tetraacetylribityl, R^2=H, R^3=R^4=CH_3
3-Methyl riboflavin tetraacetate:
R^1=tetraacetylribityl, R^2=R^3=R^4=CH_3
Lumiflavin:
R^1=CH_3, R^2=H, R^3=R^4=CH_3

Alloxazine:
R^1=R^2=R^3=R^4=H
Lumichrome:
R^1=R^2= H, R^3=R^4=CH_3

5-Deazariboflavin:
R^1=ribityl, R^2=H, R^3=R^4=CH_3
8-Hydroxy-5-deazariboflavin:
R^1=ribityl, R^2=R^3=H, R^4=OH

Scheme 1.18: Structures and names of important flavins (isoalloxazines), alloxazines and deazaflavins. Flavins can be transformed into alloxazines *via* phototautomerization and *vice versa*.

Additionally to flavins (isoalloxazines), the structurally related alloxazines and 5-deazaflavins occur in natural systems (see Scheme 1.18). 8-Hydroxy-5-deazariboflavin acts as light harvesting cofactor in the class I photolyases.[56] Lumichrome is one of the photodegradation products of riboflavin.[57] Upon excitation of alloxazines without substitution in position N1 (R^1 = H, e.g. lumichrome), the N1-proton can be transferred to position N10 and thus the excited isoalloxazine form is created.[58]

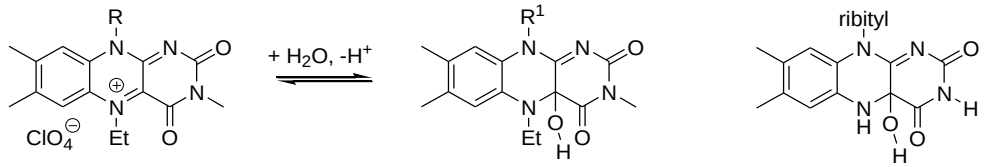
This phototautomerization can be catalyzed by proton donors or acceptors which are able to form hydrogen bonds with the alloxazine.[59]

Although the structure of alloxazines is very close to flavins, the photophysical properties of these classes of compounds differ. Particularly, fluorescence intensity and excited-state lifetimes are substantially lower for alloxazines than for flavins (see Table 1.1 for comparison). Nevertheless, there are some preliminary studies on the use of alloxazines in electron transfer processes. It was found that both singlet and triplet excited states of lumichrome are quenched with aliphatic and aromatic amines in methanol with similar rates as flavins.[60]

Table 1.1: Spectral and electrochemical characteristics of the selected flavin derivatives in acetonitrile.

Compound	λ_1 (nm)[a]	λ_2 (nm)[a]	λ_F (nm)[b]	Φ_F[c]	τ_F[d]	E^0 (V)[e]	ref
Riboflavin tetraacetate	440	343	505	0.37	6.8 ns	-1.18(-1.87)	[15]
Lumiflavin	443	342	533	0.16	7.7 ns	-0.761	[55b, 61]
5-Deazariboflavin	399	329	457	0.11	4.03 ns	-	[62]
Lumichrome	380	334	437	0.028	0.64 ns	-1.3	[60-61]
$5EtFl^+ClO_4^-$	557	414	661	-	590 ps	0.306(-0.389)[f]	[63]
5EtFlOH	348	-	496	0.003	500 fs	-	[8c]

[a] λ_1 and λ_2 are the positions of the two lowest-energy bands in the absorption spectra; [b] maximum of the fluorescence emission spectrum; [c] fluorescence quantum yield; [d] fluorescence lifetime; [e] reversible redox potentials (Fl → $Fl^{\cdot-}$ and $Fl^{\cdot-}$ → Fl^- in the brackets) measured by CV using SCE as standard electrode; [f] value for 3,10-dimethyl-5-ethyl flavinium (R = Me in Scheme 1.19).



Scheme 1.19: 5-Ethylflavinium, its water-adduct and the natural analogue 4a-hydroxyriboflavin.

5-Ethylflavinium salts ($5EtFl^+ClO^{4-}$, see Scheme 1.19) have been applied mainly in catalysis of amine and sulfide oxidations and of Baeyer-Villiger oxidations with hydrogen peroxide or oxygen proceeding in the dark.[64] Quaternization of the flavin nitrogen N5 effects spectral and electrochemical properties of the flavin moiety significantly (Table 1.1). It increases the oxidation force of the flavin as evident from reduction potentials. On the other hand, the lifetime of flavinium salts excited states is short in comparison with neutral flavins.[63a] 5-Ethylflavinium salts easily add nucleophiles at position 4a (see Scheme 1.19).[65] Water addition results in the formation of 5-ethyl-4a-hydroxyflavin (5EtFlOH) which is a suitable model compound for the investigation of the

mechanism of bacterial bioluminescence.[8b, c, 66] In bacterial luciferase, excited 4a-hydroxyriboflavin is formed during the oxidation of a long-chain aldehyde (luciferin) to carboxylic acid and it returns to the ground state with emission of blue light (λ_{max}=490 nm).[3b]

1.6. Photooxidations via singlet oxygen mechanism

Flavins and alloxazines are known to sensitize singlet oxygen production thus being able to participate on photooxidations proceeding by a singlet oxygen pathway (type II photooxidation). Singlet oxygen formation proceeds *via* energy transfer from triplet flavin to the ground state of triplet oxygen (Scheme 1.20).[67]

$$^3Fl + {}^3O_2 \longrightarrow {}^1O_2 + Fl$$

Scheme 1.20: General equation for singlet oxygen generation with flavins.

Thus, the quantum yield of singlet oxygen production may be theoretically equal to the quantum yield of triplet flavin or alloxazine (≈0.7). In Table 1.2, quantum yields of singlet oxygen generation by various flavins as well as alloxazines in different solvents are compared.

Table 1.2: Quantum yields of photosensitized production of singlet oxygen.[a]

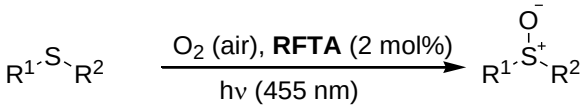
Sensitizer	Solvent	Φ_Δ (λ_{ex})[b]	τ_F (μs) [c]	Ref
riboflavin tetraacetate	acetonitrile	0.52 (355 nm)	-	[68]
riboflavin tetraacetate	ethanol	0.60 (355 nm)	-	[68]
3-methyl riboflavin tetraacetate	methanol	0.61 (355 nm)	10	[69]
riboflavin	methanol	0.51 (347 nm)	10	[70]
5-deazariboflavin	methanol	0.33 (355 nm)	10	[62]
lumiflavin	acetonitrile	0.85 (355 nm)	72	[67]
lumiflavin	methanol	0.48 (355 nm)	10	[61]
lumiflavin	water (pH 6)	0.31 (355 nm)	77	[71]
lumichrome	acetonitrile	0.73 (355 nm)	72	[67]
lumichrome	methanol	0.85 (355 nm)	10	[61]
lumichrome	water (pH 6)	0.36 (355 nm)	57	[71]

[a] for next data see also R. W. Rechmond, J. N. Gamlin, *Photochem. Photobiol.* **1999**, *70*, 391-475; [b] quantum yields of singlet oxygen production (excitation wavelength); [c] singlet oxygen lifetime.

Although singlet oxygen production by flavins is known for many decades, flavins have been utilized in type II photooxidations only rarely. This type of oxidation is rather described as side reaction pathway to the electron transfer (type I) photooxidation, namely in oxidation of ascorbic acid,[72] tryptophan,[73] indole,[74] glucose,[75] and vitamin D,[76] however, electron transfer was

described as dominant mechanism in these reactions. Flavin sensitized photooxidation of esters of unsaturated fatty acids to the corresponding hydroperoxides were studied in more detail.[77] Both types of photooxidations were found to contribute to the formation of hydroperoxides from the esters of oleic, linoleic, linolenic and arachidonic acids. While the radical pathway results in conjugated hydroperoxides, singlet oxygen oxidation leads also to hydroperoxides with non-conjugated double bonds.[77a] Singlet oxygen becomes competitive to the free radical pathway with sufficient oxygen supply.

Riboflavin tetraacetate was found as efficient sensitizer for the photooxidation of various types of sulfides to sulfoxides in alcohols (Scheme 1.21).[68] The reaction is fastest in the presence of a small amount of water with the highest rates and quantum yields in 95% ethanol (Φ up to 0.7). A dominant singlet oxygen mechanism was suggested based on significant differences of photooxidation rates in deuterated and non-deuterated solvents. It is advantageous that the reaction proceeds at low catalyst loading (2 mol%) and without side overoxidation to sulfones.



R^1=Ph, *p*-NO_2Ph, *p*-CH_3Ph, *n*-butyl
R^2=CH_3, *t*-butyl, *n*-butyl, allyl

Scheme 1.21: Oxidation of sulfides to sulfoxides: An example for the use of singlet oxygen produced by flavins.

1.7. Conclusions

Flavin photocatalysis is a versatile and green method for several oxidation reactions in organic chemistry. The photocatalysts are easy accessible and possess high redox power in the excited state. In the last years some new reactions and catalysts were reported expanding the scope and applicability of the reaction. However, there are still problems to overcome: The photostability of the catalysts must be improved. Increasing the intersystem crossing rate to the triplet state of the oxidized form of flavin after excitation is necessary to use higher substrate concentrations and substrate binding sites. The application of reduced flavins as reduction reagents in organic synthesis is largely unexplored, but very promising as their potential can be further increased to very negative values upon irradiation with UV light (360 nm).

1.8. References

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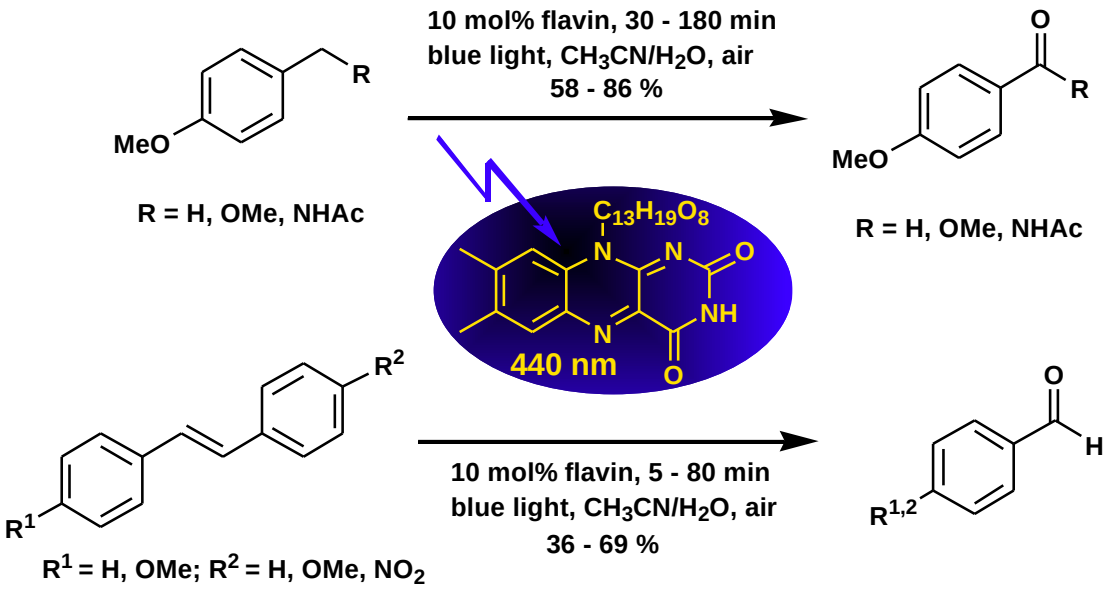
2. Visible Light Flavin Photooxidation of Methylbenzenes, Styrenes and Phenylacetic Acids‡

We report the photocatalytic oxidation of benzylic carbon atoms under mild conditions using riboflavin tetraacetate as photocatalyst and blue-emitting LEDs (440 nm) as light source. Oxygen is the terminal oxidant and hydrogen peroxide appears as the only by-product in most cases. The process oxidizes toluene derivatives, stilbenes, styrenes and phenylacetic acids to their corresponding benzaldehydes. A benzyl methyl ether and acylated benzyl amines are oxidized directly to the corresponding methyl ester or benzylimides. The mechanism of the reactions has been investigated and the results indicate that oxygen addition to benzyl radicals is a key step of the oxidation process in the case of phenylacetic acids.



Flavin-mediated blue light photo-oxidation using air as the terminal oxidant allows the selective transformation of benzylic carbon atoms.

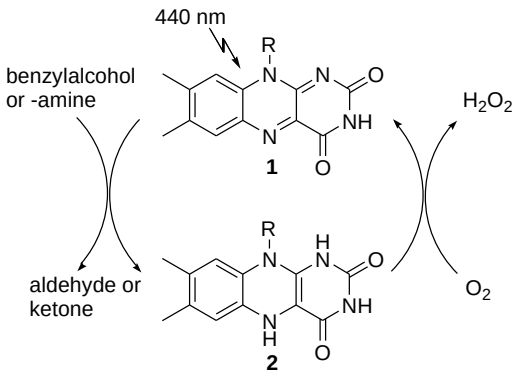
‡ The investigations presented in this chapter were carried out together with Dr. Robert Lechner and have already been published. R.L. performed the oxidations of methylbenzenes, styrenes and phenylacetic acids and did the mechanistic investigations. The oxidation of benyl ethers and amides were done by S.K..

R. Lechner, S. Kümmel, B. König, *Photochem. Photobiol. Sci.* **2010**, *9*, 1367-1377.

2.1. Introduction

Flavins have attracted much attention since they are involved in a large number of biological processes acting as redox co-factors, such as flavin adenine dinucleotide (FAD) or flavin mononucleotide (FMN)[1] and photoreceptors. Besides the application as flavoenzyme models for biochemical processes,[2] synthetic flavin derivatives have been used as organocatalysts in thermal[3] and photochemical[4] oxidation reactions. The latter processes utilize the increased oxidation power of the isoalloxazine chromophore in its oxidized form **1** upon excitation by light.[5] When an electron donor is present, the excited triplet form of **1** can undergo subsequent two electron reduction and protonation to yield dihydroflavin **2**, which is oxidized back to **1** by molecular air oxygen as the terminal oxidant. In this catalytic process hydrogen peroxide is obtained as sole stoichiometric by-product (Scheme 2.1).[4]

In previous studies we used flavin-mediated photocatalysis for the oxidation of benzyl alcohols[4b, c, 4e] and benzyl amines.[4a] The method was used for the selective photo catalytic removal of benzyl protecting groups,[4a] and is now extended to flavin-mediated photo catalytic oxidation to methylbenzenes, styrenes and phenylacetic acids. Riboflavin tetraacetate (RFTA, see Scheme 2.1)[6] is used as readily available and non-toxic photocatalyst; blue light emitting high power LEDs serve as selective and efficient light source.



Scheme 2.1: Catalytic cycle of aerobic riboflavin tetraacetate (RFTA: R = $C_{13}H_{19}O_8$) mediated photo-oxidation of benzyl alcohols or benzyl amines.

2.2. Oxidation of methylbenzenes

The aerobic photochemical oxidation of methylbenzenes under heterogeneous[7] and homogeneous[8] reaction conditions has been described. Yet the use of purely visible light is still the exception.[8b],[8c] Quenching of the excited state of flavin by methyl- and methoxybenzenes via electron transfer (ET) is known for some time,[9] but no products of the ET reactions have been

described so far. We therefore investigated the reaction as a possible C-H activation pathway to functionalize electron rich arenes at their benzyl position.

First encouraging results were obtained by subjecting *p*-methoxy toluene **3a** to standard flavin photo catalysis conditions: 0.01 mmol of substrate, 10 mol% RFTA were dissolved in 1 mL solvent and irradiated with blue light (440 nm, 3 W LED) and the course of the reaction was monitored by GC analysis. Besides *p*-methoxy benzaldehyde **3b**, the only side product that could be detected in small amounts by ^{1}H NMR was *p*-methoxy benzyl alcohol **5** as a likely intermediate of the benzyl oxidation.

Starting from this initial result, we optimized the reaction conditions by varying the solvent and oxygen content (see Table 2.1). The oxidation reaction depends heavily on the water content: nearly no conversion was obtained in pure MeCN, whereas the yield of aldehyde **4a** increased with the increasing portion of water to reach a maximum at a 1:1 mixture of H_2O:MeCN. At higher water content the yield decreased again.

Complete consumption of **3a** in H_2O:MeCN = 1:1 required the addition of another 10 mol% RFTA after 20 min of irradiation time. After 40 min of irradiation **3a** was consumed completely and aldehyde **4a** was obtained in 58% yield. Since no other side product could be detected in appreciable amounts, a parasitic side reaction, giving products that could not be detected by GC and ^{1}H NMR analysis, is proposed. From earlier studies it is known that phenolic compounds are oxidized to not detectable,[4k] presumable polymeric products under flavin mediated photo-oxidation conditions.[4a] Hence hydroxylation of the aromatic core by water and subsequent oxidation to polymeric compounds is proposed.[12]

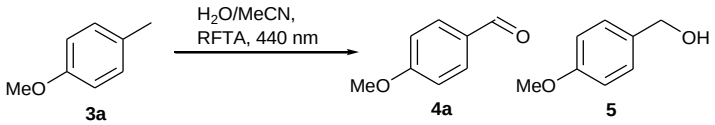
The reaction proceeded faster and RFTA did not bleach when the photo catalysis was done in an oxygen saturated system, but there was no beneficial effect on the yield of **4a**.

Without irradiation as well as when the reaction mixture was irradiated in the absence of RFTA no benzaldehyde **4a** was formed. In some oxidation reactions, *p*-methoxy benzyl alcohol **5** was detected as a side product. Since alcohol **5** is oxidized faster to aldehyde **4a** than toluene **3a**,[4b] alcohol **5** might be an intermediate in the oxidation of toluene **3a**.

To exclude a singlet oxygen oxidation pathway, which flavins can mediate under photo irradiation,[13] the photo-oxidation reaction was performed in deuterated solvents. Since the lifetime of singlet oxygen is significantly prolonged in deuterated solvents compared to the same non deuterated solvents,[14] the photo-oxidation reaction should be accelerated in deuterated solvents, if singlet oxygen formation is involved. The yield of aldehyde **4a** was lower in deuterated compared to

non-deuterated solvents at identical irradiation times, disfavouring a singlet oxygen reaction pathway and indicating the role of water as reactant.

Table 2.1: Photo catalytic oxidation of *p*-methoxy toluene 3a.



3a **4a** **5**

H_2O/MeCN (mL)	Conditions[a]	Irradiation Time (min)	Yield (%)[b]		
			Aldehyde **4a**	Alcohol **5**	Starting material **3a**
0 / 1.0		10	2	0	95
0.2 / 0.8		10	16	0	49
0.4 / 0.6		10	18	0	9
0.5 / 0.5		10	28	0	11
0.6 / 0.4		10	24	4	29
0.7 / 0.3		10	19	0	49
0.5 / 0.5		40[c]	58	0	0
0.5 / 0.5	O_2	5	29	4	33
0.5 / 0.5	O_2	10	21	0	1
0.5 / 0.5	O_2	20	51	6	0
0.5 / 0.5	no RFTA / O_2	20	0	0	65
0.5 / 0.5	in dark / O_2	20	0	0	69
0.5 / 0.5	no RFTA	20	0	0	88
0.5 / 0.5	in dark	20	0	0	90
0.5 / 0.5	D_2O/MeCN-d_3/O_2	5	10	0	11

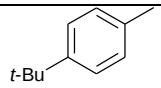
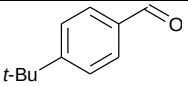
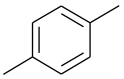
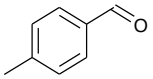
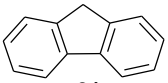
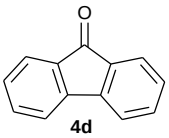
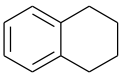
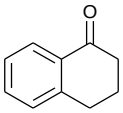
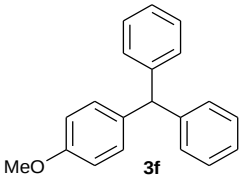
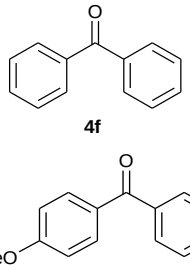
[a] O_2: oxygen saturated solution; [b] Determined by GC; [c] 20 mol% RFTA.

The change of pK_a by changing from H_2O to D_2O is not decisive since the reaction is not dependent on the pH value in a certain range. The quantum yield of the flavin-mediated photo-oxidation of *p*-methoxy toluene **3a** was determined to be 1.1% [c = 0.01 mol/L in 2 mL of H_2O/MeCN 1:1, O_2 purged].

We then applied the oxidation conditions to a variety of methylbenzenes. The results are summarized in Table 2.2. The conversion rate of methylbenzenes depends on the electronic character of the arene: benzene rings bearing electron donating substituents lead to a faster conversion, while more electron poor arenes are not active at all. This is in accordance with previous observations on flavin-mediated photooxidation of benzyl alcohols and benzyl amines.[4a, b] Toluene, benzyl bromide and ethyl benzene are not electron rich enough to be oxidized by flavin photo-oxidation. Fluorene **3d** gave fluorenone **4d** as oxidation product in 16% yield.

Tetrahydronaphthalene **3e** was oxidized to *alpha*-tetralone **4e** in 34% yield. Unreacted starting material was only partly recovered, which indicates competing polymerization processes as described above.

Table 2.2: Photo catalytic oxidation of methylbenzenes in MeCN/H_2O 1:1.

Entry	Irradiation time[a] (min)	Starting material	Product(s)	Yield (%)[b]
1	165	 **3b**	 **4b**	40[c]
2	270	 **3c**	 **4c**	43[c]
3	100	 **3d**	 **4d**	16
4	100	 **3e**	 **4e**	34
5	60	 **3f**	 **4f** **4g**	24[c,d] 35

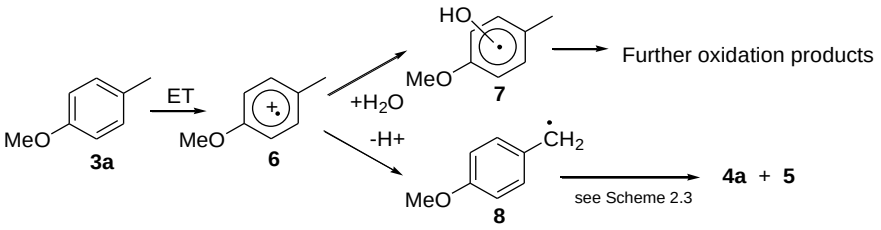
[a] The reaction mixtures were irradiated until RFTA was completely bleached; [b] Determination of yield by GC; [c] 20 mol% RFTA; [d] MeCN/H_2O 3:2.

Treating of triphenylmethane as well as triphenylmethanol with these oxidation conditions did not yield any oxidation products, whereas more electron rich *p*-methoxy triphenylmethane **3f** underwent oxidative degradation to benzophenone **4f** in 24% and *p*-methoxy benzophenone **4g** in 35% yield. This kind of oxidative degradation is known from triphenylmethane radicals derived from triphenylmethyl halides[16] or triphenylmethane.[17] It was proposed that the triphenylmethane radical cation that is formed after initial ET to excited flavin loses a proton to form a triphenylmethyl radical. This is quenched by oxygen to form a peroxy radical that collapses into benzophenone and phenol.[17]

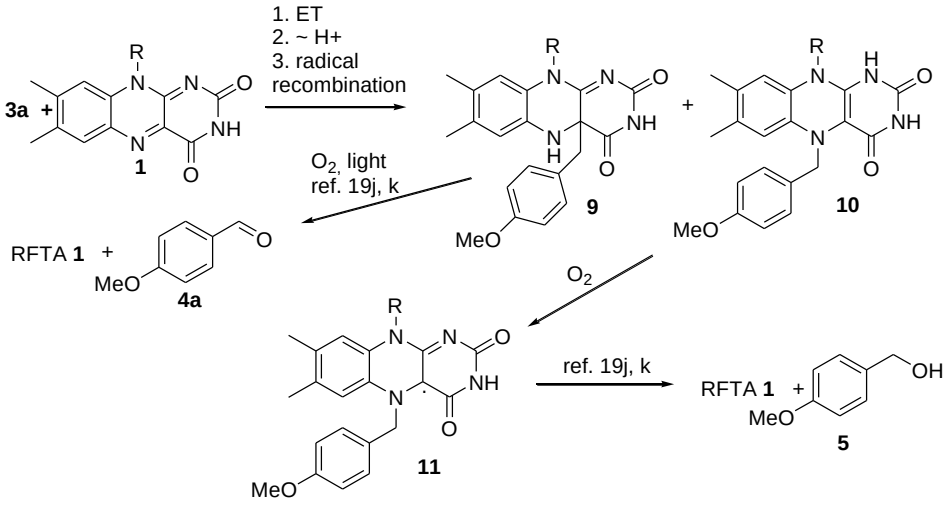
To gain more data on possible intermediates formed during the flavin-mediated photo-oxidation of **3a**, we followed the course of the UV-Vis absorption of RFTA under aerobic, oxygen saturated and anaerobic conditions (see supporting information of [18]). Strong bleaching of the RFTA **1** absorption

in the visible region with elongated irradiation times was observed. A 50% bleach of the absorption band at 446 nm is obtained after about 90s of irradiation. No recovery of the bleached signals was obtained when the system was purged with air after the irradiation. Therefore the obtained flavin species is not reduced RFTA **2**. The same course of RFTA **1** bleaching was observed when the reaction was followed in an oxygen saturated system, besides that bleaching of RFTA **1** was slowed down. The 50% bleach of RFTA **1** was retarded to roughly 150s irradiation time. The irradiation of the reaction mixture under anaerobic conditions showed a fast bleaching of RFTA **1**. When the mixture then was purged with air a blue flavin species developed, exhibiting two absorption maxima at 601 nm and 629 nm. We assign this spectrum to a neutral N5 alkyl flavin radical.[4g, 19a-c, 19e-k] This radical was stable in the dark at least for some minutes, but decayed quickly under irradiation.

Scheme 2.2 and 3 show possible pathways of flavin-mediated methylbenzene photo-oxidation by considering the presented results:



Scheme 2.2: Proposed mechanism for flavin-mediated photo-oxidation of methylbenzenes.



Scheme 2.3: Formation of covalent intermediates and decomposition to products in the photo-oxidation of methylbenzenes.

The initial step in the photo-oxidation process is an ET from methylbenzene **3a** to RFTA in the triplet excited state.[9] The so formed radical ion pair of radical cation **6** and $RFTA^{\cdot -}$ can either collapse via back ET to **3a** and RFTA **1** or follow two different productive pathways: Either the attack of water

on the radical cation **6** to give phenol **7** that is further oxidized by flavin to presumable polymeric compounds or the radical cation **6** that is a strong acid (pK_a of toluene radical cation in MeCN was estimated by Arnold[20] to be -13 and -12 by Green[21]) looses a proton to give benzyl radical **8** (Scheme 2.2). Benzyl radical **8** and $RFTA^{\cdot -}$ can recombine to form covalent intermediates.[4g, 19a-c, 19e-k] The C4a adduct **9** collapses under irradiation and oxygen present to aldehyde **4a** and RFTA.[19j, k] The N5 adduct **10** is oxidized by oxygen in a dark reaction to form the observed neutral radical **11**. The radical is undergoing an ET and subsequently fragments to RFTA **1** and benzyl alcohol **5** (Scheme 2.3).[19j, k] Whether benzyl alcohol **5** is the outcome of an intermediate benzyl cation that is trapped by water or generated via a concerted mechanism is not known.

The electron donating methoxy group on the arene in the case of *p*-methoxy toluene **3a** stabilizes the initially formed radical cation **6**.[8c, 9, 22a, 22c, d] The proposed ET pathway is further supported by the critical role of water as solvent: the triplet reduction of flavin proceeds via a dipolar intermediate. The degree of ET product formation depends on the extent of solvent interaction. With its high dielectric constant, water is stabilizing the formed separated radical cations **6** and $RFTA^{\cdot -}$.[23] Secondly, when the proton is not directly transferred from radical cation **6** to $RFTA^{\cdot -}$, water is acting as a base or proton relay, promoting the rate limiting deprotonation step of radical cation **6** to form benzyl radical **8**.[22c, d] Additional the reoxidation of flavin from its reduced state **2** to its oxidized state **1** is faster in water compared to MeCN.[24]

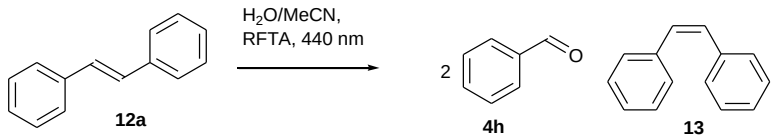
2.3. Oxidation of Phenylenes

The photo oxidative cleavage of stilbenes and styrenes has been of great interest for some time.[25] Studies towards the flavin-photosensitization of stilbene have been undertaken, but only the *trans-cis* isomerisation of stilbene has been observed.[26] An example of double bond oxidation by flavin sensitization is the oxidation of unsaturated fatty acids in MeCN that yielded hydroperoxides of fatty acids. It was proposed that the oxidation proceeds by a type II (singlet oxygen) mechanism.[27] To our delight, applying flavin photo-oxidation conditions to *trans*-stilbene **12a**, we obtained benzaldehyde **4h** in 69% yield (considering the production of 2 eq. of benzaldehyde **4h** from the oxidation of 1 eq. stilbene **12a**) within 5 min of irradiation time, leaving only 2% of starting material **12a** and 2% of *cis*-stilbene **12b** (Table 2.3).

When the oxidation was performed in pure MeCN only 5% of benzaldehyde **4h** was detected within 5 min irradiation time, but 42% of *cis*-stilbene **13** was observed. The formation of 10% *cis*-stilbene **13** already after 1 min is indicative that *trans*-stilbene **12a** is oxidized to benzaldehyde **4h**

as well. Whether *cis*-stilbene **13** is a general intermediate in the photo-oxidation process cannot be concluded from this data. No reaction was observed when the reaction mixture was irradiated without RFTA and only traces of benzaldehyde **4h** were formed when the reaction mixture was stirred in the dark. Oxygen saturation of the solution had no beneficial effect on the reaction rate of the photo-oxidation and only traces of benzaldehyde **4h** were formed when the reaction was done in deuterated solvents for 1 min. The non dependency on the oxygen content and the large effect of the solvent are indicative that water, but not oxygen is participating in the rate determining step. The quantum yield of the flavin-mediated photo oxidative cleavage of trans-stilbene 12a was determined to be 1.1% [c = 0.01 mol/L in MeCN/H2O 4:3].

Table 2.3: Photo catalytic oxidation of *trans*-stilbene



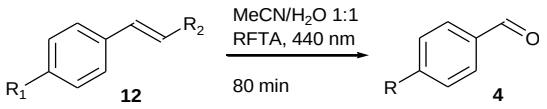
H_2O/MeCN (mL)	Conditions[a]	Irradiation time (min)	Yield (%) [b] Benzaldehyde **4h**	*cis*-stilbene **13**	*trans*-stilbene **12a**
0 / 1.0		5	5	42	38
0.4 / 0.6		5	69	2	2
0.4 / 0.6		1	19	10	72
0.4 / 0.6	no RFTA	5	0	Traces	98
0.4 / 0.6	in dark	5	Traces	5	88
0.4 / 0.6	O_2	1	13	11	70
0.4 / 0.6	D_2O/MeCN-d_3	1	Traces	28	70

[a] O_2: oxygen saturated solution; [b] Determination of yield by GC.

Next, we applied flavin-mediated photo catalytic oxidation to electron rich symmetrical stilbene **12b** and unsymmetrical stilbene **12c** (Table 2.4). As expected, the symmetrical stilbene **12b** was oxidized to *p*-methoxy benzaldehyde **4a** in 36% yield within 80 min irradiation time. The slow conversion and the low yield might be attributed to the poor solubility of **12b** and hence the low water content of the reaction mixture. The unsymmetrical stilbene **12c** was oxidized within the same time to *p*-methoxy benzaldehyde **4a** in 69% and 4-NO_2 benzaldehyde **4i** in 64% yield.

Styrene, alpha methyl styrene and *p*-methoxy styrene did not yield the desired benzaldehydes. No products or starting material could be detected with GC-MS, due to polymerization of the starting compounds under the experimental conditions. When beta nitro styrenes were subjected to the photo catalytic oxidation conditions, oxidative cleavage did not take place.

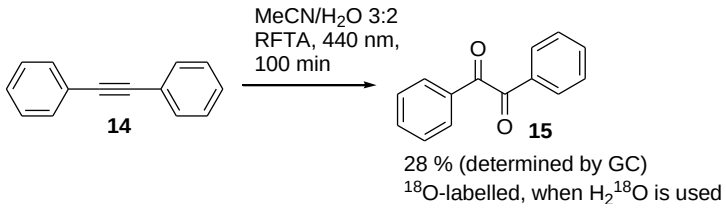
Table 2.4: Photo catalytic oxidation of phenylenes.



Entry	Starting material	Product(s)	Yield (%)[a]
1	R_1: OMe, R_2: C_6H_4-4-OMe **12b**	R: OMe **4a**	36[b]
2	R_1:NO_2, R_2: C_6H_4-4-OMe **12c**	R: OMe **4a**	69[c]
		R: NO_2 **4i**	64
3	R_1: H, R_2: COOH **12d**	R: H **4h**	68[d]

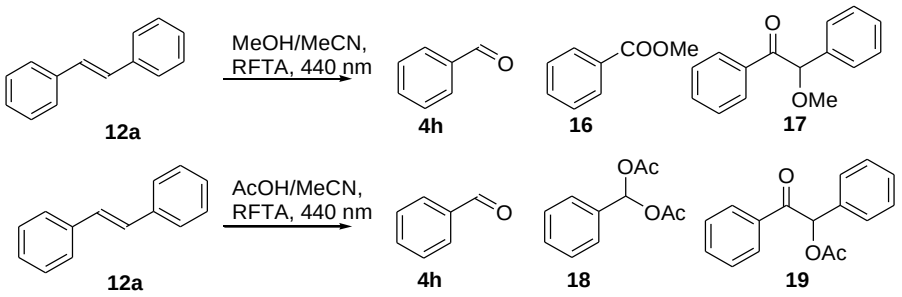
[a] Determination of yield by GC; [b] MeCN/H_2O 24:1; [c] MeCN/H_2O 5:3; [d] 20 mol% RFTA.

The photocatalytic oxidation reaction of tolane **14**[28] gave benzil **15** as sole oxidation product in 28% yield leaving 2% of starting tolane **14** (Scheme 2.4). When the oxidation of tolane **14** was done in ^{18}O labeled water (10.5% ^{18}O content), the isotope peak with m/z = 212.1 (benzil m/z = 210.1) was found in a relative abundance of a factor 5.8 higher compared to a sample obtained from non-labeled water as confirmed by EI-MS. This indicates that water is acting, at least partially, as oxygen atom source in the flavin-mediated oxidation of tolane **14** to benzil **15**.



Scheme 2.4: Photocatalytic oxidation if tolane 14.

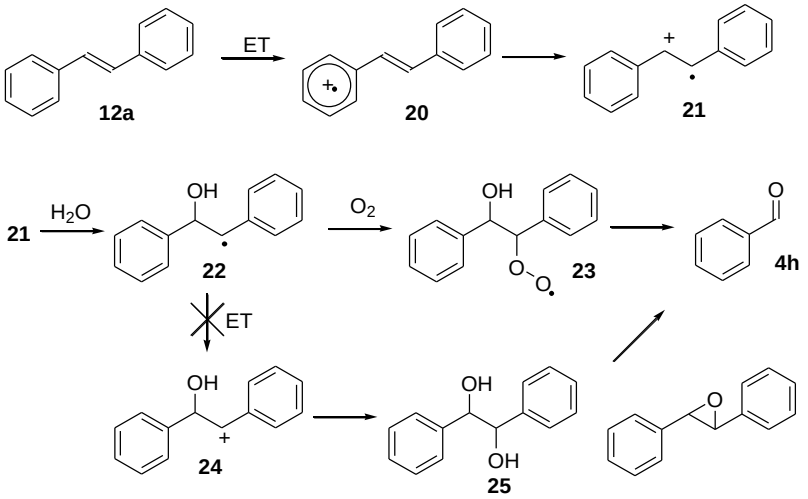
Oxidation of stilbene **12a** in a MeOH/MeCN mixture yielded benzaldehyde **4h** as main product, but benzoic acid methyl ester **16** and O-methyl benzoin **17** could be detected by GC-MS as well. A comparable reactivity was observed when the reaction was performed in an AcOH/MeCN mixture: benzaldehyde **4h** was obtained as the main product, but diester **18** and O-acetyl benzoin **19** were formed as well (Scheme 2.5). These results clearly indicate the role of the solvent acting as a nucleophile in the course of the oxidation reactions.



Scheme 2.5: Photo catalytic oxidation of stilbene 12a in organic solvents.

To gain more insight into the mechanism of the oxidative cleavage of stilbenes, *trans*-stilbene oxide, *meso*-hydrobenzoin **25** and benzoin **31** as potential intermediates, were subjected to the standard reaction conditions. All three compounds did not yield benzaldehyde **4h** as oxidation product within 1 min irradiation time, excluding the compounds as possible intermediates. In the case of *trans*-stilbene oxide no benzaldehyde **4h** was formed even after 60 min irradiation, whereas *meso*-hydrobenzoin **25** was oxidatively cleaved in 60% to benzaldehyde **4h** within the same irradiation time. Benzoin **31** did not react even after 60 min irradiation as judged by TLC. Since *meso*-hydrobenzoin **25** is not a likely intermediate in the flavin-mediated photo-oxidation of stilbene **12a**, the proposed mechanism by Fry *et al*.[29] for anodic cleavage of stilbenes is not valid for our system.

A singlet oxygen reaction pathway can be excluded, since it is known that stilbene is not oxidized by singlet oxygen.[25j, k]

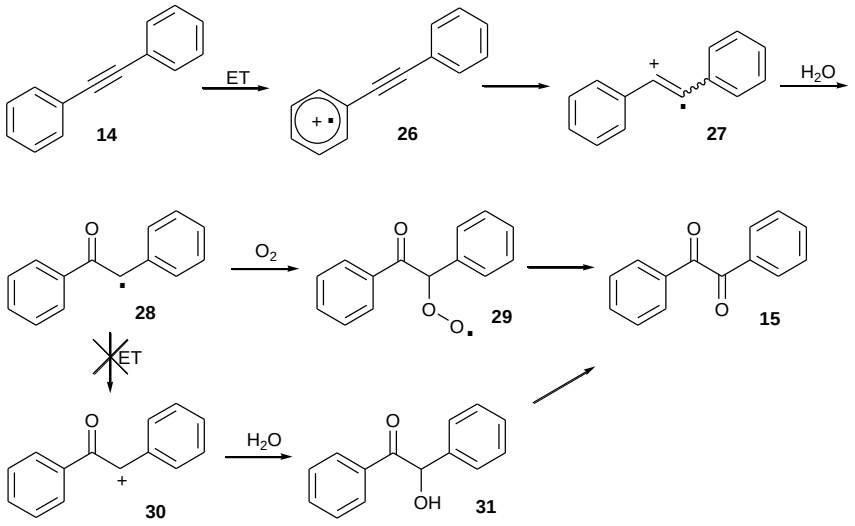


Scheme 2.6: Proposed mechanism for flavin mediated photo-oxidation of stilbene 12a.

Quenching of the radical cation **21** of stilbene radical cation **20** is not likely since oxygen hardly reacts with radical cations of aromatic olefins.[30] It has been shown that alkene radical cations behave as cations when reacting with nucleophiles,[31] which are in our case water, MeOH or acetic acid. The so formed benzyl radical **22** can now react with oxygen yielding peroxy radical **23**, which

undergoes fragmentation to benzaldehyde **4h** (Scheme 2.6). The reaction mechanism is in accordance to the proposed mechanism of Velasco *et al.* for the oxidative cleavage of stilbene in aqueous solution under aerobic conditions.[32] A second ET from benzyl radical **22** to the flavin seems not likely since the so formed carbocation **24** would give *meso*-hydrobenzoin **25** upon reaction with water or stilbene oxide which were excluded as intermediates.

For the oxidation of tolane **14** to benzil **15**, *meso*-hydrobenzoin **25** and trans-stilbene oxide were excluded as intermediates, since submitting these compounds to our oxidation conditions did not yield benzil **15**. From these results a reaction pathway in analogy to stilbene oxidation is proposed (Scheme 2.7). Here, peroxy radical ketone **29** instead of the alcohol **23** is formed, which collapses to benzil **15**.



Scheme 2.7: Proposed mechanism for flavin-mediated photo-oxidation of tolane 14.

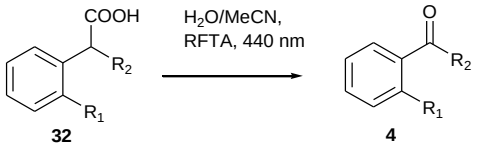
The parasitic side reaction of hydroxylation of intermediate radical cations as it was proposed for the oxidation of methylbenzenes (Scheme 2.2) seems to be true for the flavin mediated oxidation of phenylenes and tolane as well. These reaction pathways are not shown in the Schemes.

2.4. Oxidation of Phenylacetic Acids

Phenylacetic acid **32b** was photo oxidized yielding aldehyde **4h**. This decarboxylative photo-oxidation reaction of phenylacetic acids is known.[33] Anaerobic photo-decarboxylation of phenyl-acetate by excited flavin with accompanying benzylation of the flavin core[19j, k, 34] and oxidative decarboxylation of dihydrophthalates[35] has been described. Photo decarboxylation of *alpha*-hetero carboxylic acids by flavin has been reported as well.[36] We have optimized the reaction conditions of this flavin-mediated decarboxylation for synthetic preparative use.

As in the case of photo-oxidation of methylbenzenes and styrenes, the oxidation of diphenylacetic acid **32a** to benzophenone **4f** was dependent on the water content: the higher the water content, the higher the reaction rate. Oxygen saturation of the system had an inhibitory effect and the yield of benzophenone **4f** decreased (Table 2.5).

Table 2.5: Oxidation of phenylacetic acids



32 **4**

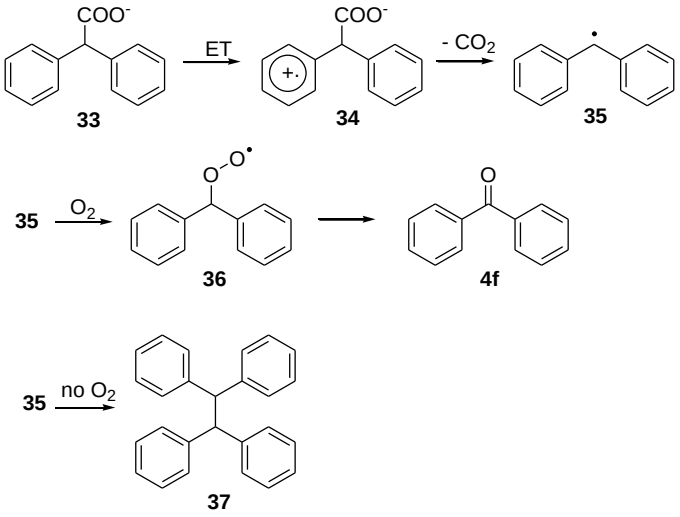
Starting material	H_2O/MeCN (mL)	Conditions[a]	Irradiation time (min)	Yield (%)[b]
R_1: H , R_2:Ph **32a**	0 / 1.0		5	2
	0.25 / 0.75		5	4
	0.5 / 0.5		5	24
	0.7 / 0.3		5	34
	0.5 / 0.5	O_2	5	11
	0.5 / 0.5	HCl	5	8
	0.5 / 0.5	NaOH	5	22
	0.5 / 0.5	open to air	5	32
	0.5 / 0.5	open to air	20	>99
	0.5 / 0.5	$H_2{}^{18}O$ (10.5%)	20	no ^{18}O labeled **4f** [c]
	0.5 / 0.5	D_2O/MeCN-d_3	5	31
R_1: H , R_2:H **32b**	0.5 / 0.5	open to air	30	45
R_1: OMe , R_2:H **32c**	0.5 / 0.5	open to air	10	43

[a] O_2: oxygen saturated solution, HCl: 0.001 N HCl instead of H_2O, NaOH: 0.001 N NaOH instead of H_2O; [b] Determination of yield by GC; [c] ^{18}O was not incorporated into benzophenone **4f**.

The reaction was accelerated when it was performed open to air in a non closed sample vial as compared to the closed system. Full conversion of diphenylacetic acid **32a** to benzophenone **4f** in an open reaction system was achieved within 20 min irradiation time. Whether the oxygen availability or the rising partial pressure of CO_2 in the head space upon expelling of CO_2 from the substrate is the limiting factor cannot be concluded from the collected data. No incorporation of ^{18}O was observed when the reaction was done in ^{18}O labeled water (10.5% ^{18}O content). Deuteration of the solvents did not have any impact on the photo-oxidation. These findings are different to the observations on the flavin-mediated oxidations of methylbenzenes, styrenes and tolane and indicate that dissolved oxygen is acting as oxygen source in the flavin-mediated photo-oxidation of diphenylacetic acid **32a**.

With the same protocol phenylacetic acid 32b was oxidized to benzaldehyde 4h in 45% yield within 30 min. The more electron rich 2-methoxy phenylacetic acid 32c was oxidized to the corresponding aldehyde 4j in 43% yield already within 10 min of irradiation.

From the obtained data, a reaction pathway for the decarboxylative oxidation of phenylacetic acid is proposed as shown in Scheme 2.8. The deprotonated diphenylacetic acid **33** undergoes an ET to excited flavin. The so formed radical cation **34** decarboxylates to give benzyl radical **35** that is trapped by oxygen present in solution yielding peroxy radical **36**, which yields benzophenone **4f** under these reaction conditions. The decarboxylation is very efficient and the yield of the reaction is nearly quantitative. No parasitic side reaction as described for the oxidation of methylbenzenes, phenylenes and tolane was observed. The occurrence of intermediate benzyl radical **35** is supported by the anaerobic photo-oxidation of diphenyl acetic acid in dry MeCN (Scheme 2.8). Tetraphenyl ethane **37** was identified as main product that most likely results from the dimerization of two diphenylmethyl radicals **35**.

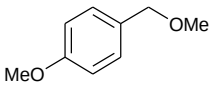
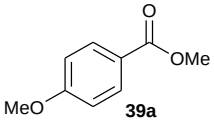
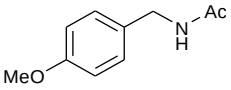
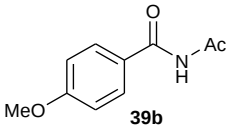
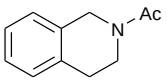
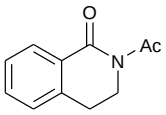


Scheme 2.8: Proposed mechanism for flavin-mediated photo-oxidation of diphenylacetic acid 33.

Benzyl ether **38a** and the acylated benzyl amines **38b** and **39** were investigated for comparison. They are photooxidized to yield the ester or imides as summarized in Table 2.6. The acylated benzylamine **38b** was converted in an acetonitrile/water mixture into imide **39b** in 83% yield, while the methyl ether **38a** and the tetrahydroisoquinoline derivative **39** showed less conversion and lower yields under these conditions. Using methanol as solvent and applying longer irradiation times the conversion of the substrates was complete and product yields increased significantly. However, the conversion and yield of **38b** decreased under these conditions. We noticed a rapid fading of flavin in

the methyl ether **38a** photooxidation in methanol and the reaction was performed adding eight times RFTA. This improves the yield of the reaction to 86%.

Table 2.6: Oxidation of *p*-methoxybenzyl methyl ether and acylated benzylamines.

Starting material	Product	Solvent	Irradiation time (min)	Conversion (%)[a]	Yield (%)[a]
 **38a**	 **39a**	CH_3CN/H_2O 1:1	30	95	55
		MeOH (abs.)	180	100	76[b]
		MeOH	3 d	100	86[c]
 **38b**	 **39b**	CH_3CN/H_2O 1:1	30	100	83
		MeOH (abs.)	180	95	69
 **38c**	 **39c**	CH_3CN/H_2O 1:1	30	49	28
		MeOH (abs.)	180	100	70

[a] Determination of conversion and yield by GCMS; [b] 6 % *p*-methoxybenzaldehyde dimethylacetal as side product; [c] 7 times 10 mol% additional RFTA, side product: 14 % *p*-methoxybenzaldehyde dimethylacetal.

2.5. Conclusions

The flavin-mediated photo-oxidation of benzylic carbon atoms in hydrocarbons, alkenes, carboxylates, ethers and amines was investigated. The potential of methylbenzenes as quenchers for excited flavins has been observed before, but the formation of aldehydes or ketones as oxidation products has not been described so far. The electron density of the arene moiety is crucial for the rate of oxidation: electron poor and very electron rich arenes are not converted to the corresponding aldehydes, whereas *p*-methoxy toluene **3a** could be oxidized in 58% to anis aldehyde **4a**.

The oxidative cleavage of stilbene **12a** and cinnamic acid 12d to benzaldehyde **4h** and the oxidation of tolane **14** to benzil **15** by flavin mediated oxidation are reported for the first time. However, the moderate yields of the photocatalytic oxidations due to competing polymerization limit their synthetic application.

The photo-oxidative decarboxylation of phenyl acetic acids by flavin has been known to produce aldehydes. Conditions to achieve quantitative product yields have been found.

Based on literature evidence and the results presented here, reaction mechanisms for the flavin photo catalyzed oxidation of methylbenzenes, stilbenes, tolane and phenyl acetic acids are proposed.

For all compound classes reported here, the initial step is ET from the substrate to the excited flavin. The experimental data do not indicate an oxidation via singlet oxygen (Type II oxidation).

Other reaction mechanism after the initial ET step than the suggested one cannot completely be excluded on the basis of our data. In addition, it is likely that different reaction pathways compete and ratios vary with changes in reaction conditions and substrate.

While some of the described conversions may already find application in organic synthesis, the majority is currently limited by narrow applicability or moderate product yields. The use of flavin photocatalysts with substrate binding sites may increase the selectivity and efficiency of some of the photooxidations.

2.6. Experimental

Quantum yields were determined with the following setup: Light from a 440 nm LED was focused in the cuvette with a lens and the power of the light was measured behind with a calibrated solar cell. A reference measurement with pure solvent provided then the determination of the amount of light that is absorbed by the probe. The chemical yield is determined via GC and the quantum yield can be calculated.

General procedure for flavin-mediated photo-oxidations:

Starting material (0.01 mmol) and RFTA (0.001 mmol) were dissolved in 1 mL solvent in a sample vial. If necessary, the vial was capped with a septa and the solution was purged with oxygen for 30 s through a canula. The capped vial was irradiated at 440 nm (3 W LED).

For GC analysis the sample was diluted with water (1 mL) and extracted with ethyl acetate (3 x 1.5 mL). The organic layer was subjected to GC measurements.

General procedure for flavin-mediated photo-oxidations in $H_2{}^{18}O$ (10.5% ^{18}O):

The sample was prepared as described above using $H_2{}^{18}O$ (10.5% ^{18}O) instead of H_2O. After irradiation, MeCN was removed under a stream of nitrogen. The residue was diluted with water (1 mL) and extracted with ethyl acetate (3 x 1.5 mL). The organic layer was dried over $MgSO_4$ and filtered. The concentrated filtrate was subjected to EI-MS measurements.

2.7. References

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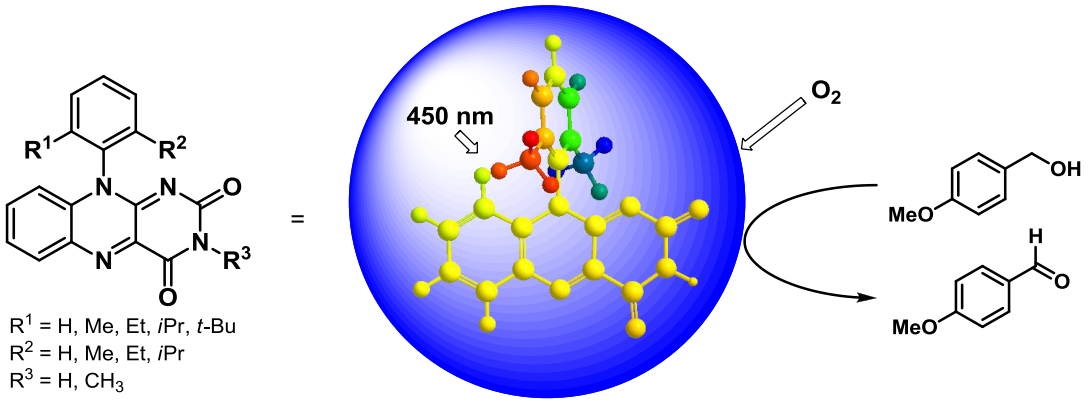
[37] Diphenylacetic acid (0.03 mmol), RFT (0.03 mmol), dry MeCN (3 mL) under N_2, irradiation with LED for 30 min (440 nm, 3 W).

3. Aggregation effects in visible light flavin photocatalysts: Synthesis, structure and catalytic activity of 10-arylflavins‡

A series of 10-arylflavins (10-phenyl- (**2a**), 10-(2',6'-dimethyl-phenyl)- (**2b**), 10-(2',6'-diethylphenyl)- (**2c**), 10-(2',6'-diisopropylphenyl)- (**2d**), 10-(2'-*tert*-butylphenyl)- (**2e**), and 10-(2',6'-dimethylphenyl)-3-methyl-isoalloxazine (**2f**)) was prepared as potentially non-aggregating flavin photocatalysts. The investigation of their structures in the crystalline phase combined with ^{1}H-DOSY NMR experiments in CD_3CN, CD_3CN-D_2O 1:1 and in D_2O confirm reduced ability of 10-arylflavins **2** to form aggregates in comparison with riboflavin tetraacetate **1**. 10-Arylflavins **2a**-**2d** do not interact by π–π interactions, which are restricted by 10-phenyl ring oriented perpendicularly to the isoalloxazine skeleton. On the other hand, N(3)-H...O hydrogen bonds have been detected in their crystal structures. In the structure of 10-aryl-3-methylflavin (**2f**) with substituted N(3) position, weak C-H···O bonds and weak π–π interactions have been found. 10-Arylflavins **2** were tested as photoredox catalysts for the aerial oxidation of *p*-methoxybenzyl alcohol to the corresponding aldehyde (model reaction) showing higher efficiency compared to riboflavin tetraacetate **1**. Quantum yields of *p*-methoxybenzyl alcohol oxidations mediated by arylflavins **2** were higher by almost one order of magnitude compared to values in the presence of **1**.



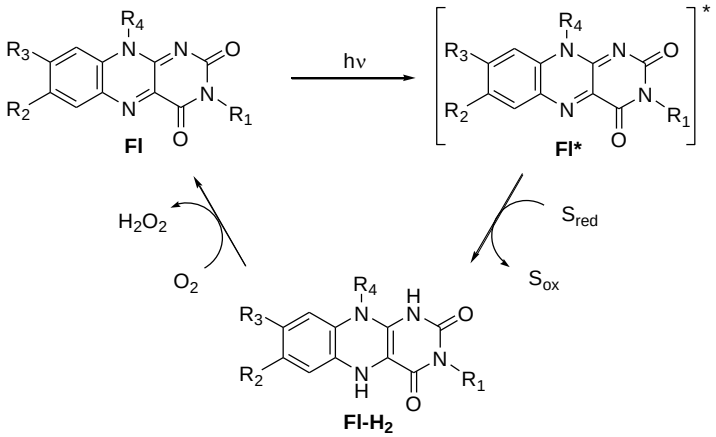
Towards highly efficient flavin photoredox catalysts: The perpendicularly oriented aryl rings relative to the flavin chromophor substantially reduce the aggregation compared to non-substituted derivatives. Such 10-arylflavins 2 are more efficient photocatalyst of the *p*-methoxybenzyl alcohol oxidation.

‡ The investigations presented in this chapter were carried out together with Jitka Daďová, Christian Feldmeier and Jana Cibulková and have already been accepted. J.D. synthesized the flavins **2a-f** with supervision of S.K. and did the photocatalytic reactions. C.F. did the DOSY NMR experiments. J.C. did the crystallization of **2a-f**. S.K. did the quantum yield measurements.

J. Daďová, S. Kümmel, C. Feldmeier, J. Cibulková, R. Pažout, J. Maixner, R. M. Gschwind, B. König, R. Cibulka, *Chem. Eur. J.* **2012**, accepted; DOI: 10.1002/chem.201202488.

3.1. Introduction

Flavins (isoalloxazines) are biologically active compounds which are responsible for redox processes in many types of enzymes, mostly in the form of flavin mononucleotide (FMN) or flavin adenine dinucleotide (FAD) co-factors.[1] Besides, synthetic flavin analogues are subject of intensive research as organocatalysts for oxidations and reductions.[2] The redox activity of flavin derivatives is dramatically enhanced by absorption of visible light; the longest wavelength absorption maximum is at around 450 nm.[3] Thus, photoexcitation of flavins enables the oxidation of substrates which cannot be oxidized thermally.[4] Until now, flavins have been applied for the photooxidation of benzyl alcohols[4a-k] benzyl amines[4l] and methylbenzenes[4m] to benzaldehydes, benzyl methyl ethers to methyl benzoates,[4m] for the photooxidation of dopamine,[4n] amino acids,[4o] indols,[4p] unsaturated lipids and fatty acids,[5] glucose,[6] and phenols[7] as well as for the selective photocatalytic removal of benzylic protecting groups.[8] The photooxidations mentioned above are usually performed in the presence of air which allows the regeneration of the flavin catalyst (**Fl**) from its dihydro form (**Fl-H_2**) being formed from flavin in the excited state (**Fl***) in the presence of a substrate (quencher) by a subsequent two-electron reduction and protonation. Therefore only a catalytic amount of flavin is required (Scheme 3.1). Flavins are also known to sensitize singlet oxygen production.[9] Until now, flavin-mediated sulfoxidations[10] and oxidations of unsaturated lipids[11] proceeding by singlet oxygen mechanism have been reported.



Scheme 3.1: Catalytic cycle for the aerobic photooxidation of a substrate S **mediated by flavin** Fl**.**

In almost all studies, the photooxidation of benzyl alcohols to benzaldehydes in acetonitrile was studied as a typical procedure to elucidate the efficiency of flavin photocatalysts. It was found that the activity of simple flavins, e.g. riboflavin tetraacetate **1** and lumiflavin (for the structure, see Figure 3.1), for *p*-methoxybenzyl alcohol the oxidation in acetonitrile is very low with quantum yields about 0.03%.[4c, 12] Several attempts to improve the efficiency of flavins have recently been reported.

Substantial higher quantum yields of benzyl alcohol oxidation were achieved if the flavin sensitizer was protonated or coordinated to rare-earth metal ions with the highest value of 17% in the case of a Sc(III) complex.[4g, h]

Also thiourea has been found to accelerate the benzyl alcohol photooxidation mediated by flavins reaching a high TON up to 580.[4c] A remarkable improvement of the catalytic efficiency of the flavin moiety was achieved by its covalent attachment to Zn(II)-cyclen or a β-cyclodextrin substrate binding site.[4d, 4f] The reaction medium enhances the photooxidation if performed in SDS micelles.[4e] A positive effect of water on the rate of photooxidations mediated by flavins was also described.[4a, 4d, 12] Immobilization of flavins on fluorinated silica gel stabilizes the chromophore.[4b]

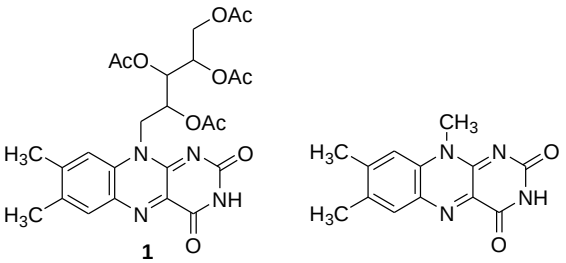
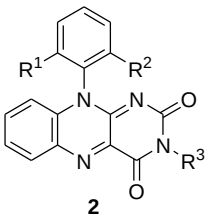


Figure 3.1: Structure of flavins typically used in photocatalysis.

Besides hydrogen bonding, flavins are known to interact with several molecules by π-π-stacking,[13] donor-π-interactions[14] and cation- or anion-π-interactions.[15] These interactions were found to be essential not only for the binding of flavin cofactors in proteins, but also for modulating their redox properties and therefore the reactivity of flavin moieties in biological systems.[13g, 15] The effect of non-covalent interactions on the properties of flavins in artificial systems is also well documented.[13-14] There is evidence for flavin dimer formation even in diluted solutions[16] and such intermolecular aggregation may reduce the photocatalytic efficiency of flavins by quenching of excited states or altered redox properties.[4a] With the aim to minimize the ability of flavins to aggregate, we prepared a series of derivatives **2b-e** with an *ortho*-substituted phenyl ring in position 10 (Figure 3.2).



2

	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

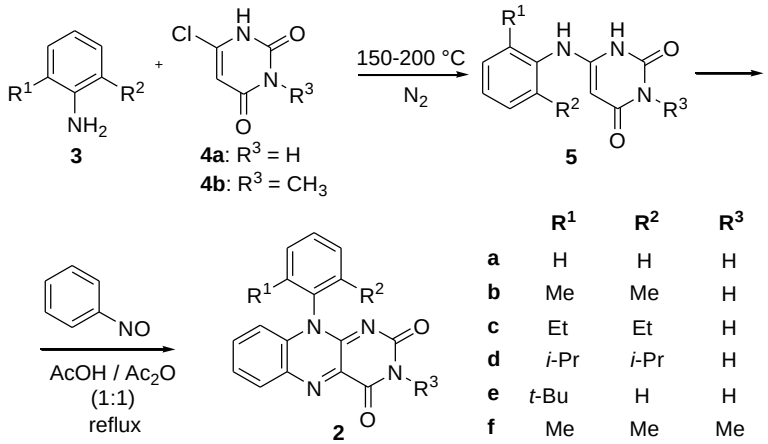
Figure 3.2: Structure of 10-arylflavins synthesized and investigated as photocatalysts.

Due to *ortho*-substitution the aryl ring should be oriented perpendicular to the flavin skeleton 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. For arylflavins **2**, photochemical, electrochemical and aggregation properties, crystal structures as well as the ability to mediate photooxidation of *p*-methoxybenzyl alcohol (model reaction) were studied and compared with those of riboflavin tetraacetate **1**.

3.2. Results and Discussion

Synthesis

The synthesis of 10-arylisoalloxazines **2** (Scheme 3.2) started by converting commercially available substituted anilines **3a-e** with 6-chlorouracil **4a** to form 6-arylaminouracils **5a-e**. It is evident from the reaction conditions and yields (Table 3.1), that the substitution becomes more difficult with increasing steric hindrance of the substituents on C(2) and C(6) of the phenyl ring. While the non-substituted phenyl derivative **5a** was obtained almost quantitatively, sterically hindered aminouracils were isolated only in moderate yields (**5c** and **5e**) or after substantially longer reaction time (**5d**).



	R1	R2	R3
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 3.2: Synthesis of 10-arylflavins 2.

The prepared aminouracils **5a-e** were converted into the target flavins **2a-e** by reaction with nitrosobenzene in a mixture of acetic acid/acetic anhydride 1:1. Whereas this synthetic approach was found to be effective for the synthesis of other sterically hindered flavins,[2e, 17] derivatives **2** were obtained in relatively low yields from 13 to 25%. Unfortunately, the yield did not increase even when acetic acid and acetic anhydride in other ratios were used as a solvent. 3-Methylderivative **2f** was prepared analogously using 6-chloro-3-methylaminouracil (**4b**) (Scheme 3.2). Interestingly, the

conversion of 6-arylamino-3-methyluracil **5f** to 3-methylflavin **2f** proceeded with substantially higher yield (44%) in comparison with the formation of **2b** (23%) possessing a non-substituted N(3) position.

Table 3.1: Reaction conditions[a] and yields for the preparation of 6-aminouracils 5 by the reaction of 6-chlorouracil 4a with substituted anilines 3.

6-amino-uracil	*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] For details see Experimental.

Crystal structures

The interaction of flavin molecules in the crystal can provide information for the aggregation behaviour in solution. For this purpose crystals for single crystal analysis were prepared for compounds **2a**, **2b**, **2c**, **2d**, and **2f**. Interestingly, of the five structures only two structures (**2b**, **2d**) exhibit one molecule in the asymmetric unit as could be expected. Three structures (**2a**, **2c**, **2f**) possess two different (although very similar) molecules *A* and *B* in the asymmetric unit. A close inspection of the structures with *A* and *B* molecules shows that a significant difference between the two molecules is displayed only by **2c** in which one ethyl group of the *ortho*-substituted phenyl ring of the molecule *B* is rotated around the C(phenyl)-CH_2 bond by 83.9(1)° (Figure 3.3Figure 3.3, c). In the structure **2f** the molecules *A* and *B* differ only by a slightly different rotation of the phenyl ring (Table 3.2). In the case of structure **2a** no marked difference between the molecules *A* and *B* is observed.

Structures of several simple flavin derivatives have already been investigated by X-ray diffraction.[18] In most cases π-stacking interactions between the isoalloxazine moieties have been recognized, which results in the packing of flavin molecules with distances between 3.3 and 3.6 Å. In such stacked systems molecules of flavins adopt an alternating orientation and the benzene ring of one flavin moiety overlaps with the pyrimidine ring of the adjacent one (and *vice versa*). Riboflavin tetraacetate **1**,[18d] 3-methyl-riboflavin tetraacetate,[18a] 3-benzyllumiflavin,[18b] and 10-methyl-alloxazine[18e] 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 arylflavins **2a**-**d** even in the

case of **2a** with the unsubstituted phenyl ring still allowing a coplanar orientation of the phenyl and the isoalloxazine subunits.

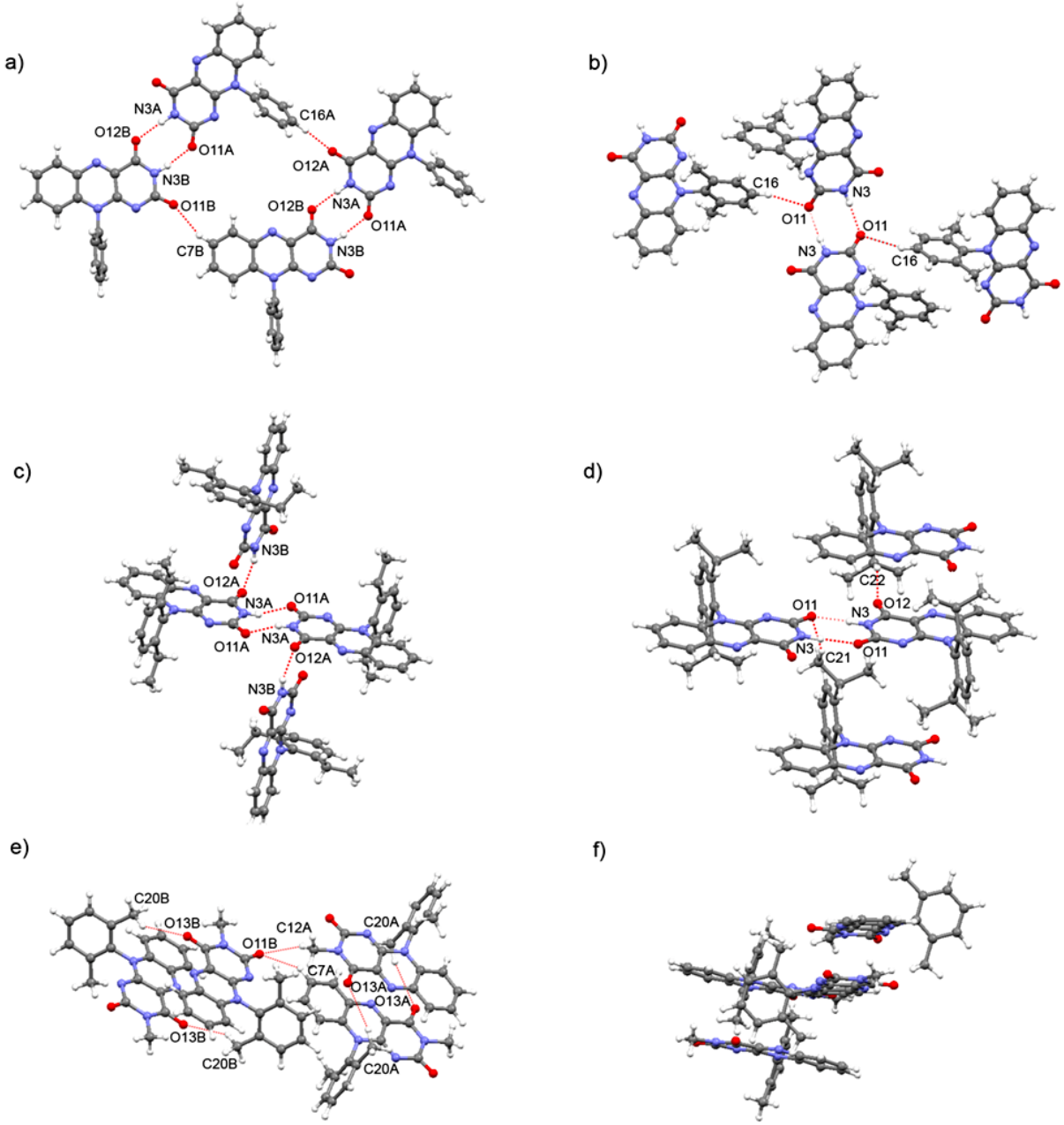


Figure 3.3: Hydrogen bonding in the crystal structures of 10-arylflavins 2a(a), 2b(b), 2c(c), 2d(d), and 2f(e) and fragment showing π-stacking of the molecules 2f (f). Hydrogen bonds are shown as dashed lines, non-hydrogen atoms participating on hydrogen bonds are labeled. For more images and hydrogen bonding data see supporting information (ESI) of ref [19].

In the structures for all flavins **2a**-**d**, the aryl ring is almost perpendicular to the mean plane of the flavin fragment with a dihedral angle ranging from 78.4° to 86.5° thus preventing the stacking of flavins (Table 3.2, Figure 3.3 and ESI of ref [19]). A similar value of the dihedral angle of 79.7° has been reported for 3-methyl-10-(2-hydroxyphenyl)isoalloxazine.[20]

Table 3.2: Dihedral angles between aryl and isoalloxazine plane 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*.

The analysis of the x-ray crystallographic data showed pairs of symmetric hydrogen N-H···O bonds between the pyrimidine rings of two adjacent molecules of flavins **2a**-**d** (Figure 3.3Figure 3.3, a-d). Additionally, a relatively short N(3B)-H···O(12A) hydrogen bond in the structure of **2c** and weak C-H···O interactions in **2a**-**d** contribute to the aggregation. Hydrogen bonds C(16)-H···O(11) in **2b** (Figure 3.3Figure 3.3, b) and C(22)-H···O(12) in **2d** (Figure 3.3, d) with participation of hydrogen atoms on the (alkyl)phenyl ring on one hand and hydrogen bond C(7B)-H···O(11B) in **2a** (Figure 3.3Figure 3.3, a) with participation of hydrogen atoms on the isoalloxazine skeleton on the other hand can be given as examples (for all hydrogen bonding data see ESI of ref [19]). In contrast to flavins with free N(3)-H bond (**2a-2d**), compound **2f** cannot form N-H···O bonds and thus, relatively weak C-H···O interactions dominate in the crystal structure of **2f** (Figure 3.3, e). Methyl groups on both N(3) 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 towards isoalloxazine ring (Table 3.2), little overlap of flavin subunits resulting into a weak π-π interaction has been found in the structure of **2f** (Figure 3.3, f). The distance between the neighbouring 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 strong π-π interactions and to form stacks similarly as simple flavin molecules.[18]One could speculate about the situation in solution due to conformational flexibility of the molecules. Flavin **2a** may show rotation of the phenyl ring, however, this is strongly limited by *ortho*-substituents in **2b**-**f**. Therefore only partial overlap of the isoalloxazine skeletons (e.g. by one ring) resulting in a weak π-π interaction could be expected in the solution. As was shown on flavoenzyme models, the binding constants based on the overlap of one and three rings of the flavin skeleton with an aromatic compound can differ by a factor of 30.[13h]

Aggregation properties determined by ^{1}H-DOSY NMR

^{1}H-DOSY (Diffusion Ordered Spectroscopy) NMR experiments[21] were used to measure the diffusion coefficients of riboflavin tetraacetate **1** and the arylflavins **2** in CD_3CN, D_2O and a mixture of CD_3CN/D_2O (1:1). The resulting aggregation numbers calculated from the experimental diffusion coefficients (see Experimental and ESI of ref [19]) are presented in Table 3.3. For **1** a significant aggregation is detected in CD_3CN with an average aggregation number of 3.0, which is reduced upon addition of water down to monomers in pure D_2O. Next the aggregation trends for the aryl-flavins **2a**-**2f** were investigated. For all compounds a significantly reduced aggregation number is found in CD_3CN compared to **1**. Again addition of water leads to disaggregation for all aryl-flavins **2a**-**2f**.

Table 3.3: Aggregation numbers of riboflavin tetraacetate 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: 300 K, 5×10^{-3} mol L^{-1} solutions (CD_3CN, CD_3CN / D_2O (1:1)) and saturated solutions (D_2O) of flavins **1**, **2a-2f**.

These data show that the basic idea to reduce π-π interactions in the aggregates by introduction of an aryl ring with steric demanding substituents works. However, there is no direct correlation between the steric demand of the substituents in **2a-2f** and the aggregation number detected experimentally. For example **2c** shows a reduced aggregation compared to **2b** as expected for ethyl groups compared to methyl groups as substituents, however a further increase of the steric demand in **2d** and **2e** does not lead to reduced aggregation numbers. This suggests that not only π-π interactions contribute to the aggregation but also other non-covalent interactions play an important role. Interestingly, an analysis of the crystal structures of **2a**-**2d** reveals N-H···O hydrogen bonding as the dominant non-covalent interaction for these arylflavins and not π-π interactions as found for **1.** In the 3-methyl derivate **2f**, the hydrogen bonding to the N(3)-H is blocked. However the diffusion measurements show only a slightly reduced aggregation number comparing to **2b**. This is in

accordance with the crystal structure of **2f** which shows besides weaker C-H···O interactions again π-π interactions. The solvent dependent disaggregation of the arylflavins **2a-2e** from CD_3CN over CD_3CN/D_2O (1:1) to D_2O correlate with the relative hydrogen bond acceptor properties of these solvents in terms of better solute/solvent interactions towards pure D_2O.[22] Interestingly, the π-π interaction driven aggregates show a similar solvent dependence. This shows that the solvent dependence in flavins cannot be used as an indicator for 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 for the aggregation of the flavins and their relative contribution can be tuned by the structure of the synthesized flavins.

Spectral and electrochemical properties

Spectral and electrochemical properties of the newly prepared 10-arylflavins **2** in acetonitrile were studied and compared to those of riboflavin tetraacetate **1** (Table 3.4 and ESI of ref [19]). The aryl substituent in position 10 of the isoalloxazine causes a small blue shift of the absorption maxima and a decrease of absorption intensity in the UV-VIS spectra. Substitution in position N(3) of the 10-arylisoalloxazine ring has no effect on the position of the absorption maxima (cf. flavins **2b** and **2f**) similarly as it was observed in the case of lumiflavin and 10-methylisoalloxazine.[23] All flavins **2** show intensive fluorescence with a maximum around 530 nm. An effect of the aryl substitution on the fluorescence maxima was only observed in the case of **2a** bearing a non-substituted phenyl ring.

Table 3.4: Spectroscopic data for flavins 1 and 2 in acetonitrile.

Flavin	λ_2 (ε)[a] [nm]([Lmol^{-1}cm^{-1}])	λ_1 (ε)[a] [nm]([Lmol^{-1}cm^{-1}])	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 using quinidine sulphate as a standard.

However, the fluorescence quantum yield of **2a** is significantly decreased by half compared to **1** and **2b-d**. Similarly, substitution on N(3) decreases the fluorescence quantum yield of arylflavins, which corresponds to the observed effect of N(3) substitution in riboflavin tetraacetate[18a, 24] and

10-methylisoalloxazine.[23b] On the other hand, fluorescence quantum yields published for lumiflavin and 3-methyllumiflavin are almost the same.[23a]

The reduction potentials of the synthesized flavin derivatives in acetonitrile corresponding to the one electron reduction (Fl → Fl$^{\bullet-}$)[24] were determined by cyclic voltammetry relative to ferrocene/ferrocenium. Moreover, the change in free Gibbs energy ΔG_{ET} of the electron transfer from the substrate (*p*-methoxybenzyl alcohol) to the excited flavins in the singlet state (Table 3.5) were calculated from the observed reduction potentials using the Rehm-Weller equation (3.1),[25]

$$\Delta G_{ET} = 96.4(E^{ox}_{1/2} - E^{red}_{1/2}) - e^2 / \varepsilon a - E^{0-0} \quad (3.1)$$

in which $E^{ox}_{1/2}$ and $E^{red}_{1/2}$ are the oxidation potential of the substrate (+1.19 V for *p*-methoxybenzyl alcohol)[4d] and the reduction potential of the flavin (Table 3.5), $e^2/\varepsilon a$ is the Coulomb term (5.4 kJ mol^{-1}; ref.[24]) and E^{0-0} is the flavin excitation energy (in kJ mol^{-1}), which was estimated from the fluorescence maximum by equation (3.2)

$$E^{0-0} = \frac{hc}{\lambda_F} \quad (3.2)$$

where the values λ_F were obtained from the flavin fluorescence spectra (Table 3.4), *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 only by 60 mV relative to riboflavin tetraacetate **1** which seems to be not enough to influence the oxidation power of the flavin significantly. According to free Gibbs energy changes, electron transfer between *p*-methoxybenzyl alcohol and flavins **1** and **2** in their singlet excited state is exergonic and thus favourable ($\Delta G_{ET} < 0$) with the values of ΔG_{ET} being less negative for riboflavin tetraacetate **1** and 10-phenylisoalloxazine **2a** by about 10 kJ/mol in comparison with **2b**-**2f**.

Fluorescence quenching for the newly synthesized derivatives **2** with *p*-methoxybenzyl alcohol was studied in acetonitrile. Stern-Volmer plots constructed from the results are linear in all cases (see ESI of ref [19]). The values of Stern-Volmer constants K_S ($K_S = k_Q\tau_F$; k_Q is the apparent rate constant and τ_F is the fluorescence lifetime) were calculated as the slope of Stern-Volmer dependence ($I_0/I = 1 + K_S[Q]$), i. e. as the slope of the ratio of the fluorescence intensities (I_0/I) in the absence and in the presence of *p*-methoxybenzyl alcohol (quencher *Q*) plotted against its concentration ([*Q*]). Interestingly, for almost all newly prepared flavins bearing substituted phenyl rings (**2b**-**2f**), higher quenching constants K_S were measured in comparison with riboflavin tetraacetate **1**. Only the value of 10-phenylisoalloxazine **2a** is equal to that of riboflavin tetraacetate **1**. The observed reduced

values of Stern-Volmer constants K_S for **1** and **2a** probably result from the decreased rate of electron transfer (k_Q), which corresponds to the decreased free Gibbs energy changes ΔG_{ET} (see Table 3.5).

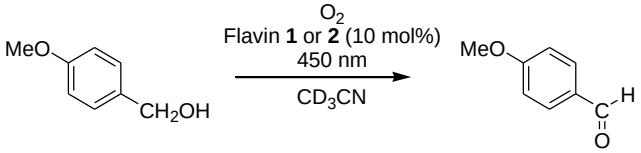
Table 3.5: Redox potentials of flavins 1 and 2, estimated free energy changes ΔG_{ET} and Stern-Volmer constants K_S for the electron transfer from *p*-methoxybenzyl alcohol to flavins 1 and 2 in acetonitrile.

Flavin	$E^{red}_{1/2}$ [V][a]	ΔG [kJ mol^{-1}] [b]	K_S [L mol^{-1}]
1	-1.18	-24	26
2a	-1.12	-24	25
2b	-1.11	-34	42
2c	-1.10	-34	44
2d	-1.11	-33	35
2e	-1.10	-33	36
2f	-1.11	-34	33

[a] Values obtained in acetonitrile at a scan rate of 50 mV s^{-1} in 0.001 mol L^{-1} solutions of the flavins with 0.01 mol L^{-1} Bu_4NPF_6 at 20 °C vs. ferrocene / ferrocenium. [b] Free energy changes calculated from equation (1) using $E_{1/2}^{ox}$ (*p*-methoxybenzyl alcohol) = 1.19 V vs. ferrocene / ferrocenium.[4d]

Photooxidation of p-methoxybenzyl alcohol

The ability of the prepared flavins **2** to mediate the photooxidation of *p*-methoxybenzyl alcohol with oxygen to the corresponding aldehyde was investigated under standard conditions: with 10 mol% of photocatalyst, in deuterated acetonitrile, at 25 °C under atmospheric pressure of air (Scheme 3.3). A high power light-emitting diode was used for irradiation of the reaction mixture. A comparison of the efficiencies of flavins in photooxidations was made by determining *i)* the conversions after a 90 minute period determined by ^{1}H NMR spectroscopy of the reaction mixture and *ii)* the quantum yields of photooxidations determined independently. It is important to note that oxidation does not proceed in the absence of flavin or light.



Scheme 3.3: Model photooxidation.

With riboflavin tetraacetate **1** as photocatalyst, only 5% conversion was achieved after 90 minutes of irradiation (Table 3.6, Entry 1). The use of 10-phenylisoalloxazine **2a** without substitution on the phenyl leads to only a small improvement of the conversion (Entry 2). On the other hand, introduction of an aryl ring with substituents in *ortho*-positions resulted in a substantial increase of

flavin efficiency to mediate photooxidation reaching conversions up to 37% after 90 minutes of irradiation in the presence of **2b** (Entry 3). The character of 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** (cf. Entries 3 and 4) while the activity of **2d** and **2e** with branched isopropyl and tert-butyl substituents is slightly reduced (Entries 5 and 6). Interestingly, the alkylation of nitrogen N(3) decreases the efficiency of the flavin chromophore in photooxidations, too (Entry 7). The conversions of photooxidations in the presence of **2b**-**2f** are relatively high after 1.5 hours of irradiation, but they are not remarkably increased during the next irradiation period. This fact is caused by degradation of flavin photocatalysts during photooxidations as evident from bleaching of the reaction mixtures (see Table 3.6 and ESI of [19]). Nevertheless the photostability is not the most important factor influencing the activity of flavin photocatalysts. Least stable flavin **2c** showed relatively high efficiency. Interestingly, all synthesized catalysts **2** are less photostable than flavin **1**.

Table 3.6: Photooxidation of *p*-methoxybenzyl alcohol to *p*-methoxybenzaldehyde in CD_3CN sensitized by riboflavin tetraacetate **1 and 10-arylflavins 2a-f.**

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

The results of quantum yield measurements are in accordance with the observed conversions (Table 3.6). Introduction of disubstituted aryl rings in position 10 of the isoalloxazine ring causes a substantial increase of the quantum yield of *p*-methoxybenzyl alcohol oxidation, which is in the case of **2b** by almost one order of magnitude higher than the photooxidation in the presence of **1**. However, the quantum yield increase of the flavin photocatalyst is approximately half with bulky isopropyl or *tert*-butyl substituents or if the position N(3) of isoalloxazine is substituted by a methyl

group. As expected, the quantum yields of oxidations are not affected by deuteration of the solvent indicating that a singlet oxygen pathway is not involved.[26b-d]

One could speculate that lower efficiency of **2a** in comparison to **2b**-**2f** is a result of its smaller oxidation power, but differences in reduction potentials and in estimated ΔG_{ET} are not sufficient to explain the observed significant differences in reactivity. Low activity of **2a** can also be attributed to the possible free rotation of the non-substituted aryl ring allowing its coplanar arrangement relative to the isoalloxazine plane. This may increase its ability to aggregate in solution with flavins or substrates thus supporting fast unproductive charge recombination.[4a] Interestingly, hydrogen bonds N(3)-H···O dominating among intermolecular interactions of flavins **2b**-**2e** seem to have no negative effect on the catalytic activity of flavin photocatalysts as evident from the comparison of **2b** and **2f** (cf. Entries 3 and 7).

3.3. Conclusion

10-Arylisoalloxazines **2a-f** were prepared as potentially non-aggregating flavin photocatalysts by condensation of the appropriate 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 strong π-π interactions and to form stacks similarly as simple flavin molecules which is caused by steric hindrance of the substituted phenyl ring oriented perpendicularly to flavin skeleton. X-ray diffraction studies also revealed that N-H···O hydrogen bonding dominates in the crystals of **2a-d**. Blocking of the N(3) position by 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 experiments, nevertheless it was shown that there is no direct correlation between the steric demand of the substituents in **2a-2f** and the aggregation numbers, probably due to the contributions of other non-covalent interactions, e.g. 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**.

The flavins **2b-f** are far more effective photocatalysts for the photooxidation of *p*-methoxybenzyl alcohol than riboflavin tetraacetate **1**. The observed quantum yield of this oxidation in the presence of **2b** (the best photocatalyst among 10-arylflavins **2**) exceeds that of compound **1** by almost one order of magnitude. Unfortunately, the increased reactivity of **2** is accompanied with their lower photostability. Although the conversions of *p*-methoxybenzyl alcohol photooxidations catalyzed by

flavins **2b**-**2f** are not quantitative, they are among the most active flavins tested so far in the photooxidations of benzyl alcohols.

The results show that the efficiency of a flavin photocatalyst can be altered and improved by changing structural elements, which influence the aggregation properties. However, intermolecular interactions affect the ability of flavins to mediate the *p*-methoxybenzyl alcohol photooxidation not by a simple correlation. While 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 be both taken into account designing the structure of new flavins for photocatalysis. Additionally, photophysical properties (e.g. quantum yields of singlet and triplet flavin excited state formation) are influenced by substitution.

3.4. Experimental Section

Materials and methods

NMR spectra were recorded on a *Varian Mercury Plus 300* (299.97 MHz for ^{1}H and 75.44 MHz for ^{13}C), *Bruker Avance 300* (300.13 MHz for ^{1}H and 75.03 MHz for ^{13}C), Bruker Avance 400 (400.13 MHz for ^{1}H and 100.03 MHz for ^{13}C) and *Bruker Avance 600* (600.13 MHz for ^{1}H and 150.03 MHz for ^{13}C) spectrometers. Chemical shifts δ are given in ppm, using residual solvent or tetramethylsilane 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 (both *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* analyser. MS spectra were recorded on a *ThermoQuest Finnigan TSQ 7000* mass spectrometer in tandem with *Janeiro* LC system. HPLC analyses were carried out on an *Ingos* HPLC System (column: *Phenomenex Luna 5u* Silica, 150 × 4.6 mm) with UV-VIS spectrophotometric detector. Starting materials and reagents were purchased from *Sigma-Aldrich*, *Eurorad* (deuterated solvents: $CDCl_3$, DMSO-*d6*, acetonitrile-*d3*) and *Lach-Ner* (acetonitrile, propan-2-ol, *n*-heptane for HPLC). The solvents were purified and dried using standard procedures.[27] Riboflavin tetraacetate,[28] 6-chlorouracil,[29] 6-chloro-3-methyluracil,[2e] nitrosobenzene[30] were prepared according to the described procedure.

General procedure I: Synthesis of 6-aminouracils 5a-f (ref.[17])

A mixture of 6-chlorouracil **4a** (or 6-chloro-3-methyluracil **4b** for **5f**) and substituted aniline **3** was heated under nitrogen atmosphere. After cooling, methanol was added and the resulting suspension was stirred for 15 minutes at room temperature. The white precipitate was filtered off, washed twice with diethylether and methanol and dried in vacuo to give 6-arylaminouracils as a white powder.

6-N-Phenylaminouracil (5a): According to the general procedure I, 6-chlorouracil **4a** (500 mg, 3.42 mmol) and aniline **3a** (6 mL, 1.022 g mL^{-1}, 65.84 mmol) were heated for 1 hour at 150 °C to yield aminouracil **5a** (680 mg, 98 %). M.p. 318 - 321 °C (332 - 333 °C, ref.[31]); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.70 (s, 1H), 7.09-7.30 (m, 3H), 7.31-7.47 (m, 2H), 8.28 (s, 1H), 10.19 (s, 1H), 10.48 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 76.32, 123.19, 125.15, 129.88, 138.36, 151.28, 152.66, 164.83 ppm; HRMS (ESI): *m/z* calcd. for $C_{10}H_{10}N_3O_2$ $[M+H]^+$ 204.07675; found 204.07671; elemental analysis calcd (%) for $C_{10}H_9N_3O_2$: C 62.33, H 5.67, N 18.17, found: C 62.19, H 5.65, N 18.02.

6-N-(2',6'-Dimethylphenyl)aminouracil (5b): According to the general procedure I, 6-chlorouracil **4a** (1 g, 6.82 mmol) and 2,6-dimethylaniline **3b** (2.5 mL, 0.984 g mL^{-1}, 20.47 mmol) were heated for 40 minutes at 180 °C to yield aminouracil **5b** (1.2 g, 74 %). M.p. 263 - 267 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.16 (s, 6H), 3.70 (s, 1H), 7.05-7.24 (m, 3H), 7.67 (s, 1H), 10.32 (s, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 17.97, 73.79, 128.10, 128.84, 134.43, 136.67, 151.37, 153.67, 164.67 ppm; HRMS (ESI): *m/z* calcd. for $C_{12}H_{14}N_3O_2$ $[M+H]^+$ 232.10805; found 232.10799; elemental analysis calcd (%) for $C_{12}H_{14}N_3O_2$: C 62.33, H 5.67, N 18.17; found: C 62.19, H 5.65, N 18.02.

6-N-(2',6'-Diethylphenyl)aminouracil (5c): According to the general procedure I, 6-chlorouracil (**4a**) (1 g, 6.82 mmol) and 2,6-diethylaniline (**3c**) (5 mL, 0.906 g mL^{-1}, 40.94 mmol) were heated for 6.5 hours at 180 °C to yield aminouracil **5c** (1 g, 58 %). M.p. 297 - 301 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.12 (t, *J* = 8 Hz, 6H), 2.50 (m, 4H), 3.68 (s, 1H), 7.12-7.23 (m, 2H), 7.23-7.33 (m, 1H), 7.66 (s, 1H), 10.23 (s, 1H), 10.30 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 15.21, 24.45, 73.97, 127.20, 128.72, 133.09, 142.63, 151.25, 154.44, 164.56 ppm; HRMS (ESI): *m/z* calcd. for $C_{14}H_{18}N_3O_2$ $[M+H]^+$ 260.13935; found 260.13934; elemental analysis calcd (%) for $C_{14}H_{17}N_3O_2$: C 62.33, H 5.67, N 18.17; found: C 62.19, H 5.65, N 18.02.

6-N-(2',6'-Diisopropylphenyl)aminouracil (5d): According to the general procedure I, 6-chlorouracil **4a** (500 mg, 3.42 mmol) and 2',6'-diisopropylaniline **3d** (6 mL, 0.94 g mL^{-1}, 31.82 mmol) were heated for 24 hours at 200 °C to yield aminouracil **5d** (735 mg, 75 %). M.p. 269 - 270 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.14 (s, 12H, C*H*$_3$), 3.01 (m, 1H, -C*H*-), 3.65 (s, 1H, =CH-), 7.25 (m, 2H, Ar-*H*), 7.36 (m, 1H, Ar-*H*), 7.64 (s, 1H, Ar-N*H*), 10.17 (s, 1H, N*H*), 10.32 (s, 1H, N*H*) ppm; ^{13}C NMR (100 MHz,

DMSO-d_6): δ = 23.52, 24.68, 74.24, 124.27, 129.14, 131.43, 147.19, 151.22, 155.01, 164.52 ppm; HRMS (ESI): *m/z* calcd. for $C_{16}H_{22}N_3O_2$ $[M+H]^+$ 288.36478; found 288.17069; elemental analysis calcd (%) for $C_{16}H_{21}N_3O_2$: C 62.33, H 5.67, N 18.17; found: C 62.19, H 5.65, N 18.02.

6-N-(2'-Tert-butylphenyl)aminouracil (5e): According to the general procedure I, 6-chlorouracil **4a** (500 mg, 3.42 mmol) and 2-*tert*-butylphenylaniline **3e** (10 mL, 0.957 g mL^{-1}, 64.14 mmol) were heated for 10 hours at 180 °C to yield aminouracil **5e** (508 mg, 57 %). M.p. 272 - 275 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.33 (s, 9H), 3.97 (s, 1H), 7.20 (m, 1H), 7.30 (m, 2H), 7.47 (m, 1H), 7.54 (s, 1H), 10.21 (s, 1H), 10.35 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 30.91, 31.13, 35.19, 75.19, 127.53, 127.72, 128.19, 131.26, 135.53, 147.33, 151.18, 154.73, 164.57 ppm; HRMS (ESI): *m/z* calcd. for $C_{14}H_{18}N_3O_2$ $[M+H]^+$ 260.13935; found 260.13937; $C_{14}H_{18}N_3O_2$ (259.30): elemental analysis calcd (%) for $C_{14}H_{17}N_3O_2$: C 64.85, H 6.61, N 16.20, found: C 64.49, H 6.51, N 16.12.

6-N-(2',6'-Dimethylphenyl)-3-methylaminouracil (5f): According to the general procedure I, 6-chloro-3-methyluracil **4b** (250 mg, 1.56 mmol) and 2,6-dimethylaniline **3b** (2 mL, 0.984 g mL^{-1}, 16.24 mmol) were heated for 1 hour at 180 °C to yield aminouracil **5f** (100 mg, 26 %). M.p. 282 - 284 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.15 (s, 6H, C*H*$_3$), 3.03 (s, 3H, C*H*$_3$), 3.85 (s, 1H, =C*H*-), 7.16 (m, 3H, Ar-*H*), 7.73 (bs, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 17.97, 26.45, 73.67, 128.10, 128.85, 134.38, 136.72, 151.54, 152.09, 163.58 ppm; HRMS (ESI): *m/z* calcd. for $C_{14}H_{18}N_3O_2$ $[M+H]^+$ 260.13935; found 260.13937; elemental analysis calcd (%) for $C_{14}H_{17}N_3O_2$: C 64.85, H 6.61, N 16.20, found: C 64.84, H 6.41, N 16.17.

General procedure II: Synthesis of 10-arylisoalloxazines 2a-f

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

10-Phenylisoalloxazine (2a): According to general procedure II, aminouracil **5a** (0.68 g, 3.35 mmol) and nitrosobenzene (1.00 g, 10.4 mmol) were refluxed to yield 10-phenylisoalloxazine **2a** (0.32 g, 33 %) as a green-yellow powder. M.p. 215 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.75 (dd, *J*(H,H) = 8.5, 0.8 Hz, 1H), 7.44 (dd, *J*(H,H) = 5.2, 3.2 Hz, 2H), 7.85 – 7.54 (m, 5H), 8.19 (dd, *J*(H,H) = 8.1, 1.3 Hz, 1H, Ar-*H*), 11.43 (s, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 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_3CN): $\lambda_{max}(\varepsilon)$ = 335 (6200), 436 (8900). MS-ESI: $[M+H]^+$ 290.8 (100 %); $[2M+H]^+$ 581.0 (32 %). 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): According to general procedure II, aminouracil **5b** (360 mg, 1.56 mmol) and nitrosobenzene (500 mg, 4.67 mmol) were refluxed 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. decomposition at 350 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.93 (s, 6H, C*H*$_3$), 6.80 (dd, J = 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 (s, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 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_3CN): $\lambda_{max}(\varepsilon)$ = 330 (7000), 437 (10000); MS-ESI: $[M+H]^+$ 318.8 (100 %); $[2M+H]^+$ 637.1 (82 %); 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): According to general procedure II, aminouracil **5c** (405 mg, 1.56 mmol) and nitrosobenzene (500 mg, 4.67 mmol) were refluxed 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. decomposition at 350 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, J(H,H) = 7.6 Hz, 6H, CH3), 2.07 (dq, J(H,H) = 15.1, 7.5 Hz, 2H, CH2), 2.24 (dq, J(H,H) = 15.2, 7.6 Hz, 2H, CH2), 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 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 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_3CN): $\lambda_{max}(\varepsilon)$ = 331 (7000), 434 (10100); MS-ESI: [M+H]+ 346.9 (100 %); [2M+H]+ 693.2 (70 %); 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): According to general procedure II, 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. decomposition at 350 °C; ^{1}H NMR (400 MHz,

$CDCl_3$): 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, C*H*), 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 (s, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 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_3CN): $\lambda_{max}(\varepsilon)$ = 330 (6200), 436 (8900); MS-ESI: $[M+H]^+$ 374.9 (100 %); $[2M+H]^+$ 749.4 (24 %); 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): According to general procedure II, aminouracil **5e** (390 mg, 1.50 mmol) and nitrosobenzene (483 mg, 4.50 mmol) were refluxed 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. decomposition at 300 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (s, 9H, CH_3), 6.83 (dd, *J*(H,H) = 8.6, 0.9 Hz, 1H, Ar-*H*), 6.91 (dd, J = 7.9, 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, 1.3 Hz, 1H, Ar-*H*), 8.34 (dd, *J*(H,H) = 8.2, 1.3 Hz, 1H, Ar-*H*), 8.80 (s, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 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_3CN): $\lambda_{max}(\varepsilon)$ = 332 (7000), 437 (9900); MS: $[M+H]^+$ 346.9 (100 %); $[2M+H]^+$ 693.2 (60 %); 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.

3-Methyl-10-(2',6'-dimethylphenyl)isoalloxazine (2f): According to general procedure II, 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. decomposition at 350 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 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, 1.4 Hz, 1H, Ar-*H*), 8.39 (dd, *J*(H,H) = 8.1, 1.4 Hz, 1H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 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_3CN): $\lambda_{max}(\varepsilon)$ = 321 (5500), 427 (6500); MS-ESI: $[M+H]^+$ 332.8 (100 %); $[2M+H]^+$ 665.2 (86 %); 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 the 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 mL, 1.00 mL, 0.50 mL and 0.20 mL, respectively). The single crystal of **2c** was prepared by slow cooling of the solution of **2c** (3.2mg, 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**, **2b**, **2c**, **2d**, and **2f** were measured at 170 K on a four circle CCD diffractometer *Geminy* of *Oxford Diffraction, Ltd.*, with graphite monochromated Cu Ka radiation (λ = 1.5418 Å). Data reduction including empirical absorption correction using spherical harmonics were performed with *CrysAlisPro*[32] (Oxford Diffraction). The crystal structure was solved by chargeflipping method using program *Superflip*[33] and refined with the *Jana2006* program package[34] by full-matrix least squares technique on F. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were positioned geometrically and refined using riding model. The molecular structure plots were prepared using the *ORTEP* III,[35] intermolecular interactions were viewed in *Mercury*.[36] Selected data for **2a**-**d** and **2f** are collected in the ESI of ref [19].

CCDC 887842 – 887846 (for **2c**, **2a**, **2b**, **2d**, and **2f**, respectively) contain the supplementary crystallographic 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

^{1}H-DOSY NMR measurements were conducted on a *Bruker Avance 600* spectrometer (600.13 MHz) equipped with a TBI ^{31}P/^{13}C-selective probe. Temperature stability was ensured by a BVT 3000 unit. Data were processed and evaluated with *Bruker TOPSPIN* 2.1 with the software package t1/t2. Measurements were conducted at 300 K with solutions of $c_{flavin} = 5 \times 10^{-3}$ mol L^{-1} in CD_3CN and CD_3CN/D_2O (1:1) and saturated solutions in D_2O ($c_{flavin} < 5 \times 10^{-3}$ mol L^{-1}). The aggregation numbers are based on diffusion coefficients measured by ^{1}H-DOSY experiments using a convection compensating pulse sequence developed by A. Jerschow an N. Müller.[37] Diffusion coefficients of tetramethylsilane (TMS) served as viscosity reference. Assuming a spherical shape of the molecules and considering a microfriction factor, calculation of the hydrodynamic volumes from experimental diffusion coefficients was done according to the reported procedure.[21, 38] The comparison of this experimental determined hydrodynamic volumes with theoretical volumes calculated according to

Zhao *et al.*[39] 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 to 0.8. This factor is in accordance with previous studies on experimental diffusion coefficients of aromatic systems[40] 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[39] to the experimental hydrodynamic volume of flavin **2b** (for data see ESI of ref [19]).

Cyclic voltammetry

Cyclic voltammetry measurements were carried out on an *Autolab* PGSTAT 302N set-up at 20 °C in acetonitrile and acetonitrile/water (1:1) solutions containing flavin ($c = 1 \times 10^{-3}$ mol L^{-1}) under argon atmosphere with 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. Redox potentials were referenced against ferrocenium / ferrocene. In all experiments, the scan rate was 50 mV s^{-1} and $Bu_4N^+BF_4^-$ (tetrabutylammonium tetrafluoroborate) was used as supporting electrolyte ($c = 0.1$ mol L^{-1}).

Fluorescence quantum yields and quenching

The relative fluorescence intensities were measured on a *Varian Eclipse* spectrometer (λ_{exc} = 498-524 nm according to the flavin derivative and solvent). Fluorescence quantum yields Φ_F of flavins **1**, **2a-f** were determined by a standard procedure at $c = 3 \times 10^{-6}$ mol L^{-1} in acetonitrile and ethanol using quinidine sulfate ($c = 1 \times 10^{-7}$ mol L^{-1}) in 0.5 mol L^{-1} sulfuric acid as a standard.[41] Fluorescence quenching by *p*-methoxybenzyl alcohol was measured in acetonitrile and ethanolic solutions containing **1** or **2a-f** ($c = 3 \times 10^{-6}$ mol L^{-1}) and *p*-methoxybenzyl alcohol ($c = 0 - 9 \times 10^{-3}$ 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 using *Origin* 6.1 software.

Photooxidations

The photooxidation of *p*-methoxybenzyl alcohol ($c_{MBA} = 4 \times 10^{-3}$ mol L^{-1}, $c_{flavin} = 4 \times 10^{-4}$ mol L^{-1}) was performed in quartz cuvettes ($d = 1$ cm). Deuterated acetonitrile was used as solvent. The mixture was purged with oxygen for 2 minutes before the reaction was started. The reaction mixture was

stirred, tempered to 25 °C and irradiated with a diode (LED LUXEON STAR/0 1 W, 220 mW @ 350 mA, 2.8 - 4 V, 440 - 460 nm, $\Delta\lambda_{1/2}$ = 20 nm). Conversion was monitored by ^{1}H NMR using the ratio of integral intensities of Ar-*H* signals. Quantum yields of the photooxidations were measured with a simple apparatus based on the absorption of light from an LED focused with a lense in a common quartz cuvette and measured by a calibrated solar cell as described before.[12] The concentration of the *p*-methoxybenzyl alcohol was c = 4 × 10^{-3} mol L^{-1} with 10 mol% of flavin catalyst in acetonitrile or deuterated acetonitrile, respectively. The yield of *p*-methoxybenzaldehyde was determined after 20, 30, 60, 120, 180 and 240 minutes *via* GC with chlorobenzene as internal standard and the quantum yield was determined as an average from all these measurements.

3.5. References

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4. Improving Flavin Photocatalysts: Influence of the Solvent and Heavy-Atom-Substitution‡

4.1. Introduction

Flavin photocatalysts have been investigated and used for different organic reactions, mainly oxidations, in the last years.[1] The mechanism of these reactions has been studied in detail for a model reaction (see Scheme 4.1Scheme 4.1), i.e. the oxidation of *p*-methoxybenzyl alcohol (**MBA**) to the corresponding aldehyde (*p*-methoxybenzaldehyde, **MBAld**) with riboflavin tetraacetate (**RFTA**) as photocatalyst.[2]

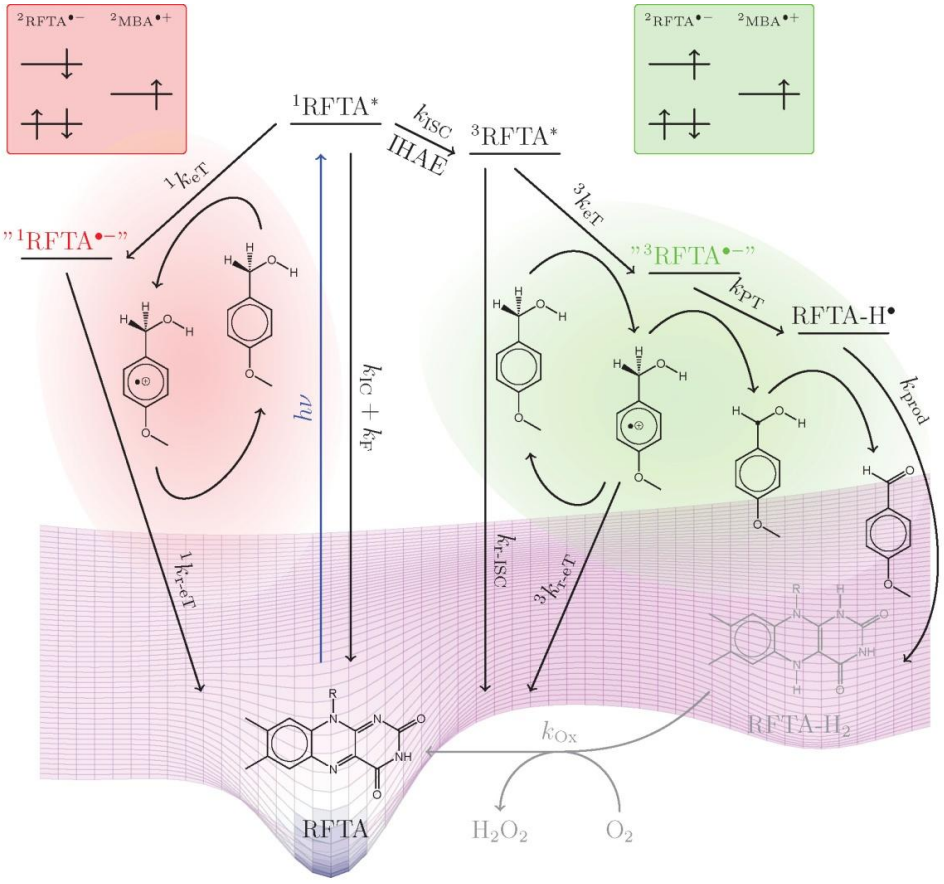
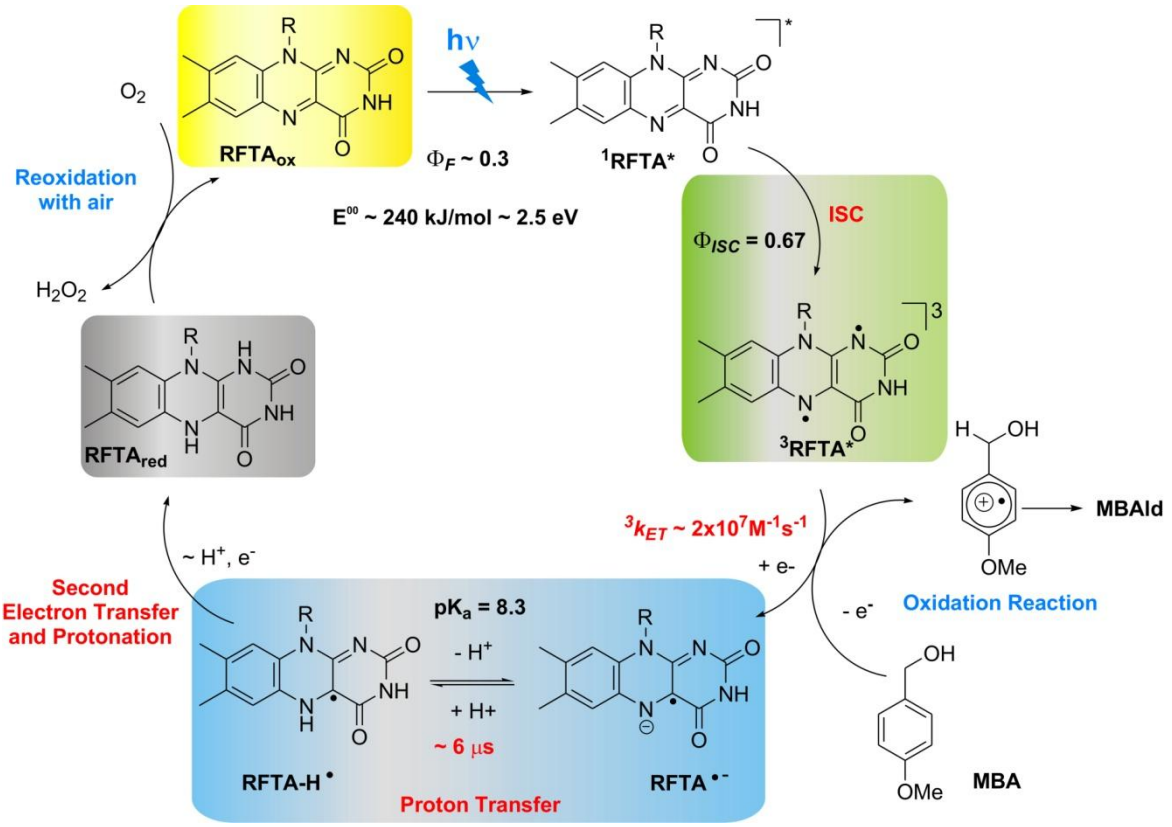


Figure 4.1: Detailed mechanism of the flavin catalyzed oxidation of MBA. Left side: Reaction from the singlet state ^{1}RFTA* occurring when high substrate concentrations are used; right side: Reaction from the triplet state ^{3}RFTA* of the flavin, leading to the final product MBAld.[3]

‡ The investigations presented in this chapter were performed together with Dr. Roger-Jan Kutta. R.-J. K. did the spectroscopic measurements and S.K. synthesized the flavin derivatives 5a-c and measured the quantum yields (absolute values).

These investigations show that the reaction of **MBA** with the flavin singlet excited state **^{1}RFTA*** is an unproductive reaction because of the fast back electron transfer ($^1k_{et}$ = 50 ps^{-1})[2] leading to the starting material in the ground state (left side in Figure 4.1). This step is diffusion controlled and therefore important when high substrate concentrations are used.

The reaction of **MBA** with the triplet excited state **^{3}RFTA*** enables a sequence of electron and proton transfers to the final product **MBAld** (right side in Figure 4.1). This suggests the use of low concentrations to avoid the early collision of **MBA** with the excited flavin in the singlet state, i.e. to give the flavin enough time for inter system crossing (ISC) ($k_{ISC} \geq 1.3 \cdot 10^8$ s^{-1}).[2] The proton and electron transfer sequence is further enhanced if the flavin anion radical **RFTA$^{\cdot -}$** is protonated fast (~ 6 µs in water/acetonitrile 1:1).[2]



Scheme 4.1: Proposed mechanism of flavin photocatalysis in detail: Excitation to the singlet state ^{1}RFTA*, Inter-System-Crossing (ISC) to the triplet state ^{3}RFTA* (green box), electron transfer from the substrate (MBA), protonation of the radical anion (blue box) and subsequent second reduction to the fully reduced form, which is easily reoxidized by oxygen from the air.

In conclusion, there are two stages in the mechanism that determine the reaction rate mainly: The formation of the flavin triplet state **^{3}RFTA** *via* inter-system crossing (ISC) (green box in Scheme 4.1Scheme 4.1) and the protonation of the radical anion **RFTA$^{\cdot -}$** (blue box in Scheme 4.1).

The former is depending mainly on the triplet state quantum yield and its lifetime, the latter can be influenced by the pH value of the reaction mixture.

Regarding synthetic applications of the system, the most observed factor influencing the turn over number (TON)[4] and the product quantum yield (PQY)[5] is the water content of the reaction mixture. The best results in synthesis applications were obtained in an acetonitrile/water 1:1 mixture.[5b, 6] For this reason the influence of the water content has been further investigated in the present work.

4.2. Dependence of the Water Content

The typical model reaction (oxidation of **MBA** to **MBAld**) was studied with **RFTA** at different amounts of water in acetonitrile *via* transient absorption measurements in the µs-time scale.

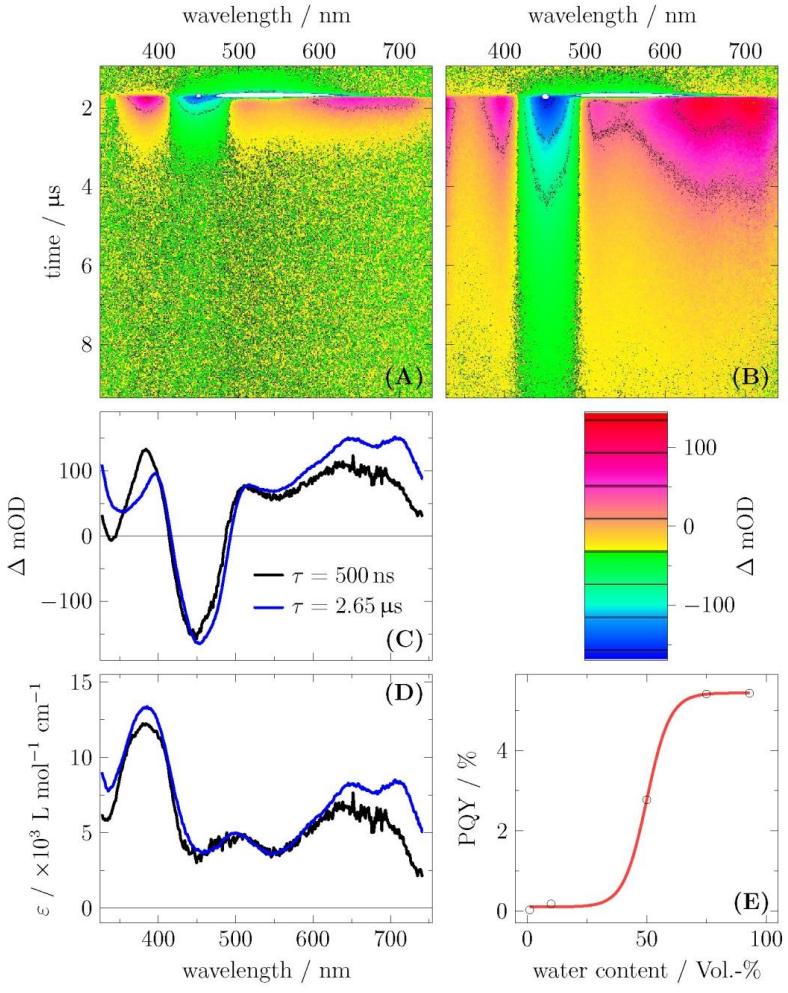


Figure 4.2: Comparison of the 2D-TA-data of RFTA in dependence of the H_2O amount in acetonitrile after excitation at 450 nm. (A): In MeCN; (B): In H_2O; (C): DADS from the corresponding global fits: Black line: in MeCN; Blue line: in H_2O; (D): Species associated spectra after addition of 75% of the corresponding ground state spectrum. Black Line: In MeCN; Blue line: In H_2O; (E): PQY in dependence of the H_2O amount at a substrate concentration of 50 mM of MBA.[7]

The results are presented in Figure 4.2, transient absorption measurements are shown for the reaction in pure acetonitrile (A) and in water (B). The amplitudes of the triplet state spectra are equal in both solvents at 510 nm (see Figure 4.2 C) where the extinction coefficient ε is the same in both solvents (see Figure 4.2 D), i.e. the triplet quantum yield is the same in both solvents, too. However, the lifetime of the triplet state ^{3}**RFTA** increases with increasing water content of the solvent, in pure acetonitrile the lifetime of the triplet state is about 500 ns, in water it is 2.65 µs. This prolonged lifetime in water is one contribution to the dependence of the PQY on the water content (Figure 4.2 E). The more water is used in the reaction, the more PQY is observed, at about 75% of water content this effect diminishes. Due to the prolonged lifetime of ^{3}**RFTA** in water the probability of a collision between an **MBA** molecule and the flavin in the reactive triplet state ^{3}**RFTA** (the active species of the mechanism[2]) is increased.

But this is only one possible reason for the better quantum yields in water: Another explanation could be the better H-bonding network in water that enables a faster protonation of the radical anion **RFTA**$^{\cdot -}$ which is formed from ^{3}**RFTA** upon reaction. When the protonation of this radical anion is complete (pure water environment), the concurrent back electron transfer to **MBA**$^{\cdot +}$ (cation radical) is less likely.

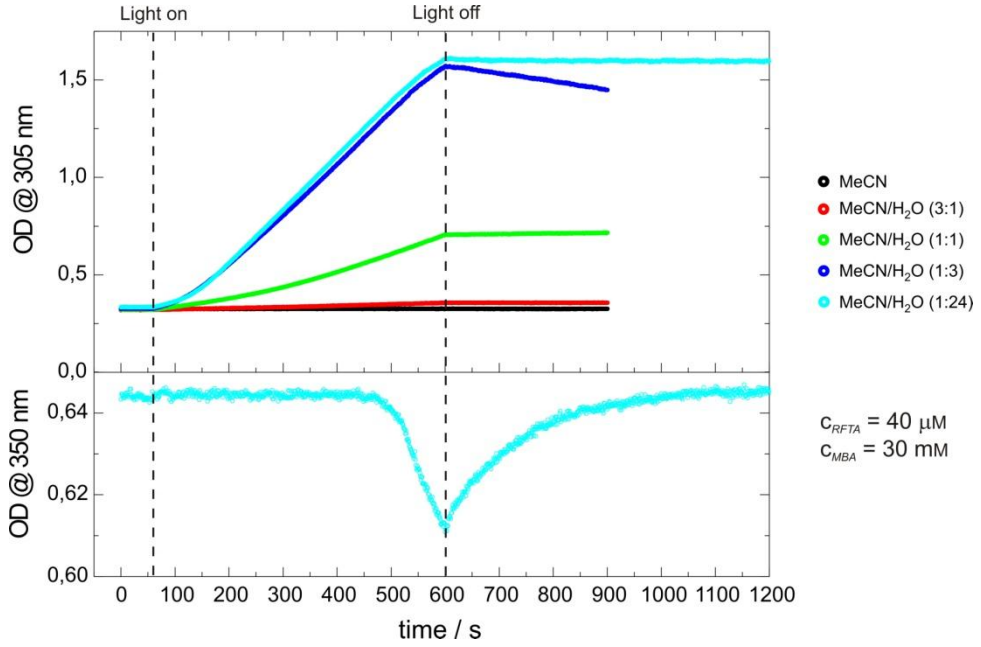


Figure 4.3: Reaction kinetics with different acetonitrile/water mixtures. The light was switched on after 60 seconds and switched off after 600 seconds. Top: observation of the aldehyde at 305 nm, bottom: observation of the flavin band at 350 nm.

Looking at the reaction kinetics (see Figure 4.3), the effect of water addition is obvious: In this experiment the reaction was monitored, detecting the aldehyde band at 305 nm and the flavin band

at 350 nm. Increasing the water content to 25 vol% has only little influence on the aldehyde formation in the first 10 minutes. Using 50 vol% of water in the solvent mixture already increases the rate a lot (like already shown in synthesis before)[4] and with 75 vol% of water the maximal improvement is reached.

Regarding the flavin spectra at 350 nm at the same time (see Figure 4.3, bottom), there is a loss of concentration of oxidized flavin after approximately 450 seconds of irradiation. The oxygen in solution seems to be consumed at that point and the flavin is faster reduced than oxygen can diffuse into the solution. After switching off the light the slow oxygen diffusion enables the regeneration of the flavin confirming that this method is a catalysis.

The importance of water for the mechanism is evident from these experiments. Since the explanation by the better H-bonding network in water suggests that the protonation step is influenced by the solvent positively. Therefore the experiment was repeated with addition of HCl (see Figure 4.4).

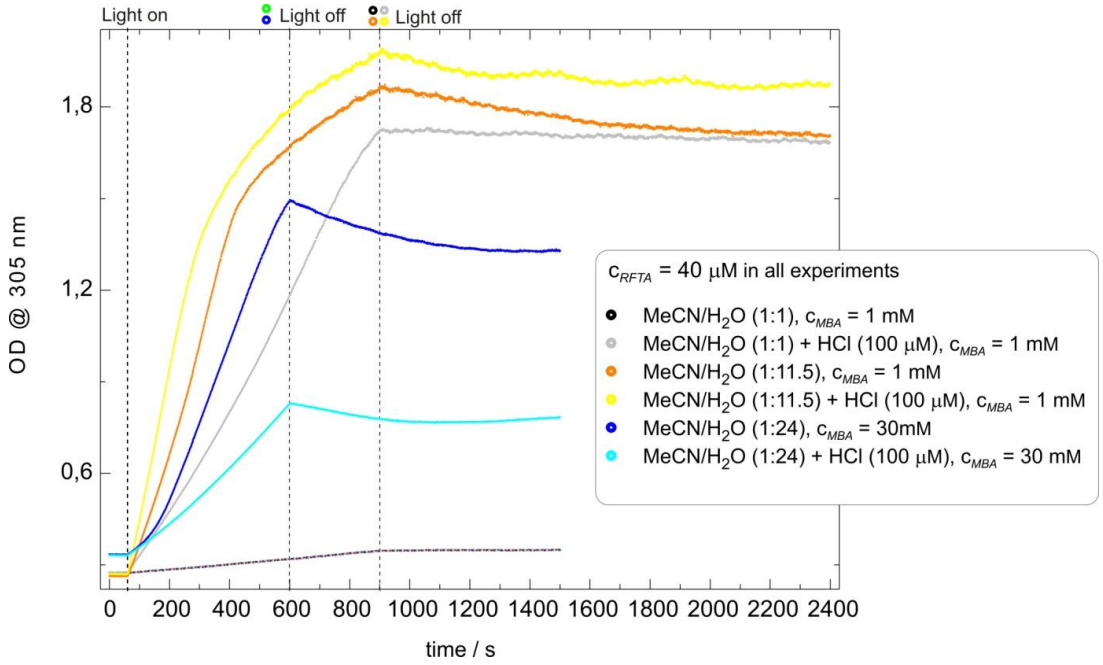


Figure 4.4: Effect of HCl-addition on the reaction kinetics with different concentrations and solvent mixtures.

Surprisingly the reaction turned out to be even less efficient when HCl (~ pH 4) is added at an **MBA** concentration of 30 mM (change from blue to cyan in Figure 4.4). The experiment was retried with 1 mM substrate concentration and a 1:1 solvent mixture of water and acetonitrile and here the HCl addition causes a five times higher signal than without the acid (see Figure 4.4, black and grey).

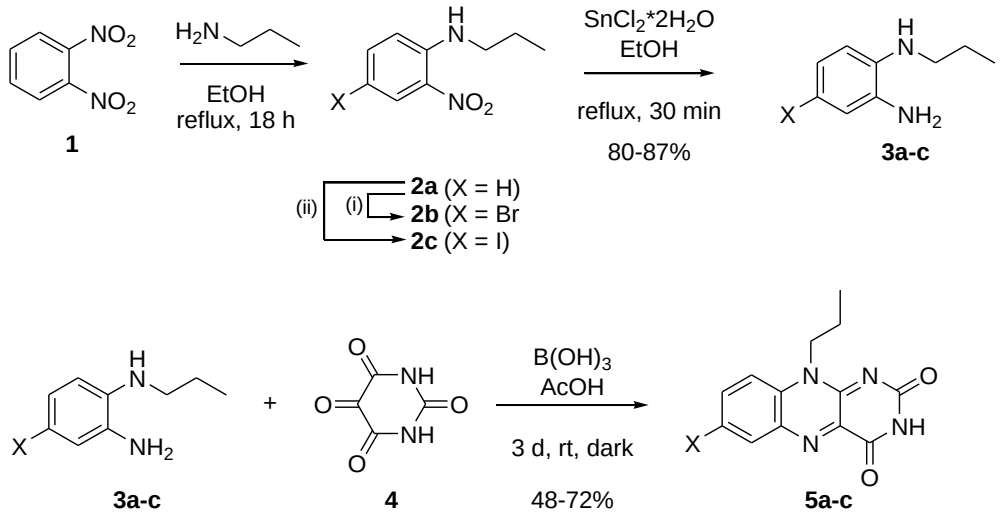
If the water content of the solvent is higher the effect is less pronounced (only 7% increase) which is shown in the orange and yellow graphs in Figure 4.4. However, the system is very sensitive for every change of reaction conditions: If the wrong substrate concentration is chosen the addition of HCl can even have a negative effect (see above), so every new reaction conditions should be tested in different concentrations first.

In conclusion of these experiments it is evident that the water content of the reaction mixture influences the two stages of the mechanism that can improve the product quantum yield: The protonation step is enhanced with higher water content and also the lifetime of the important triplet state.

The triplet quantum yield is not affected by the addition of water and remains constant in water and in acetonitrile. To investigate the influence of the triplet quantum yield on the product quantum yield we prepared flavin derivatives with improved ISC abilities. Therefore heavy-atom substituted isoalloxazines were synthesized that should enhance the ISC due to their good spin-orbit-coupling. To simplify the synthesis a propyl chain was chosen instead of the ribityl side chain and the substituents in position 7 were chosen to be iodine and bromine, the hydrogen substituted analogue was synthesized for comparison.

4.3. Synthesis of New Flavin-Derivatives

The synthesis of flavins followed the *Kuhn*-method[8] *via* condensation of the corresponding *N*-propyl-benzene-1,2-diamines **3a-c** with alloxan **4** and boronic acid as additive. The halogen substituents were introduced in the starting material before. Therefore, dinitrobenzene **1** was converted to (2-nitro-phenyl)-propyl-amine **2a** and subsequently halogenated to yield the corresponding bromo- or iodo-compound (**2b** and **2c**). The so obtained 2-nitro-phenyl-propyl-amine derivatives **2a-c** were reduced to the corresponding diamines **3a-c** which are oxygen sensitive compounds and were used for the *Kuhn* synthesis without purification to yield the desired isoalloxazines (flavins) **5a-c** (see Scheme 4.2).



Scheme 4.2: Synthesis of 4-substituted flavins *via* Kuhn synthesis; (i) Br_2, CCl_4, 0 °C/rt, overnight, 61%; (ii) ICl, KOAc, AcOH, 80 °C, 30 min., 96%.

4.4. Properties of the New Flavin Derivatives

The measurements of the stationary absorption and emission spectra, the fluorescence quantum yields, the relative product quantum yield as well as the transient absorption of the newly synthesized flavins were investigated. In Table 1 the individual photo-physical rates for each flavin compound are listed. In the row from H to I the fluorescence lifetime drops as well as the fluorescence quantum yield.

In the row from **5a** to **c** (H to I) the fluorescence lifetime drops as well as the fluorescence quantum yield does, while the radiative rate k_{rad} is almost constant. Therefore, it is most likely that the quenching of the singlet state arises from a greater inter system crossing rate k_{ISC}.

Table 4.1: Photo-physical properties of the new flavin derivatives: fluorescence quantum yield, fluorescence lifetime, rate of radiative decay and the triplet state lifetime.

solvent	Flavin	Φ_F/%	τ_F/ns	k_{rad} / $10^7 s^{-1}$ [a]	τ_T / µs
MeCN	**5a**	40	7.0	5.7	0.450
	5b	9	1.6	5.6	0.436
	5c	2	0.02[b]	-	0.430
MeCN/H_2O 1:1	**5a**	27	5.5	4.9	1.29
	5b	5	0.9	5.6	1.19
	5c	1	0.03[b]		1.13

[a] calculated due to $k_{rad} = \Phi_F \cdot (\tau_F)^{-1}$. [b] beyond the time resolution of about 800 ps.

The absorption spectra of the new derivatives **5a-c** are similar to those of **RFTA** (Figure 4.5 (A)); the extinction coefficient of **RFTA** has an ε of 13450, the new derivatives have slightly lower values of about 9530 (**5a** and **c**) to 10140 (**5b**) for the highest maximum absorption in the blue range. The absorption band is also shifted slightly in the case of **5a** (10 nm to the blue) and slightly red shifted (5 nm) in the case of **5c**. All spectra of the new derivatives show a blue shift of the maximum in the near UV.

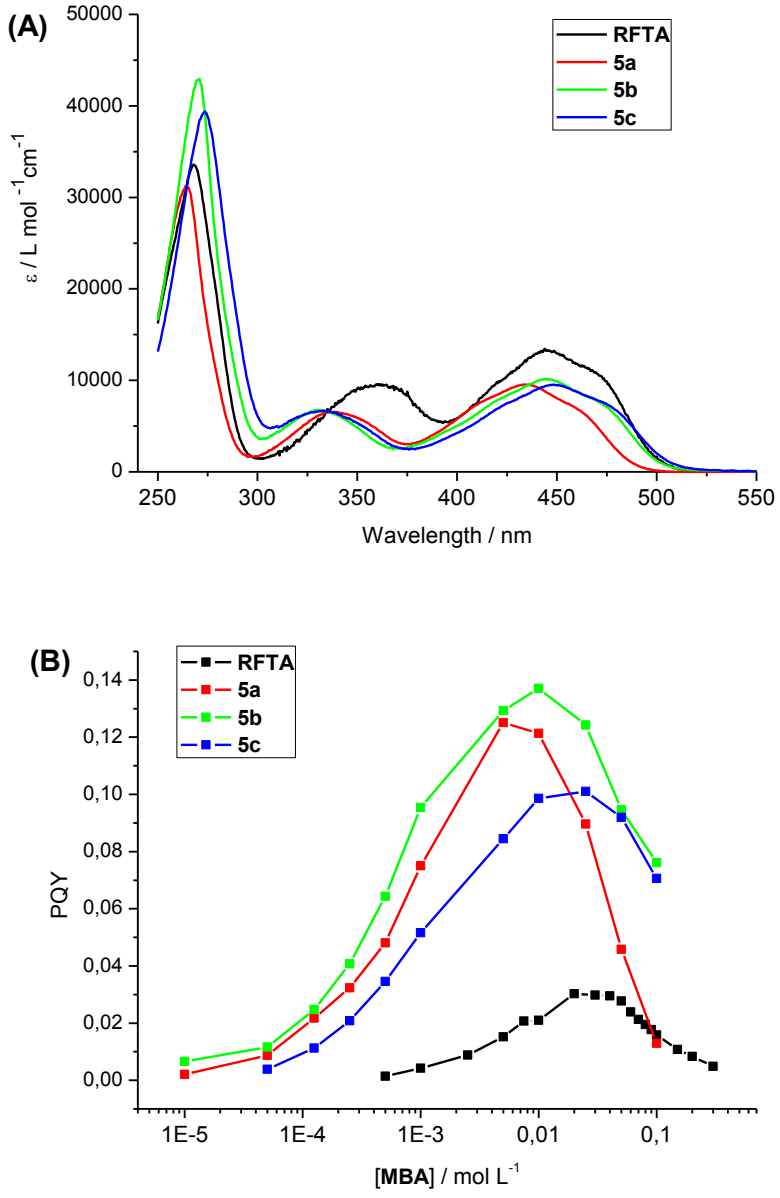


Figure 4.5: (A) Absorption spectra of the new flavin derivatives 5a-c in MeCN/H_2O 1:1 compared to RFTA. (B) Product quantum yield (PQY) of the model reaction (MBA to MBAld) for the different flavin derivatives in dependence of the MBA concentration.

The PQY dependence of the model reaction (**MBA** to **MBAld**) shows that the new derivatives **5a-c** are performing better than **RFTA** (see Figure 4.5 (B)). As expected, the bromine and iodine substituted derivatives **5b** and **c** show better PQYs than the unsubstituted flavin when higher concentrations of **MBA** are used, indicating the efficient ISC to the triplet state. Unfortunately, compound **5c** experiences such a good spin-orbit-coupling that also the back-ISC ($k_{r\text{-}ISC}$ in Figure 4.1) is enhanced so fast that the triplet is depleted over this pathway. This leads to a less effective conversion compared to the unsubstituted derivative **5a** at lower concentrations. Nevertheless the iodine compound **5c** is a better catalyst when higher concentrations are used (0.1 M) allowing diffusion controlled collision of the substrate and the catalyst in the triplet state.

The better performance of the simple 10-propylisoalloxazine **5a** compared to **RFTA** is remarkable. This may be explained because of different diffusion coefficients of these two derivatives, all of the reactive steps are diffusion controlled and hence this may have a big influence on the reaction kinetics. This could be clarified by DOSY-NMR experiments and comparing the diffusion coefficients of both flavins.

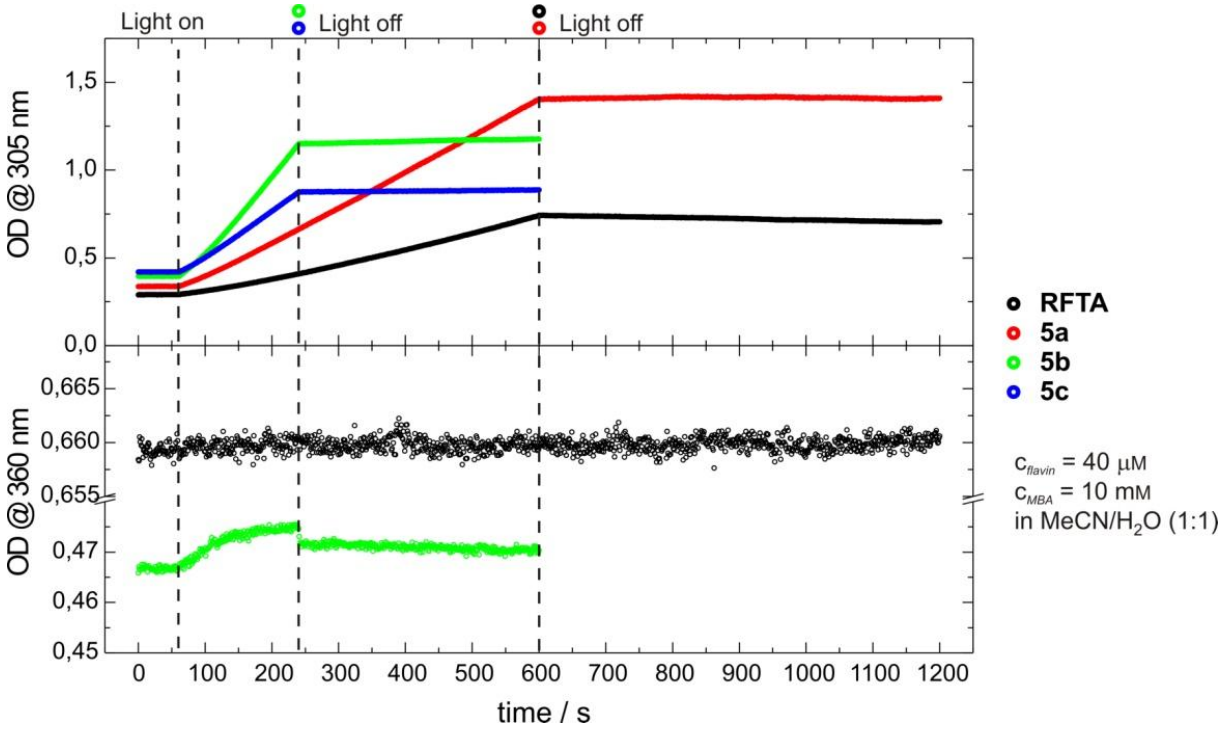


Figure 4.6: Comparison of reaction kinetics with teh new flavin photocatalysts. Top: Observation of the aldehyde band at 305 nm, bottom: observation of the band at 360 nm (flavin species).

Regarding the reaction kinetics with these flavins the same effects can be seen (see Figure 4.6): The slope of the aldehyde formation is increased by more than 100% if **5a** is used instead of **RFTA**, if the brominated derivative **5b** is used, the reaction is so fast that the light was switched off after only

three minutes, since the reaction with bromine is so fast, that after three minutes the dissolved oxygen is consumed and the flavin is not regenerated fast enough. The iodinated flavin **5c** behaves similar. Comparing the slopes of the signal increase, **5a** and **c** are 2.5 times steeper ($2 \cdot 10^{-3}$) and **5b** ($4 \cdot 10^{-3}$) is even more than 5 times steeper than the **RFTA** curve ($7 \cdot 10^{-4}$).*

Comparing the extinction of the flavin at 360 nm the **RFTA** seems to stay constant during the measurement with a substrate concentration of 10 mM. In contrast the substituted derivative **5b** shows an increase in extinction (**5c** behaves likewise, not depicted here). After switching off the light, one part of the gained extinction decreases very rapidly while another part decays very slowly. This means that two more species accumulated before; one of these is only visible under photo stationary conditions.

The quantum yields of this reaction have been measured additionally for absolute values using a 10 mM solution of **MBA** with 0.4 mol% of photocatalyst with an LED/solar-cell-based quantum yield determination apparatus as described before.[5b]

Table 4.2: Quantum yield measurements of the oxidation of *p*-methoxybenzyl alcohol by 7-substituted isoalloxazines compared to RFTA.[a]

Flavin	Quantum Yield Φ (%)	
RFTA	0.5	±0.2
5a	2.0	±0.7
5b	3.1	±0.5
5c	2.0	±0.3

[a] Conditions: $c_{alcohol}$ = 0.01 mol/L, c_{flavin} = 40 µmol/L in MeCN/H_2O 1:1, irradiation with 3 W LED (λ_{max} = 433 nm, 20 mW light at the sample), T = 25 °C, monitoring by GC with chlorobenzene as internal standard.

The determined absolute values (see Table 4.2) confirm the results from laser spectroscopy by showing the same trend. The new flavins are much better catalysts than **RFTA**, the iodinated flavin **5c** yields a quantum yield similar to the non-substituted 10-propylflavin **5a**. The 7-bromo-10-propylflavin **5b** shows a better reactivity since the inter system crossing is enhanced by the bromine heavy atom effect in the right balance to have a higher population of the triplet state and long enough triplet lifetimes for the reaction time scale. With iodine on the other hand (**5c**) the population of the triplet state is as well increased at first but also depleted very fast due to fast back-

* The slopes were determined *via* linear fit, for **5a** and **RFTA** over the first 300 seconds, for **5b** and **c** over the first 120 seconds of irradiation. The curves are not strictly linear but the linear fit was done to have an approximate value for comparison.

inter system crossing which is also enhanced by the heavy atom effect. These to effects compensate each other to give the same yield as the non-substituted derivative **5a**.

4.5. Conclusion

The influence of the water content in water/acetonitrile mixtures on the reaction of *p*-methoxybenzyl alcohol (**MBA**) to *p*-methoxybenzaldehyde (**MBAld**) catalyzed by riboflavin tetraacetate (**RFTA**) has been investigated with transient absorption spectra in the µs-time scale and the reaction kinetics have been recorded in the first 10 minutes. It is evident from these experiments that a water content of the solvent mixture of more than 75 vol% is the optimum solvent for such reactions. When low substrate concentrations are used the addition of acid (HCl) is also improving the reaction rate. This can be explained by a faster protonation of the flavin radical anion **RFTA**$^{\bullet -}$. The large effect of water is furthermore attributed to the prolonged lifetime of the triplet state in water compared to acetonitrile resulting in an increased probability of the triplet excited state of the flavin to react with the substrate molecule.

Flavin photocatalysts with propyl chain (**5a**) and bromine (**5b**) and iodine (**5c**) substituents in position 7 were prepared. These new flavins achieve much better quantum yields than **RFTA**, the brominated (**5b**) being the best catalyst for this reaction in terms of product quantum yield using the heavy atom effect to enhance the ISC (k_{ISC}) in the right balance for the reaction timescale.

From the synthetic point of view these analogues with improved triplet quantum yield are interesting, because they could enable the introduction of a substrate binding site. This is not possible in the classical system, because of the fast back electron transfer from the singlet state excited flavin; the efficient ISC might help to overcome this problem.

4.6. Materials and methods

Synthesis of new flavin derivatives

NMR spectra were recorded on a *Bruker Avance 300* (300.13 MHz for ^{1}H and 75.03 MHz for ^{13}C) spectrometer. Chemical shifts δ are given in ppm, using the residual solvent as internal standard. Coupling constants are reported in Hz. Mass spectra were obtained with *an Agilent 6540 Ultra High Definition (UHD) Accurate-Mass* with a Q-TOF LC/MS System (ESI-HR) and *ThermoQuest Finnigan* ***TSQ 7000*** (ESI-LR). ATR-IR spectroscopy was carried out on a *Biorad Excalibur FTS 3000* spectrometer, equipped with a *Specac Golden Gate Diamond Single Reflection* ATR-System.

Starting materials and reagents were purchased from *Sigma-Aldrich* or *Alfa Aesar* and were used without further purification. The solvents were purified and dried using standard procedures. Riboflavin tetraacetate was prepared according to a literature procedure.[9]

(2-Nitro-phenyl)-propyl-amine (2a):[10] 1,2-Dinitrobenzene **1** (3.36 g, 20 mmol, 1.0 eq) was dissolved in ethanol (10 mL) under nitrogen and *N*-propylamine (8.2 mL, 5.90 g, 100 mmol, 5.0 eq) was added. After refluxing for 18 hours water was added (100 mL) and the product was extracted with diethyl ether (3 times 80 mL). The organic layer was washed with saturated NH_4Cl (twice, 80 mL) and dried with $MgSO_4$. Evaporation of the solvent and drying yielded the title compound **2a** as brown oil (3.59 g, 19.9 mmol, 99%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.17 (dd, $^4J_{H3\text{-}H5}$ = 1.6 Hz, $^3J_{H3\text{-}H4}$ = 8.6 Hz, 1H, H3), 8.08 (br s, 1H, NH), 7.45-7.40 (m, 1H, H5), 6.85 (dd, $^4J_{H6\text{-}H4}$ = 0.8 Hz, $^3J_{H6\text{-}H5}$ = 8.7 Hz, 1H, H6), 6.65-6-60 (m, 1H, H4), 3.28 (td, $^2J_{H1'geminal}$ = 5.3 Hz, $^3J_{H1'\text{-}H2'}$ = 7.0 Hz, 2H, H1'), 1.78 (qt, $^3J_{H2'\text{-}H3'}$ =7.3, $^3J_{H2'H1'}$ = 7.3 Hz, 2H, H2'), 1.06 (t, $^3J_{H3'\text{-}H2'}$ = 7.4 Hz, 3H, H3'). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 145.8, 136.3, 127.1, 115.2, 113.9 (2C), 44.9, 22.4, 11.7.

(4-Bromo-2-nitro-phenyl)-propyl-amine (2b):[11] (2-Nitro-phenyl)-propyl-amine **2a** (1.80 g, 10 mmol, 1.0 eq) was dissolved in carbon tetrachloride (20 mL) and cooled to 0 °C. A bromine solution (0.51 mL, 1.60 g, 10 mmol, 1.0 eq) in carbon tetrachloride (10 mL) was added dropwise, with the temperature of the mixture maintained less than 10 °C. The mixture was stirred for 1 day at room temperature. The precipitate was then filtered off and washed with CCl_4 and water. The filtrate was then washed with aqueous $Na_2S_2O_3$ (10% solution, 50 mL), aqueous NaOH (10% solution, 50 mL), water (40 mL) and brine (40 mL). The organic layer was then dried with $MgSO_4$ and removal of the solvent gave the product **2b** as red solid (1.58 g, 6.1 mmol, 61%).^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.32 (d, 1H, $^4J_{H3\text{-}H5}$ = 2.4 Hz, H3), 7.48 (dd, 1H, $^3J_{H5\text{-}H6}$ = 9.2 Hz, $^4J_{H5\text{-}H3}$ = 2.4 Hz, H5), 6.76 (d, 1H, $^3J_{H6\text{-}H5}$ = 9.2 Hz, H6), 3.26 (t, 2H, $^3J_{H1'\text{-}H2'}$ = 7.1 Hz, H1'), 1.82-1.70 (m, 2H, H2'), 1.05 (t, 3H, $^3J_{H3'\text{-}H2'}$ = 7.4 Hz, H3').^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 143.7 (C1), 138.0 (C5), 131.1(C3), 128.0 (C2), 114.7 (C6), 105.3 (C4), 44.0 (C1'), 21.3 (C2'), 10.7 (C3').

(4-Iodo-2-nitro-phenyl)-propyl-amine (2c):[12] Crude 2-nitro-N-propylbenzenamine **2a** (1.8 g, 10 mmol, 1.0 eq) and KOAc (1.1 g, 11 mmol, 1.1 eq) were suspended in AcOH (10 mL) and ICl (2.0 g, 12 mmol, 1.2 eq) was added. The mixture was heated to 80 °C for 30 minutes, poured into water and extracted with diethyl ether (3 x 80 mL). The organic layer was washed with 10% Na_2SO_3 (2 x 50 mL), dried over $MgSO_4$ and the solvent was removed to yield (4-Iodo-2-Nitro-phenyl)-propyl-amine **2c** as red oil (2.95 g, 9.6 mmol, 96%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.45 (d, J = 1.9 Hz, 1 H, Aryl), 8.06 (bs, 1 H, NH), 7.61 (dd, $^3J_{H5\text{-}H6}$ = 9.0 Hz, $^4J_{H5\text{-}H3}$ = 2.1 Hz, 1 H, H5), 6.64 (d, $^3J_{H6\text{-}H5}$ = 9.1 Hz, 1 H, H6),

3.25 (td, $^{3}J_{H1'-H2'}$ = 7.1 Hz, $^{2}J_{H1'-H1'}$ = 5.3 Hz, 2 H, H1'), 1.81-1.69 (m, 2 H, H2'), 1.05 (t, $^{3}J_{H3'-H2'}$ = 7.4 Hz, 3 H, H3'). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 145.1 (C1), 144.3 (C5), 135.0 (C3), 132.7 (C2), 116.1 (C6), 74.2 (C4), 44.9 (C1'), 22.3 (C2'), 11.7 (C3').

General Procedure I: 4-substituted N¹-propylbenzene-1,2-diamines (3a-c)

The corresponding 4-substituted-(2-nitro-phenyl)-propyl-amine (1.0 eq) and tin(II) chloride dihydrate (5.0 eq) were suspended in ethanol (10 mL) under nitrogen atmosphere. After 30 minutes refluxing, water was added (200 mL) and the pH was set to 9 by 2 N Na_2CO_3 (ca. 50 mL). Extraction with diethyl ether (5 times 80 mL), treating of the organic layer with activated charcoal and drying with $MgSO_4$ was followed by removal of the solvent to yield the title compounds as oil. The oxygen sensitive compound was used without further purification.

(2-Amino-phenyl)-propyl-amine (3a): The reaction of (2-nitro-phenyl)-propyl-amine (1.26 g, 7 mmol) according to General Procedure I yielded the title compound as yellow oil (0.87 g, 5.8 mmol, 83%).

4-Bromo-N¹-propylbenzene-1,2-diamine (3b): The reaction of (4-bromo-2-nitro-phenyl)-propyl-amine (1.58 g, 6.1 mmol) according to General Procedure I yielded the title compound as orange oil (1.22 g, 5.3 mmol, 87%).

4-Iodo-N¹-propylbenzene-1,2-diamine(3c): The reaction of (4-iodo-2-nitro-phenyl)-propyl-amine (2.14 g, 7.0 mmol) according to General Procedure I yielded the title compound as yellow oil (1.46 g, 5.6 mmol, 80%).

General Procedure II: 4-substituted isoalloxazines (5a-c)

The corresponding crude 4-substituted *N*-propyl-benzene-1,2-diamine **3** (1.0 eq), boronic acid (10.0 eq) and alloxan monohydrate **4** (3.0 eq) were suspended in acetic acid under nitrogen. The mixture was stirred in the dark for 17 hours and then poured on water. The precipitate was collected by filtration and washed with water and diethyl ether. Drying of the residue yielded the title compounds as a solid.

10-Propyl-10H-benzo[g]pteridine-2,4-dione (5a): The reaction of *N*-propyl-benzene-1,2-diamine **3a** (0.25 g, 1.7 mmol) in acetic acid (10 mL) according to General Procedure II yielded the title compound **5a** as yellow solid (208 mg, 0.81 mmol, 48%). ^{1}H-NMR (300 MHz, DMSO-d6): δ (ppm) = 11.39 (s, 1H, H3), 8.13 (dd, 1H, $^{4}J_{H6-H8}$ = 1.3 Hz, $^{3}J_{H6-H7}$ = 8.1 Hz, H6), 8.01-7.91 (m, 2H, H7 and 8), 7.67-7.62 (m, 1H, H9), 4.57-4.51 (m, 2H, H1'), 1.82-1.69 (m, 2H, H2'), 1.03 (t, 3H, $^{3}J_{H3-H2}$ = 7.4 Hz,

H3').^{13}C-NMR (75 MHz, DMSO-d6): δ (ppm) = 159.8 (1C, C4), 155.7 (1C, C2), 150.4 (1C, C10a), 138.7 (C4a), 134.9 (C5a), 134.9 (C9a), 132.4 (C6), 131.8 (C8), 126.0 (C9), 116.4 (C7), 45.6 (C1'), 19.9 (C2'), 11.0 (C3'). FT-IR (ATR): ν [cm^{-1}] = 3190, 3073, 2882, 2810, 1722, 1709, 1688, 1678, 1672, 1666, 1649, 1641, 1612, 1584, 1562, 1547, 1535, 1531, 1512, 1503, 1493, 1485, 1462, 1452, 1404, 1358, 1277, 1246, 1211, 1179, 1103, 837, 770. ESI-MS (pos.): LR: m/z = 256.9 [M+H]$^+$. HR: calcd.: 257.1039, found 257.1034.

7-Bromo-10-propyl-10H-benzo[g]pteridine-2,4-dione (5b): The reaction of 4-bromo-N^1-propyl-benzene-1,2-diamine **3b** (1.2 g, 5.2 mmol) in acetic acid (20 mL) according to General Procedure II yielded the title compound **5b** as yellow solid (1.19 g, 3.55 mmol, 68%). ^{1}H-NMR (300 MHz, DMSO-d6): δ (ppm) = 11.45(s, 1H, H3), 8.34 (d, 1H, $^4J_{H6\text{-}H8}$ = 2.3 Hz, H6), 8.04 (dd, 1H, $^3J_{H8\text{-}H9}$ = 9.2 Hz, $^4J_{H8\text{-}H6}$ = 2.3 Hz, H8), 7.94 (d, 1H, $^3J_{H9\text{-}H8}$ = 9.2 Hz, H9), 4.53-4.48 (m, 2H, H1'), 1.79-1.66 (m, 2H, H2'), 1.01 (t, 3H, $^3J_{H3\text{-}H2}$ = 7.4 Hz, H3'). ^{13}C-NMR (75 MHz, DMSO-d6): δ (ppm) = 159.5 (1C, C4), 155.7 (1C, C2), 150.4 (1C, C10a), 139.9 (C4a), 137.0 (C5a), 135.6 (C9a), 133.3 (C6), 131.9 (C8), 118.5 (C9), 117.7 (C7), 45.8 (C1'), 19.8 (C2'), 11.0 (C3'). FT-IR (ATR): ν [cm^{-1}] = 3040, 2833, 1711, 1659, 1649, 1601, 1584, 1549, 1512, 1470, 1427, 1400, 1358, 1294, 1246, 1177, 1109, 910, 835, 818. ESI-MS (pos.): [M+H]$^+$. HR: calcd.: 335.0144, found 335.0140.

7-Iodo-10-propyl-10H-benzo[g]pteridine-2,4-dione (5c): The reaction of 4-iodo-N^1-propyl-benzene-1,2-diamine **3c** (1.4 g, 5.0 mmol) in acetic acid (20 mL) according to General Procedure II yielded the title compound **5c** as orange solid (1.37 g, 3.58 mmol, 72%). ^{1}H-NMR (300 MHz, DMSO-d6): δ (ppm) = 11.43 (s, 1H, H3), 8.46 (d, 1H, $^4J_{H6\text{-}H8}$ = 2.0 Hz, H6), 8.16 (dd, 1H, $^3J_{H8\text{-}H9}$ = 9.0 Hz, $^4J_{H8\text{-}H6}$ = 2.0 Hz, H8), 7.78 (d, 1H, $^3J_{H9\text{-}H8}$ = 9.1 Hz, H9), 4.51-4.46 (m, 2H, H1'), 1.78-1.66 (m, 2H, H2'), 1.01 (t, 3H, $^3J_{H3\text{-}H2}$ = 7.4 Hz, H3'). ^{13}C-NMR (75 MHz, DMSO-d6): δ (ppm) = 159.5 (1C, C4), 155.6 (1C, C2), 150.3 (1C, C10a), 142.5 (C4a), 139.5 (C5a), 139.4 (C9a), 135.8 (C6), 132.2 (C8), 118.4 (C9), 90.0 (C7), 45.6 (C1'), 19.8 (C2'), 11.0 (C3'). FT-IR (ATR): ν [cm^{-1}] = 3902, 3854, 3744, 3676, 3649, 2961, 2924, 2853, 2515, 2448, 2361, 2342, 2160, 2031, 2021, 1977, 1869, 1734, 1717, 1699, 1684, 1653, 1636, 1616, 1558, 1541, 1522, 1506, 1458, 1420, 1261, 1086, 868, 802. ESI-MS (pos.): LR: m/z = 382.9 [M+H]$^+$. HR: calcd.: 383.0005, found 382.9998.

Spectroscopy and analysis

Stationary absorption and emission spectroscopy

Absorption spectra were recorded with a Lambda 9a spectrometer (Perkin-Elmer) at 20±0.1 °C and Emission spectra at room temperature were measured with a steadystate fluorescence spectrometer (Jobin Yvon Fluorolog 3). Absolute luminescence quantum yields with estimated relative error of about 10% were determined with a commercially available system using an integrating sphere (Hamamatsu Photonics C9920-02).

Determination of the product quantum yield

The product quantum yield (PQY) for the flavin based photocatalytic oxidation from MBA to the corresponding aldehyde MBAld at different conditions was monitored by the change in extinction at 305 nm over continuous illumination with a single LED working at low intensity (current through LED I = 3 mA). This was possible because of two reasons. On the one side the extinction of the product MBAld is much stronger than the extinction of the MBA, and on the other side the concentration of the flavin derivative in question stays constant as long as enough oxygen is present in solution. These kind of experiments were performed in a self made cuvette holder which is temperature controlled by a Peltier element in the range between -10 to 60 °C equipped with two high power LEDs (Conrad, Luxeon III Emitter LXHL-PBO9, at 460 nm) orthogonal to the probe beam for excitation. The intensity of the LEDs can be adjusted by the current flowing through the LEDs in the range from 0.35 to 300 mA. In the range from 0.35 to 50 mA the intensity is linear to the current. The LEDs can also be pulsed by external or manual trigger with adjustable and reproducible pulse widths in the range between 30 to 1300 ms. Here only one LED is used at a typical current of 3 mA. The change in extinction at 305 nm was monitored with a Lambda 9a spectrometer (Perkin-Elmer). To prevent an overload of the PMT inside the spectrometer by the excitation light a band pass filter UG11 (Schott) was used in front of the detector. A quartz cuvette (2mm 10 mm) with four polished windows was used. The path length for probe was 10mm and for the excitation 2 mm. The sample volume was 300 mL to ensure that the complete sample is excited homogenously. The temperature was fixed to 20 °C.

For the comparability between the single measurements one has to consider that on the one side the absorption spectrum of the chromophores depend on the used conditions, e.g. different solvents, and that on the other side the absorption spectra of different chromophores differ to each other. Due to this the overlap integral between the normalized emission spectrum of the excitation

LED and the corresponding absorption spectra before illumination are calculated. These measures are proportional to the number of absorbed photons per time increment Δt_i. Subsequently, the overlap integrals of all measurements i are normalized to the highest value so that i correction factors $f_i = \{0 \leq f_i \leq 1\}$ are generated. The illuminationtime increment Δt_i was then corrected *via* $\Delta t_{corr,i} = f_i \Delta t_i$. Finally the initial slope of the data (first 2 min.) was used as a measure which is proportional to the PQY of each system under investigation. Previously, the PQY at 2mM of RFTA and 20 mM of MBA was determined to be 3% with a different method.[5b] They followed the formation of MBAld after a defined illumination time with 20.2 mW at 443 nm by gas chromatography. The values determined in this work were scaled to a value of 3% at 20 mM of MBA in order to receive absolute numbers.

Time resolved emission spectroscopy

The time resolved emission data were measured with a self made TC-SPC apparatus in a reversed Start-Stop method. For excitation a NanoLED-450 (Horiba Jobin Yvon) with an emission maximum at 443 nm and a pulse duration of about 1.1 ns was used. As detection system a combination of a monochromator and a photo multiplier tube (PMT) R928 (Hamamatsu) wasused. The PMT is cooled by a peltier element to -25 °C. The used constant fraction discriminators (CFD) TC 455 (Tennelec) have a jitter less than 80 ps. The optical density over 10 mm at the excitation wavelength of 443 nm was adjusted to 0.2. An orthogonal configuration for excitation and detection was used.

Microsecond transient absorption measurements

For microsecond transient absorption, the sample was excited with 8-10 ns pulses at 450 nm from a 10 Hz Optical Parametric Oscillator (OPO, Continuum) pumped by the third harmonic of a Nd:YAG laser (Surelite II, Continuum). A pulsed 150 W Xe flashlamp (MSP-05, M¨uller Elektronik-Optik) was used as probe light and the full time range (5-20 ms) was monitored at once with a streak camera (C7700, Hamamatsu Photonics). A fused silica flow cuvette with 2 mm of optical path length for excitation and 10mm for probe light was used. Including the storage vessel and the peristaltic pump, the overall volume was about 5 mL. The control of the peristaltic pump was included into the timing of the measuring process. So the sample was exchanged stepwise in a laminar flow between each individual measurement. The excitation light was focused into the sample with a cylindrical lens (f = 150 mm), and the pulse energy was adjusted to about 10 - 0.3 mJ per pulse at the sample. Mechanical shutters were used to select pump and probe pulses. The probe light with a very flat intensity profile of 1 ms duration was refocused three times by a series of toric mirrors: on a

mechanical shutter to block the continuous light from the Xe flashlamp, on the sample cell, and on the entrance slit of the imaging spectrograph (Bruker 200is, grating 100 grooves per mm) in front of the streak camera. The streak camera converts the coupled spectral and temporal information into two-dimensional images of the intensity distribution of the probe white light. Each transient absorption data set was calculated from four images taken with a frequency of 0.5 Hz: An image (D_{FL}) with both flash lamp and laser, an image (D_0) without any incoming light and an image (D_F) only with the flash lamp. Results represent the average of 100 individual measurement sequences with a time window of 10 ms and a time resolution of 20 ns. The transient absorption is calculated from these data as $A(t,\lambda) = \log\left(\frac{D_F - D_0}{D_{FL} - D_0}\right)$.

Femtosecond transient absorption measurements

For femtosecond transient absorption spectroscopy a Ti:sapphire amplifier system (CPA 2001; Clark MXR) was used to pump a noncollinear optical parametric amplifier tuned to 480 nm. The pulses were compressed to ~ 50 fs and attenuated to 400 nJ at the sample position. By focusing another part of the Ti:sapphire laser into a moving CaF2disk (4mm thickness), a probe white light was generated ranging from below 300 nm to 750 nm. A computer controlled delay line was used to set pumpprobe delays up to 1 ns. The pump and probe pulses were focused into the sample to spot sizes of 120 µm and 30 µm FWHM using spherical mirrors. After the interaction in the sample, the probe beam was dispersed with a fused silica prism and detected with a photodiode array of 512 pixels. The relative polarizations between the pump and probe were set to the magic angle (54.71) by a half-wave plate in the pump-beam path. The ~1.5 ps chirp of the white light was corrected for prior to the data analysis using the coherent artifact as an indicator for time zero at each wavelength. Throughout the probe range, the spectral resolution was better than 100 cm^{-1} and the temporal resolution was better than 150 fs. For the experiments in MeCN/H2O (50:50-v/v) solution, the temperature of the sample was set to 300 K. A flow cell with 1mm thickness was used and the flavin concentration was 0.5 mM. The measurements in pure MBA and in MeCN/DMSO (98:2-v/v) were performed with a flow cell of 120 µm thick-ness at ambient temperature. Here, the flavin concentration was 2 mM.

4.7. References

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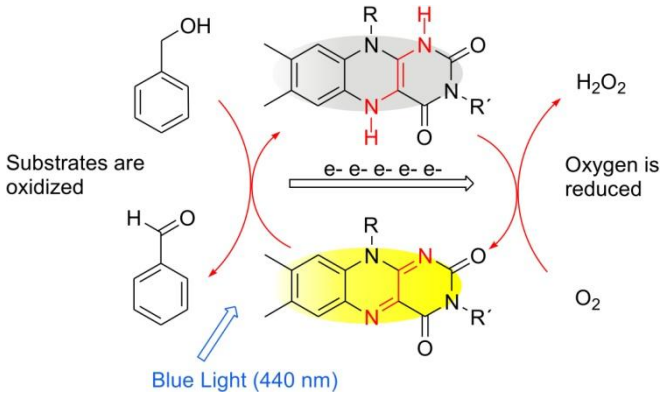
5. Synthesis and Photophysical Properties of Phenanthroline-Flavin Hybrids

5.1. Introduction

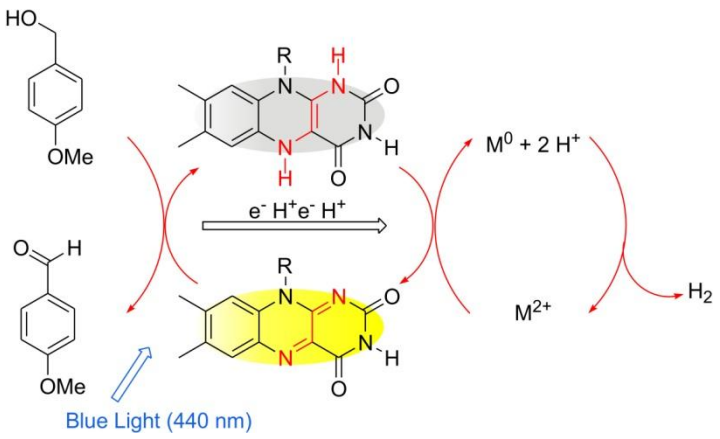
Photooxidation reactions catalyzed by flavin were intensively investigated in the last years. All these reactions have in common, that they use oxygen to regenerate the catalyst, i.e. oxygen is reduced by the reduced form of flavin (see Scheme 5.1).



Scheme 5.1: Catalysis principle of oxidation reactions with flavins.

Synthetic applications for reductions with flavins are still less investigated but are also very interesting since they are catalyzed in nature by flavin coenzymes, too. One way of using flavins for reductions is to exclude oxygen in the reaction shown above and reduce a substrate instead. The reduction power could even be increased by irradiating additionally with UV light (360 nm) where the reduced form of the flavin is absorbing. But first examples of such reactions[1] show little applicability and bad reproducibility.[2] However, the presence of an electron mediator could enhance the electron transport from the flavin to a reducible substrate, e.g. a metal salt, as it has been shown before for other photocatalytic reactions.[3]

To investigate this, a series of experiments has been performed with riboflavin tetraacetate as photocatalyst and different metal salts as additives using the reaction of *p*-methoxybenzyl alcohol to *p*-methoxybenzaldehyde under anaerobic conditions as model reaction. The conversion of the alcohol was compared with the same experiment under aerobic conditions (see Table 5.1). When more aldehyde is formed, the flavin should be reoxidized by the metal salt which can produce hydrogen from the protons and electrons of the aldehyde (see Scheme 5.2).



Scheme 5.2: Proposed principle of direct hydrogen production from benzyl alcohols *via* flavin photocatalysis with metal salts as co-catalysts.

Table 5.1: Oxidation of *p*-methoxybenzyl alcohol without oxygen.[a] Different metal salts are tested to produce hydrogen from the alcohol instead of hydrogen peroxide from air.

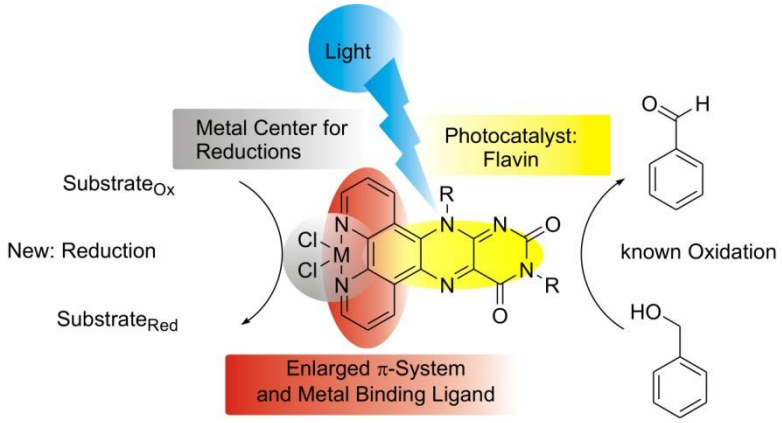
Entry	Metal Salt	Conversion of *p*-Methoxybenzyl Alcohol [%][b]
1	K_2PtCl_4	13.2
2	$PtCl_2(dmso)_2$	9.4
3	$Pd(OAc)_2$	7.6
4	-	40.5
5	-[c]	59.8

[a] degassed solution with 0.01 M *p*-methoxybenzyl alcohol in MeCN/H_2O 1:1, 0.4 mol% riboflavin tetraacetate and 0.4 mol% metal salt, irradiation for 1 hour; [b] determined *via* GC; [c] with oxygen from the air.

The results show that the applied degassing procedure was too simple and not good enough to have an oxygen free atmosphere. The comparison between the degassed reaction and the open air reaction shows only a difference of about 20%. Surprisingly the reaction seems to be impeded in the presence of metal salts; another remarkable effect is the prevention of flavin bleaching by the addition of the metal salts, after 1 hour both metal free solutions were completely bleached while the others maintained yellow fluorescing. These observations could be explained by the coordination of the metal centers in a position of the flavin that is needed for the photocatalysis.

Since the metal salt addition did not seem to enable the oxidation with hydrogen production as side reaction, a new catalyst concept was conceived: A phenanthroline-flavin hybrid molecule as a ligand should enable fast intramolecular electron transfer to a coordinated metal center (see Scheme 5.3). Furthermore the enlarged π-system should enable faster electron transfer as it is used similarly in other systems as a bridge between a metal based photocatalyst and a catalytically active metal

center on the other side.[4] The reduction on the metal center can then be a dark reaction which is driven by the known oxidative half-reaction on the other side of the catalytic cycle.

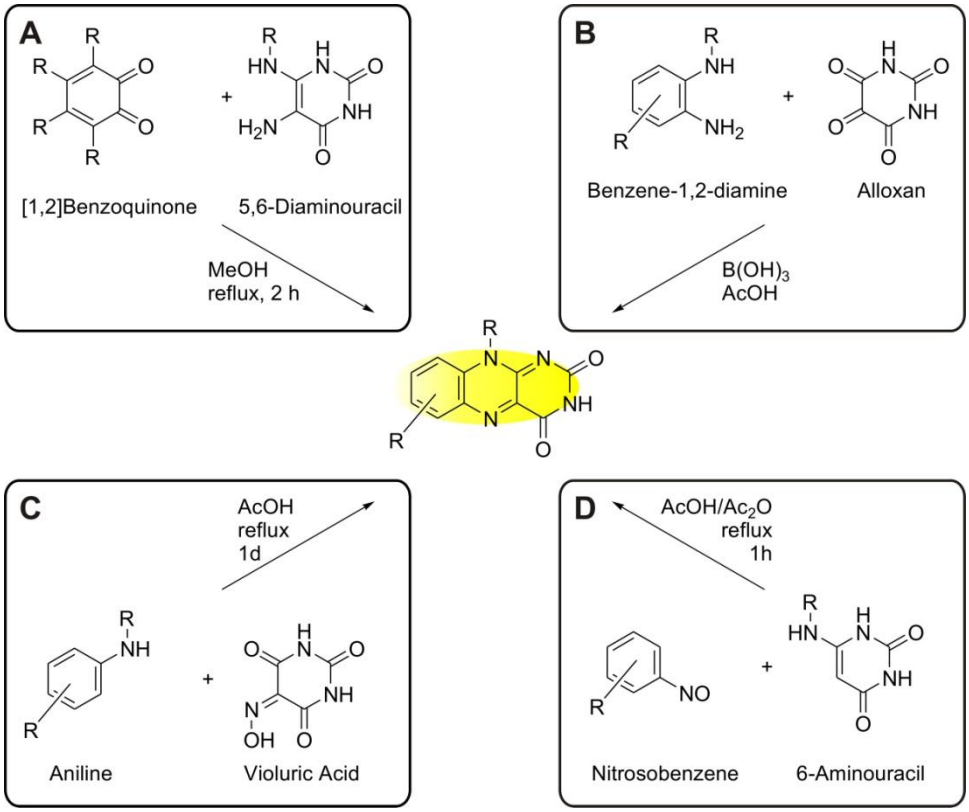


Scheme 5.3: Principle of phenanthroline-flavin hybrids as new photocatalysts for reductions.

5.2. *Synthesis of Flavins in General*

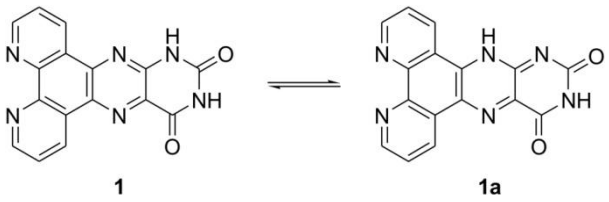
There are four different ways to synthesize the flavin core in principle: The most common method is the condensation of alloxan with the corresponding diamine catalyzed by boronic acid, also known as the *Kuhn* synthesis (Method **B** in Scheme 5.4),[5] the three other methods use the same mechanism with different combinations of carbonyls and amines.

King et al. discovered method **C** in 1948[6] which was then only used twice by *Hemmerich et al.* in 1959[7] and by *Kasai et al*. in 1987[8] and finally resurfaced in the last years in some patents.[9] This seldom application is due to the strong dependence on the substitution of the corresponding aniline.[7] Method **D** enables reaction pathways where the classical *Kuhn* synthesis is not appropriate; such as the synthesis of flavins with bulky substituents[10] and for the inclusion of flavins in a macrocycle,[11] for example. Method **A** has only been used with 1,10-phenanthroline-5,6-dione as the dione to produce the ligand pteridino[6,7-*f*][1,10]phenanthroline-11,13(10*H*,12*H*)-dione **1** (ppd) (see Scheme 5.5).



Scheme 5.4: Four ways to synthesize the flavin core - different starting materials are condensed to form the isoalloxazine.

This ligand is very similar to the structure we wanted to use for the new catalyst system. The only difference is that it is not substituted at position 10 of the flavin core and so there are two possible tautomeric forms: The alloxazine **1** and the isoalloxazine **1a**. Its bad solubility prevents it from the use in homogeneous photocatalytic applications. Hence, we wanted to introduce a sidechain at the flavin 10-position to improve the solubility. This was not possible directly from ppd **1**, because of low solubility, stability towards bases and the unpredictable changing between the two tautomeric forms resulting in steadily changing properties like color, polarity and solubility.

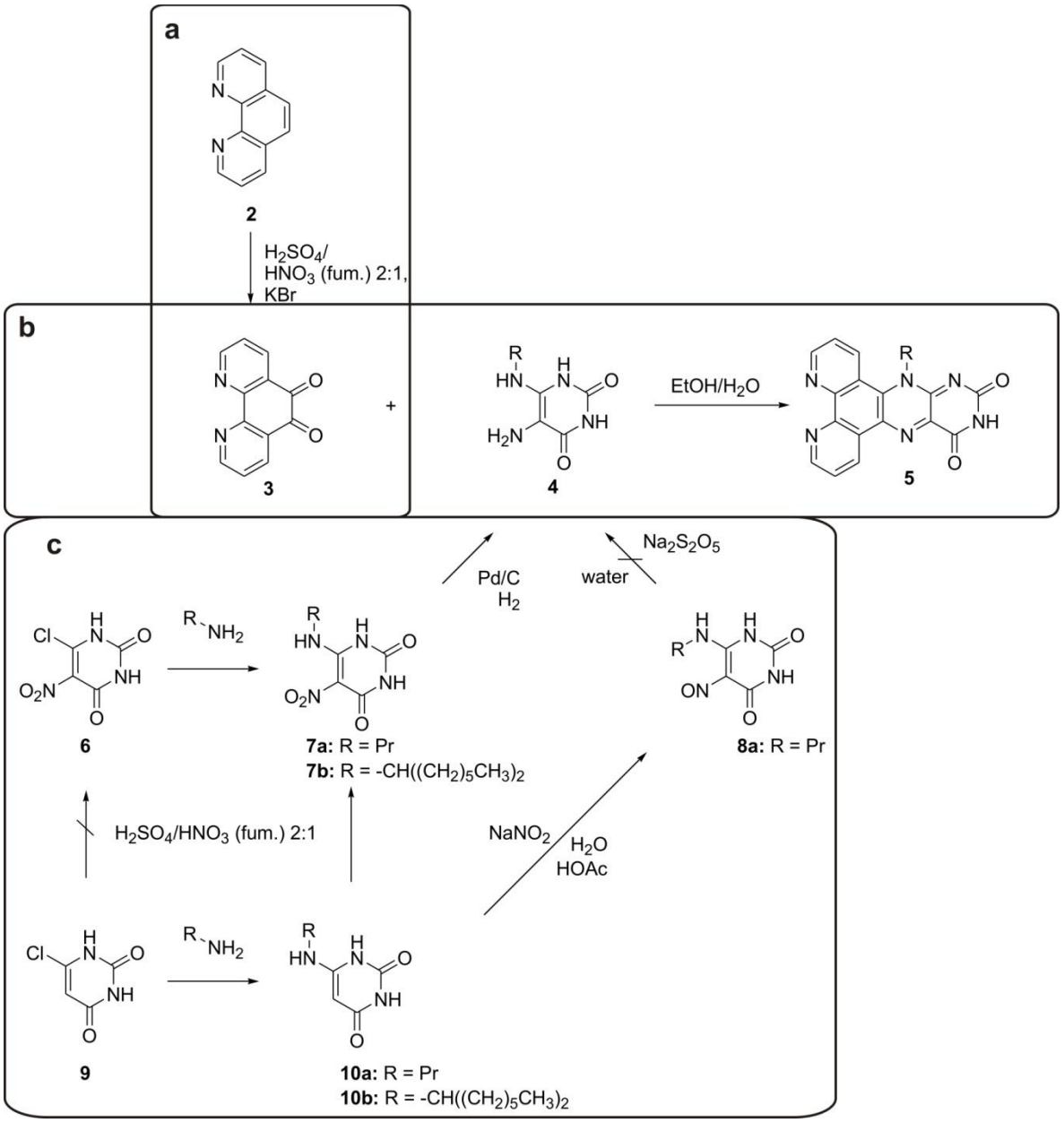


Scheme 5.5: Structure of the ligand pteridino[6,7-*f*]-1,10-phenanthroline-11,13(10*H*,12*H*)-dione (ppd) with its two tautomeric forms: The alloxazine on the right and the iso-alloxazine on the left.

5.3. Synthesis of Phenanthroline-Flavins

Method A*

The synthesis *via* method **A** (see Scheme 5.4) suggested itself for substituted ppd-derivatives **5** because it worked for simple ppd **1**. The method is depicted in detail in Scheme 5.6.



Scheme 5.6: Synthesis of the phenanthrolin-flavin 4 *via* method A (see Scheme 5.4).

* The investigation of the synthesis *via* method **A** (see Scheme 5.6) was performed together with Tomás Slanina and Zlatko Paric under supervision of S.K.

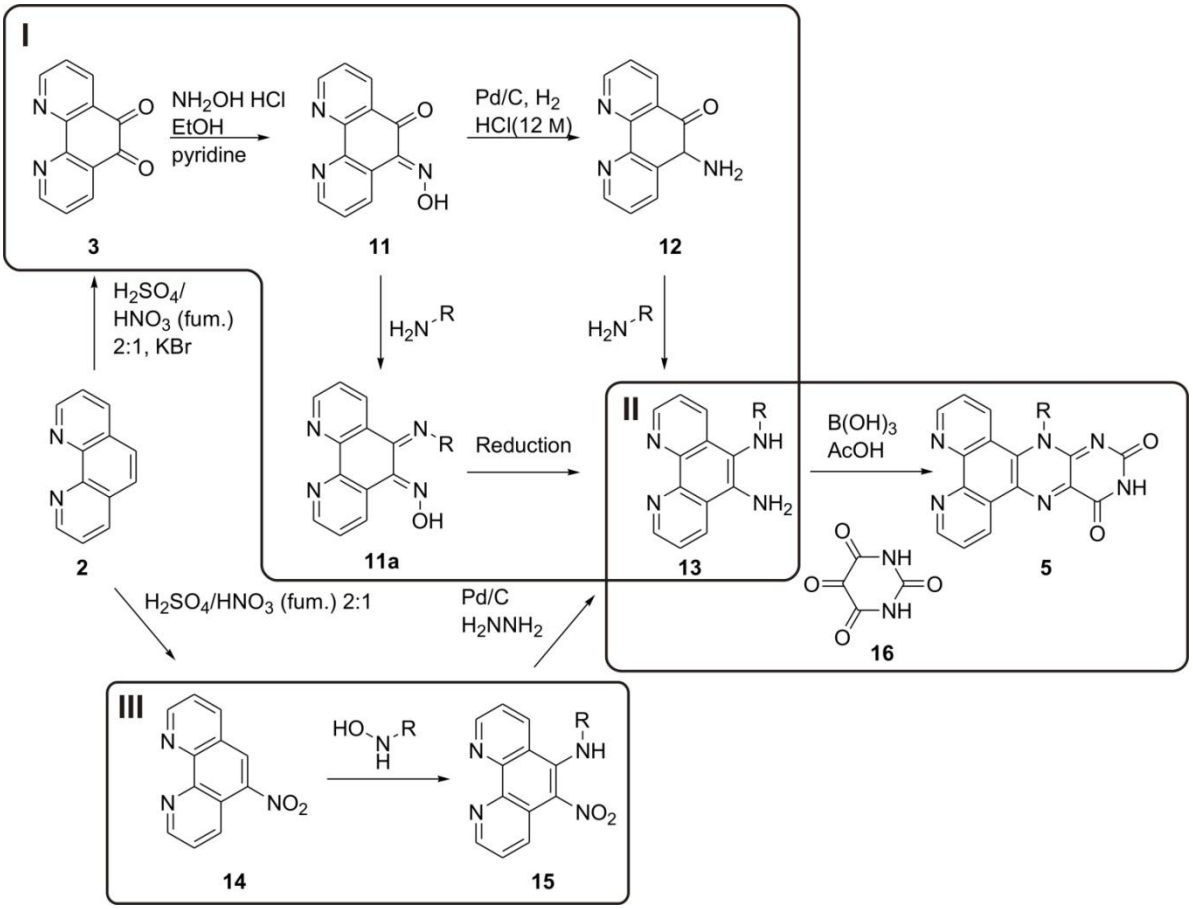
The [1,10]phenanthroline-5,6-dione **3** (dipyridobenzoquinone, dpq) is easily accessible *via* oxidation of phenanthroline **2** with nitrosulfuric acid and KBr (reaction **a** in Scheme 5.6).[12] The introduction of a substituent in the target compound **5** requires another starting material **4** than the -ppd synthesis, a 5,6-diaminouracil with only one substituent at the amine in position 6. The best method to introduce only one alkyl chain in a diamine is *via* the corresponding alkyl-amino-nitro-compound, i.e. compound **7** in this case (synthesis **c**, left side, in Scheme 5.6). One way to obtain compound **7** is described in literature *via* 6-chloro-5-nitrouracil **6**.[13] Unfortunately the nitration of 6-chlorouracil **9** suffered from bad reproducibility and was difficult to handle because of the very instable product **6**. Therefore the strategy was changed to the inverted sequence of reactions. The amination of chlorouracil **9** was easy with moderate to good yields depending on the alkyl chain. The nitration of the so obtained 6-aminouracil **10** was more difficult because of the high polarity of the product **7**. It was impossible to extract product **7** from the aqueous solution into any organic solvent. The water phase was therefore evaporated to dryness and the residue was then extracted with methanol several times, sonicated, decanted and filtered to yield 5-nitro-6-(alkylamino)uracil **7**. In the case of 6-propylamine derivative **7a** the yield was good (88%), tridecan-7-amine derivative **7b** could only be isolated in bad yields and as a mixture with salts.

The synthesis of the alkyl substituted diamine **4** was also tried *via* nitroso-compound **8a** which was obtained by the reaction of **10a** with sodium nitrite[14] but the subsequent reduction with sodium disulfite did not lead to the desired product (synthesis c, right side, in Scheme 5.6). The condensation reaction (**b** in Scheme 5.6) was done according to the lumazine synthesis of *Eugster et al.*.[15] The reaction of *N*-propyldiaminouracil **4a** led to a precipitate that could not be characterized due to its insolubility. In case of tridecan-7-amine derivative **4b** the reaction did not lead to the desired product, only half condensation took place (as determined by NMR spectroscopy) what can be explained by the sterical demand of the substituent.

Since the phenanthroline-flavin **5** could not be obtained with method **A** (Scheme 5.4) the strategy was changed and the other methods were taken into account. Since there is no synthesis known for the 5-nitroso-phenanthroline which would be the starting material for method **D**, this method was excluded.

Method B[†]

Method **B** (see Scheme 5.4) would need an *N*-alkylated 5,6-diamino-phenanthroline **13** as starting material for the *Kuhn* synthesis (Reaction **II** in Scheme 5.7).



Scheme 5.7: Synthesis of phenanthroline-flavin 5 according to method B (see Scheme 5.4).

There are two possible routes to get there: Route **A** (Scheme 5.7) starts again from phenanthroline **2**, proceeds *via* oxidation to the dione **3** like described above (**a** in Scheme 5.6). Dione **3** is then converted to the monooxime **11** by adding one equivalent of hydroxylamine hydrochloride and recrystallizing carefully from ethanol to remove the sideproduct, the dioxime, and the starting material (for this route see **I** in Scheme 5.7).

The monooxime **11** can then be reduced by 5% palladium on active charcoal in hydrogen atmosphere with a yield of 67%. The addition of hydrochloric acid helps to dehydrate the oxime and prevents self-condensation of the product.

[†] Method **B** (see Scheme 5.7) was investigated together with Tomás Slanina. The pathway *via* the oxime **11** (I in Scheme 5.7Scheme 5.7) was done by T.S., the route *via* nitrophenanthroline **14** (III in Scheme 5.7) was investigated by S.K.

The 1,10-phenanthroline-5,6-diamine **13** has been synthesized by a condensation reaction with propylamine as solvent under nitrogen atmosphere. It is assumed that it is unstable towards oxidation and therefore the reaction mixture was only evaporated to remove non-reacted propylamine and used without purification in the condensation with alloxan **16**.[16] The product of the condensation was again so insoluble that it could not be characterized, as already shown by the condensation of **4a** with the phenanthroline-5,6-dione **3** (**b** in Scheme 5.6) which yielded the same product.

Another pathway to the diamine **13** would be the direct reaction of the monooxime **11** with propylamine and afterwards a selective reduction of the oxime in presence of the imine. The imine formation works with a yield of 97% but the selective reduction was not yet investigated.[17]

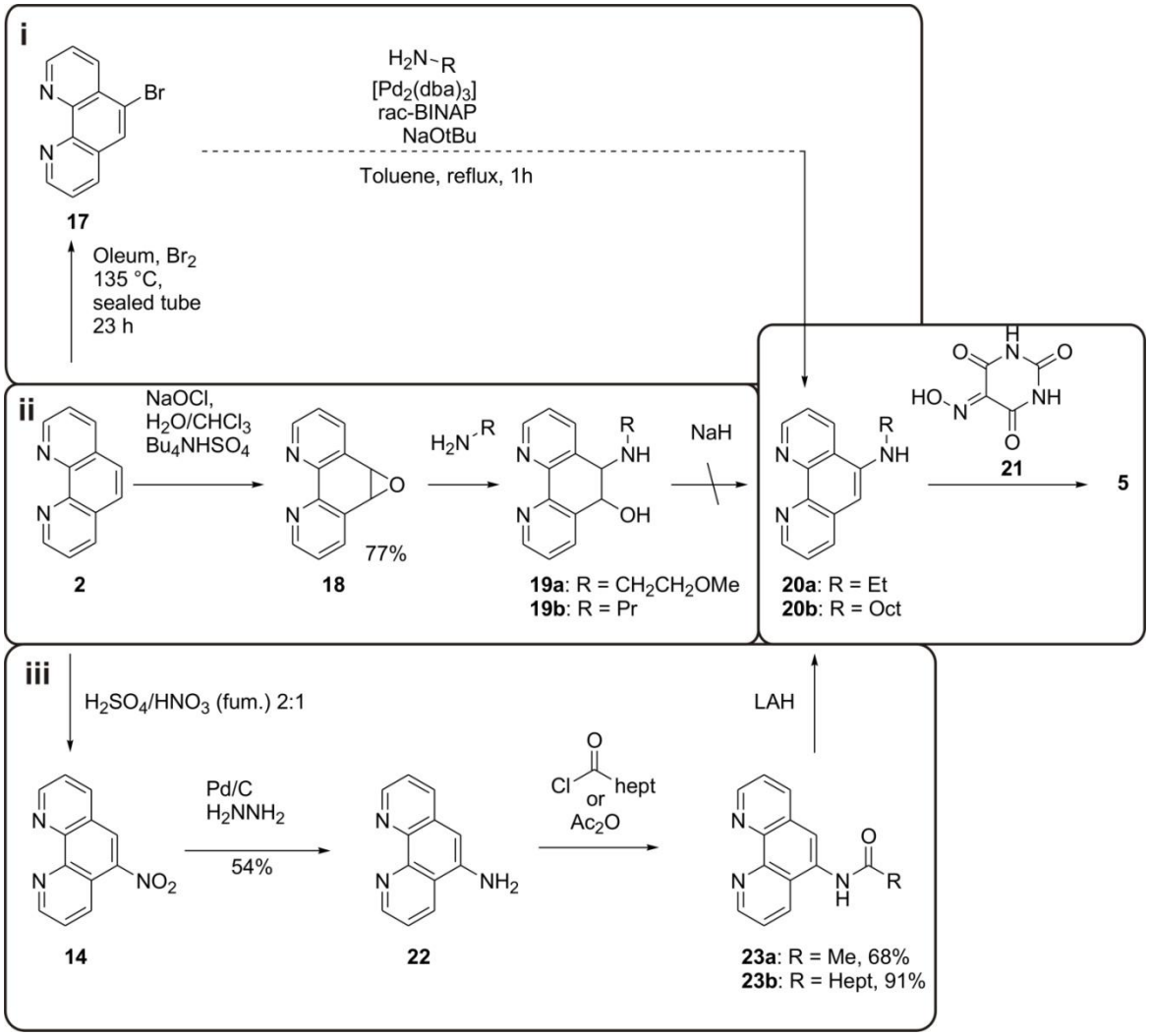
The third way to synthesize the diamine **13** is described in the literature with poor yield (33%) and only for the parent system without substituents (see **III** in Scheme 5.7):[18] The reaction of 5-nitrophenanthroline **14** with hydroxylamine to yield the 5-alkyl-amino-6-nitro-phenanthroline **15**. This route was also tried, but did not lead to the desired product **15** which could have been reduced to the desired diamine **13**.

Method C‡

Since the reactions in method A were very sensitive to the reaction conditions and difficult to repeat with any other substituent the method was changed to a method **C** (Scheme 5.4). With this method a 5-(alkylamino)-phenanthroline has to be synthesized as starting material. This is conceivable in three feasible ways (Scheme 5.8):

i. Synthesis of 5-bromo-phenanthroline **17** and subsequent *Buchwald* coupling.
ii. Oxidation of phenanthroline **2** to the epoxide **18**, opening with the desired amine to the 5,6-dihydrophenanthroline **19** and finally elimination to rearomatize the phenanthroline.
iii. Nitration of the phenanthroline **2** as described above, reduction to the primary amine **22**, followed by peptide bond formation to the amide **23** and reduction to the desired product **20**.

‡ Method **C** was investigated together with Tomás Slanina. T.S. investigated the bromination pathway (i in Scheme 5.8) under supervision of S.K.; all other experiments were done by S.K..

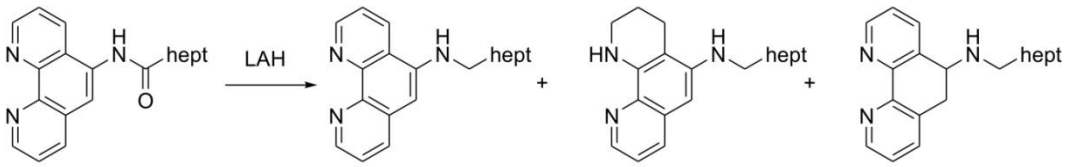


Scheme 5.8: Synthesis of 5-(alkylamino)-phenanthroline 20 as starting material for method C: Condensation with violuric acid 21.

The bromination of phenanthroline (route **i**) was tried according to the method of *Hissler et al.*[19] but the product could not be obtained in more than 50% yield and it was difficult to separate from the starting material. Because of the bad yield and the harsh conditions of this reaction the method was abandoned.

The second attempt to synthesize 5-(alkylamino)phenanthroline **20** (route **ii**) is described in literature with other substituents as amine components.[20] The epoxidation of phenanthroline **2** reported by Moody, Paris *et al.*[20a, b] depends strongly on the pH value of the reaction mixture and is therefore also not easily reproducible. The opening of the epoxide with propylamine or 2-methoxy-ethylamine yielded **19a** and **b**, respectively, by using the conditions reported in literature[20]. The last reaction step, the elimination of the hydroxygroup *via* sodiumhydride was not possible with the conditions given by Moody, Riklin *et al.*[20a, 20c].

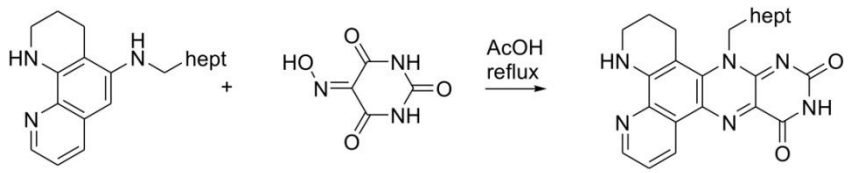
Finally the most classical organic synthesis (route **iii**) was leading to the product: The nitration and reduction to the primary amine **22** reported in literature[21] were well reproducible in good yields and the amide formation was possible using acetic anhydride or octanoyl chloride. The reduction with lithium aluminum hydride (LAH) performed under standard conditions yielded the amines **20** but the equivalent of LAH has to be added carefully to avoid reduction of the phenanthroline: If more equivalents of LAH are added or the solvent is not absolutely dry the phenanthroline can be over-reduced in a sidereaction by the hydrogen which is produced *in situ* either to the 1,2,3,4-tetrahydroderivative **24** or the 5,6-dihydroderivatitve **25** (see Scheme 5.9). This mixture of products is difficult to separate und purify.



23b **20b** **24** **25**

Scheme 5.9: Reduction of octanoic acid [1,10]phenanthrolin-5-ylamide 23b with LAH: Different products depending on the amount of LAH.

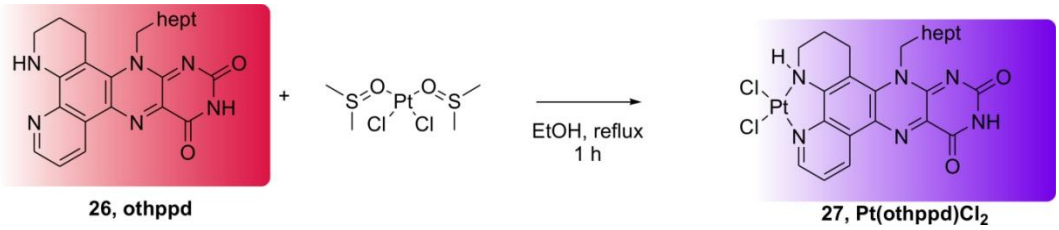
Finally the condensation of the primary amine **20a** with violuric acid **21** yielded - as expected from the propyl derivative synthesis – an insoluble precipitate while the reaction of **20b** under the same conditions did not lead to the expected product. When the crude mixture of reduction products (Scheme 5.9) was used instead of the pure amine **20b** the 1,2,3,4-tetrahydrophenanthroline derivative **26** (see Scheme 5.10) could be isolated as a pink solid which is orange fluorescing in solution. The purification *via* column chromatography (DCM/MeOH 10:1) was not possible but preparative TLC treatment yielded the pure product which was only separable from TLC material by dissolution and ultra-sonification in methanol. Flavin derivative **26** is expected to be a good ligand and was therefore tested for photocatalysis and metal complexation. The compound 9-**o**ctyl-6,7,8,9-**t**etra**h**ydro**p**teridino[6,7-f]-1,10-**p**henanthroline-11,13(5H,12H)-**d**ione **26** will be called **othppd** as a ligand from now on.



24 **21** **26, othppd**

Scheme 5.10: Final reaction leading to a flavin ligand with appropriate properties for catalysis.

The complexation (see Scheme 5.11) of Pt^{2+} was easily possible by refluxing $Pt(dmso)Cl_2$ in ethanol with a stoichiometric amount of **othppd** yielding a dark violet solution of the corresponding complex **27, Pt(othppd)Cl_2**.



26, othppd

27, Pt(othppd)Cl_2

Scheme 5.11: Complexation of platinum with the new ligand: The pink starting material (orange in solution) changes to violet in the complex.

5.4. Photophysical properties

The flavin ligand and its platinum complex were investigated spectroscopically. The absorption maxima of the new compounds are shifted far to the red (see Figure 5.1); **othppd** has an absorption maximum of 510 nm, i.e. a shift of 70 nm compared to **RFTA**, the absorption maximum of the metal complex is shifted even further to 567 nm.

While the flavin derivative **othppd** shows a bright fluorescence with a maximum of 556 nm the metal complex is not fluorescing at all. This could be helpful for the flavin photocatalysis reaction mechanism, since the fluorescence is usually a competing process to photocatalytic reactions that need the triplet state of the flavin as active species.

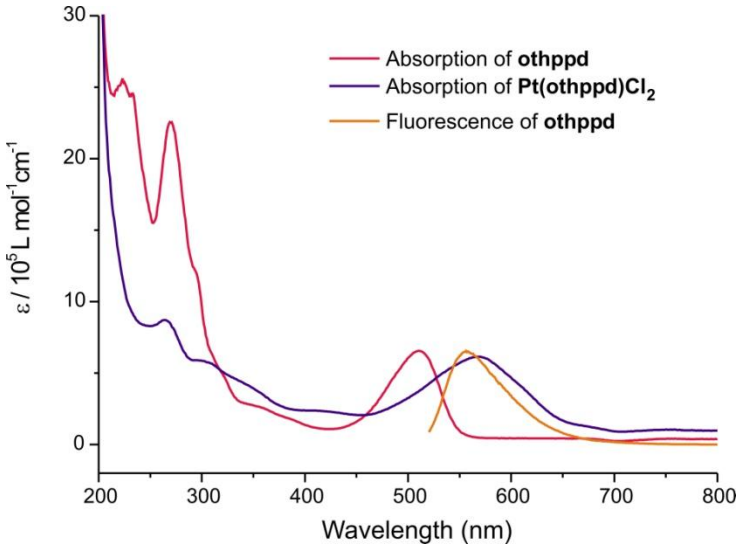


Figure 5.1: UV/Vis spectra of the new ligand and its platinum complex and fluorescence spectrum of the ligand (the complex is not fluorescent).

5.5. Photocatalysis with the New Flavin Derivatives

The model reaction was carried out under similar conditions as before but the solvent had to be changed to methanol instead of acetonitrile/water 1:1 for solubility reasons. The control experiments with **RFTA** and with metal salt addition were therefore repeated in methanol, too, for a better comparability. It is known that the water content of the solvent mixture is crucial for the yields[22] and therefore the irradiation time was prolonged to two hours to have high enough yields in methanol. The new derivatives were irradiated at 530 nm where they both absorb (cf. Figure 5.1). The results are shown in Table 5.2.

Table 5.2: Model reaction of *p*-methoxybenzyl alcohol to *p*-methoxybenzaldehyde in methanol: Comparison of RFTA with the new flavin ligand (othppd) and the corresponding Pt-complex.

Entry	Flavin	Additive	Wavelength [nm]	Conversion of *p*-Methoxybenzyl Alcohol [%][b]
1	**RFTA**	-[c]	440	65
2	**RFTA**	-	440	49
3	**RFTA**	$PtCl_2(dmso)_2$ (0.4 mol%)	440	19
4	**othppd**	-	530	<1
5	**Pt(othppd)Cl_2**	-	530	<1

[a] degassed solution with 0.01 M *p*-methoxybenzyl alcohol in MeOH, 0.4 mol% flavin derivative, irradiation for 2 hour; [b] determined *via* GC; [c] with oxygen from the air.

The reaction with **RFTA** works as good as in the acetonitrile/water 1:1 mixture (cf. Table 5.1 Entries 4 and 5, Table 5.2 Entries 1 and 2). In the case of simple metal salt addition (Table 5.2, Entry 3) the reaction is in methanol less impeded as in the previous solvent mixture. Interestingly, the flavinoide compound **othppd** leads only to traces of the product (Entry 4) and a reaction with the platinum complex **Pt(othppd)Cl_2** (Entry 5) has the same result.

5.6. Electrochemical Properties

The cyclic voltammogram of the new derivatives was measured in DMF in the window from +1 to -2.5 V and compared to **RFTA** (see Figure 5.2). The ligand **othppd** can be reduced in several steps but they are irreversible and the voltammogram does not show very distinct peak potentials. A reduction peak can be seen at -1.47 V,[§] small steps at -1.92 V, -2.27 V and -2.47 V and two definite reductions take place at -2.71 V and -2.86 V. The potential at -3.00 V belongs probably not to **othppd** since it is observed in the baseline, too. The six reduction potentials can be explained as follows: First a

[§] All potentials here are given as anodic peak potential vs. the ferrocene/ferrocenium half wave potential because of the irreversibility of the reductions.

reduction of the flavin diimine moiety with two electrons takes place because the first potentials are similar to those of **RFTA** (-1.27 V and -1.95 V), then the phenanthroline can be further reduced to the octa-hydro form (four more electrons).

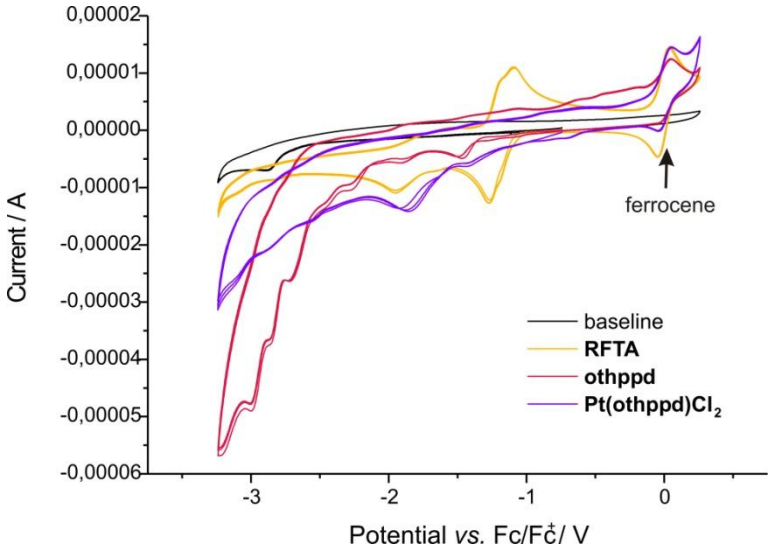


Figure 5.2: Cyclic voltammetry of RFTA, the ligand othppd and the complex Pt(othppd)Cl_2 in DMF calibrated to the half wave potential of ferrocene/ferrocenium.

Regarding the complex **Pt(othppd)Cl_2** the shape of the voltammogram looks similar to that of **othppd** but less pronounced. The first reduction peaks are at -1.43 V and 1.87 V, they can be assigned to the flavin diimine moiety, while other possible reduction peaks are barely visible.

The irreversibility of the reduction steps may indicate that reductive quenching steps of the photocatalysts might not be possible preventing their use in catalysis.

In the test-reaction, however, the flavin derivative is not bleached after two hours of irradiation, which shows that the dye is not decomposed or reduced irreversibly. Calculating the change in free energy ΔG_{ET} for the expected electron transfer by the Rehm-Weller equation explains this observation, as the electron transfer step would be endothermic.

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

Equation 1: Rehm-Weller equation for the calculation of the free energy in photochemical electron transfer reactions.[**]

[**] In this case: $E_{1/2}^{ox}$ = +1.19 V vs. Fc/Fc+ (oxidation potential of the substrate), E^{red} = 1.47 vs. Fc/Fc+ (reduction potential of the flavin), $e^2/\varepsilon a$ = Coulomb term, 5.4 kJ/mol, $E^{0\rightarrow 0}$= 224.01 kJ/mol (zero spectroscopic energy of the excited state of the flavin, estimated by the equation hc/λ_{avg} with λ_{avg} = wavelength at the average of fluorescence and absorption spectra (λ_{avg} = 534 nm for othppd, λ_{avg} ≈ 640 nm for Pt(othppd)Cl_2, estimated at the end of the absorption spectrum), h = Planck constant, c = velocity of light).

The calculations with the observed potentials show that the oxidation of *p*-methoxybenzyl alcohol is not possible with these compounds as catalysts (see Table 5.3).

Table 5.3: Reduction potential of the new compounds and estimated free energy changes for the conversion of *p*-methoxybenzyl alcohol.

Flavin	E^{red} [V][a]	ΔG [kJ mol^{-1}] [b]
RFTA	-1.27	-7.5
othppd	-1.47	+27.0
Pt(othppd)Cl$_2$	-1.43	+60.3

[a]Values obtained in DMF at a scan rate of 50 mV s^{-1} in 1.67 mmol L^{-1} solutions of the flavins with 0.01 mol L^{-1} Bu_4NPF_6 at 20 °C vs Fc/Fc^+. [b] Free energy changes estimated from Equation 1 using $E_{1/2}^{ox}$ (*p*-methoxybenzyl alcohol) = 1.19 V *vs.* Fc/Fc^+.[23]

To enable a productive oxidation reaction another electron donor must be used which has an oxidation potential <0.91 V vs. Fc/Fc^+ to be suitable for the ligand **othppd** as photocatalyst or < 0.57 vs. Fc/Fc^+ for the platinum-complex, respectively. A test-reaction with an electron donor like triethylamine or triethanolamine should be possible according to their redox potentials. Therefore another test-reaction was performed with triethanolamine (0.01 M) as electron donor and tolan (0.01 M) as substrate for reduction in DMF. The ligand and the catalyst were used as photocatalysts in 0.4 mol% concentration as used before. Both solutions were bleached after 2 hours of irradiation indicating a decomposition of the dyes. The reaction mixtures were analyzed by GC showing no conversion of the tolan with neither of the catalysts.

This means that either the flavin derivative is reduced irreversibly and not able to be reoxidized anymore as already assumed above (cf. cyclic voltammogram, Figure 5.2) or that the tolan has not the right reduction potential to be reduced by the reduced flavin derivative or its platinum complex. This free energy of this reaction cannot be calculated because of the missing oxidation peaks in the voltammograms.

5.7. Conclusion

Three routes of synthesis towards the phenanthroline flavin derivative **5** were investigated, the desired product could not be synthesized, instead the corresponding tetrahydrophenathroline **26** (**othppd**) was synthesized and used for platinum complexation. The new photoactive ligand and its Pt-complex were characterized spectroscopically and electrochemically and first attempts of photocatalysis were done. The reduction potentials of the new flavin derivative is lower than the

first reduction potential of **RFTA** and the absorption is red-shifted compared to **RFTA** resulting in a reduced oxidation power in the excited state. The new compound is not able to oxidize *p*-methoxybenzyl alcohol. The reduction of tolan was not possible with triethanolamine as electron donor and the new derivatives as photocatalysts. This indicates an irreversible reduction of the tetrahydrophenanthroline-flavins, which are therefore not useful for photocatalysis.

5.8. Experimental Part

Materials and methods

NMR spectra were recorded on a *Bruker Avance 300* (300.13 MHz for ^{1}H and 75.03 MHz for ^{13}C) spectrometer. Chemical shifts δ are given in ppm, using the residual solvent as internal standard. Coupling constants are reported in Hz. Mass spectra were obtained with an Agilent 6540 Ultra High Definition (UHD) Accurate-Mass with a Q-TOF LC/MS System (ESI-HR) and ThermoQuest Finnigan TSQ 7000 (ESI-LR).

Starting materials and reagents were purchased from *Sigma-Aldrich* or *Alfa Aesar* and were used without further purification. The solvents were purified and dried using standard procedures. Riboflavin tetraacetate was prepared according to a literature procedure.[24]

Pteridino[6,7-f]-1,10-phenanthroline-11,13(10H,12H)-dione (1):[25] [1,10]Phenanthroline-5,6-dione (417 mg, 2.0 mmol, 1.00 eq) and 5,6-diaminouracil sulfate (650 mg, 2.7 mmol, 1.35 eq) were dissolved in methanol (50 mL) and refluxed for 1.5 hours. After cooling to room temperature the mixture was put in the fridge for 5 days and the precipitate (yellowish) was filtrated and dried to yield quantitatively the pteridinophenanthrolinedione **1** (ppd). ^{1}H-NMR (300 MHz, DMSO-d6) δ (ppm) = 11.87 (bs, 1H, NH, H10), 10.69 (br s, 1H, NH, H12), 9.25-9.15 (m, 4H, H1/3/6/8), 7.94 (dd, $^{3}J_{H7\text{-}H6}$ = 4.4 Hz, $^{4}J_{H7\text{-}H8}$ = 8.7 Hz, 1H, H7), 7.91 (dd, $^{3}J_{H2\text{-}H3}$ = 4.4 Hz, $^{4}J_{H2\text{-}H1}$ = 8.4 Hz, 1H, H2).

[1,10]Phenanthroline-5,6-dione (3):[12] Potassium bromide (2.00 g, 17 mmol, 1.5 eq) and 1,10-phenanthroline monohydrate monohydrochloride (2.58 g, 11 mmol, 1.0 eq) were placed in a flask and an ice-cold mixture of concentrated sulfuric acid (20 mL) and fuming nitric acid (10 mL) was added carefully. Then the mixture was refluxed for 3 hours and stopped afterwards by pouring on ice (ca. 500 g) and neutralizing with NaOH (10% aqueous solution) until neutral to slightly acidic pH. Then the product was extracted with chloroform (3 x 200 mL), the combined organic layers were dried with $MgSO_4$ and the solvent was removed. After recrystallization from ethanol

[1,10]Phenanthroline-5,6-dione was obtained as yellow needles (1.30 g, 6.2 mmol, 56%). ^{1}H-NMR (400 MHz, CDCl3) δ (ppm) = 9.13 (dd, $^{4}J_{H2/9\text{-}H4/7}$ = 1.8 Hz, $^{3}J_{H2/9\text{-}H3/8}$ = 4.7 Hz, 2H, H2/9), 8.51 (dd, $^{4}J_{H4/7\text{-}H2/9}$ =1.8 Hz, $^{3}J_{H4/7\text{-}H2/9}$ = 7.9 Hz, 2H, H4/7), 7.59 (dd, $^{3}J_{H3/8\text{-}H2/9}$ = 4.7 Hz, $^{4}J_{H3/8\text{-}H4/7}$ = 7.9 Hz, 2H, H3/8).

5-Nitro-6-(propylamino)uracil (7a):[26] 6-(Propylamino)uracil **10a** (0.508 g, 3.00 mmol, 1.0 eq.) was mixed with concentrated sulfuric acid (1.4 mL, 85.2 mmol, 28 eq.). The solution was cooled down to 0°C with ice/water cooling bath and fuming nitric acid (0.7 mL, 16.8 mmol, 5.6 eq.) was added. It was left reacting for 15 minutes and the color of the solution changed to yellowish. Then it was allowed to warm to room temperature and the color changed to intense yellow. After 15 min it was poured on 20 g of ice. After basification to pH = 7 the solution was evaporated to dryness. The solid (mixture of **7a** with sodium sulfate and nitrate) was treated four times with 20 mL of MeOH, the suspension was sonicated, decanted and filtrated. The solution was solidified to give 565 mg (88%) of **7a**; yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) = 9.97 (bs, 1H, *H*N-4), 7.83 (bs, 2H, *H*N-6, 9), 2.73 (t, *J* = 7.4 Hz, 2H, H_2C-10), 1.55 (tq, J_1 = 7.4 Hz, J_2 = 7.4 Hz, 2H, H_2C-11), 0.89 (t, *J* = 7.4 Hz, 3H, H_3C-12). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 170.89 (C-3), 159.39 (C-1), 149.68 (C-5), 40.37 (C-10), 20.29 (C-11), 10.74 (C-12). ESI-MS (+, m/z, LR): $[M+H]^+$ 215.0, $[MNH_4^+]$ 232.0 , $[MH+MeCN]^+$ 256.1.

5-Nitro-6-(tridecan-7-ylamino)uracil (7b): 6-(tridecan-7-ylamino)uracil **10b** (0.187 g, 0.60 mmol, 1 eq.) was mixed with concentrated sulfuric acid (1.4 mL, 85.2 mmol, 47 eq.) . The solution was cooled down to 0°C with ice/water cooling bath and fuming nitric acid (0.7 mL, 16.8 mmol, 27 eq.) was added. The color changed to yellow and the emulsion was created. It was left reacting for with cooling to 0 °C (the reaction is exothermic). After 45 min it was poured on 20 g of ice. After basification to pH = 7 (4.1 g of NaOH) the color changed to orange red. The reaction mixture was solidified and the solid was extracted by MeOH. It was not possible to isolate product from its mixture with salts and therefore the yield was not determined. 150 mg of **7b** in mixture with Na_2SO_4 and $NaNO_3$ was isolated after extraction; yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) = 9.76 (bs, 1H, *H*N-6), 9.32 (bs, 1H, *H*N-4), 8.43 (s, 1H, *H*N-9), 3.69 (s, 1H, *H*C-10), 1.47 (m, 4H, H_2C-11, H_2C-12), 1.22 (m, 16H, H_2C-13, 14, 15, 16, 17, 18, 20, 21), 0.83 (t, *J* = 7.5 Hz, 6H, H_3C-18, H_3C-22). ESI-MS (+, m/z, LR): $[M+H]^+$ 355.1, $[MH+NH_4^+]$ 372.1, $[2MH]^+$ 710.5.

5-Nitroso-6-(propylamino)uracil (8a): 6-(Propylamino)uracil **10a (**200 mg, 0.59 mmol, 1 eq.) was mixed with 160 mg of sodium nitrite in a 7.5 mL Schlenk flask. 3.6 mL of distilled water was added and the suspension was heated to 90 °C for 1 hour. The solid dissolved in 5 minutes and the solution turned yellow. The heating was stopped after 1 hour and the reaction was cooled down to

room temperature. To the yellow solution 3 drops of 100 % acetic acid were added and a gas evolution was observed. Immediately after addition of acid the heating was removed and the reaction was cooled down to 0 °C. The color changed to red. After 5 minutes a brick-red precipitation appeared. The precipitation was filtered on Büchner funnel and dried over vacuum to give 58 mg (25%) of impure **8a**; orange red solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) = 8.84 (s, 1H, *H*N-6), 8.13 (s, 2H, *H*N-9, 4), 2.69 (t, J = 7.6 Hz, 2H, H_2C-10), 1.58 (tq, J_1 = 7.5 Hz, J_2 = 7.6 Hz, 2H, H_2C-11), 0.89 (t, J = 7.5 Hz, 3H, H_3C-12). ESI-MS (-, m/z, LR): $[M-H]^-$ 196.9, $[MHCOO^-]$ 242.9.

6-Chlorouracil (9):[16] 2,4,6-Trichloropyrimidine (10 g, 54.5 mmol) was added to a stirring solution of sodium hydroxide (8.8 g, 0.22 mol) in water (90 mL). The resulting mixture was heated under reflux for 4 hours. After cooling the pH value was adjusted to 3 with concentrated hydrochloric acid (11 mL 37% HCl). The white precipitate was filtered off, washed with acetone (2 $\times$ 10 mL) and dried in vacuo to give 6-chlorouracil **9** as white powder (7.4 g, 93 %). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) = 12.11 (bs, 1H, N*H*), 11.13 (s, 1H, N*H*), 3.86 (s, 1H, =C*H*-). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 162.86 (C-3), 150.94 (C-5), 146.17 (C-1), 99.07 (=*C*H-).

6-(Propylamino)uracil (10a):[27] 6-chlorouracil **9** (2.93 g , 20.0 mmol, 1 eq.) was mixed with 10 mL (121.8 mmol, 6 eq.) of propylamine under nitrogen atmosphere. The reaction was heated to 60 °C on oil bath and cooled by cooling finger. The color changed to yellowish after 20 min and the white flakes were observed in the reaction mixture. The reaction was quenched by addition of 20 mL MeOH and the precipitate of impurity was filtered out. The filtrate was then evaporated to dryness and mixed with 10 mL of $CHCl_3$. The crystals formed were filtered of and dried under vacuum to give 3.21 g (94 %) of **10a**; beige solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) = 8.17 (bs, 3H, N*H*), 5.07 (s, 1H, =C*H*-), 2.76 (t, J = 7.5 Hz, 2H, H_2C-10), 1.53 (tq, J_1 = 7.5 Hz, J_2 = 7.5 Hz, 2H, H_2C-11), 0.89 (t, J = 7.5 Hz, 3H, H_3C-12). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 165.54 (C-3), 160.31 (C-5), 158.01 (C-1), 93.23 (=*C*H-), 40.38 (C-10), 20.41 (C-11), 10.74 (C-12). ESI-MS (+, m/z, HR): $[M+H]^+$ 170.1, $[2MH]^+$ 339.2.

6-(Tridecan-7-ylamino)uracil (10b): To a 10 mL Schlenk flask was weighed tridecan-7-amine (272 mg, 1.36 mmol, 2 eq., synthesized *via* literature procedure, see ref. [28] and [17]). The content of the flask was heated with a heat gun to 50°C and the amine liquidized. 6-Chlorouracil **9** (100 mg, 0.68 mmol, 1 eq.) was added and the reaction was heated to 140 °C. The reaction progress was monitored by TLC ($CHCl_3$/MeOH 10:1; **9**: R_f = 0.1; **10b**: R_f = 0.2). After 4 hours as the slightly orange red viscous solution was observed the conversion was almost complete and the heating was stopped. The reaction mixture solidified, 3 mL of MeOH was added and the suspension was vigorously stirred for 15 minutes. The white solid precipitation of impurity appeared in the solution. It was filtered and

the mother liquor was solidified. The crude reaction mixture contained tridecan-7-amine and therefore it was purified by column flash chromatography on silica gel (CH2Cl2/MeOH 10:1) to get 130 mg (62 %) of **10b**; ivory solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) = 10.15 (bs, 1H, *H*N-6), 9.62 (bs, 1H, *H*N-4), 5.91 (s, 1H, *H*N-9), 4.40 (s, 1H, =C*H*-), 3.34 (s, 1H, *H*C-10), 1.42 (m, 4H, H_2C-11, H_2C-12), 1.24 (m, 16H, H_2C-13, 14, 15, 16, 17, 18, 20, 21), 0.85 (t, J = 6.3 Hz, 6H, H_3C-18, H_3C-22). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 164.27 (C-3), 153.81 (C-5), 150.76 (C-1), 72.29 (C-1), 51.29 (C-10), 34.15 (C-11, 12), 31.22 (C-13, 15), 28.65 (C-14, 16), 25.11 (C-18, 20), 22.04 (C-18, 21), 13.93 (C-19, 22). ESI-MS (+, m/z, LR): $[M+H]^+$ 310.1, $[M+MeCN]^+$ 351.2, $[2MH]^+$ 619.5. ESI-MS (+, m/z, HR): $[M+H]^+$ calcd. 310.2489, found: 310.2497.

1,10-Phenanthroline-5,6-dione oxime (11):[29] Phenanthroline-5,6-dione **3** (711 mg, 3.38 mmol, 1 eq.) was dissolved in 70 mL of ethanol. Pyridine (408 µL, 5.07 mmol, 1.5 eq.) was added as drops and hydroxylamine hydrochloride (234 mg, 3.38 mmol, 1 eq.) was added in one batch. After 75 min of refluxing the reaction mixture was cooled down, poured on 50 g of ice and fine yellow crystals occurred. They were filtered on a Büchner funnel to give 427 mg of dirty yellow crystals. The filtrate was concentrated to volume 20 ml and was left in the fridge over weekend to give second portion of impure **11**. The monooxime was carefully recrystallized from ethanol to give 731 mg (96 %) of **11**; dirty yellow powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) = 9.05 (dd, J_1 = 4.6 Hz, J_2 = 1.8 Hz, 1H, *H*C-1), 8.85 (dd, J_1 = 4.6 Hz, J_2 = 1.6 Hz, 1H, *H*C-12), 8.46 (dd, J_1 = 7.9, J_2 = 1.8 Hz, 1H, *H*C-9), 8.44 (dd, J_1 = 8.2, J_2 = 1.6 Hz, 1H, *H*C-14), 7.70 (dd, J_1 = 7.9, J_2 = 4.6 Hz, 1H, *H*C-13), 7.64 (dd, J_1 = 8.2, J_2 = 4.6 Hz, 1H, *H*C-6). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 154.87 (C-10), 154.70 (C-1), 152.21 (C-12), 150.48 (C-7), 146.59 (C-9), 135.61 (C-3), 134.86 (C-14), 127.64 (C-5), 125.04 (C-4), 124.90 (C-13), 124.53 (C-6), 123.22 (C-8). ESI-MS (+, m/z, HR): $[M+H]^+$ 225.9 (100), $[MH+MeCN]^+$ 266.9 (20), $[2MH]^+$ 451.0 (5).

6-(Propylimino)-1,10-phenanthrolin-5(6H)-one oxime (11a): Phenanthroline mono-oxime **11** (32 mg, 0.142 mmol, 1 eq.) was mixed with propylamine (1 mL, 12.2 mmol, 86 eq.) under nitrogen atmosphere. The monooxime dissolved immediately to green solution. The reaction was stirred for 3 hours at room temperature and the precipitation was observed. To finish the reaction 5 mL of MeOH has been added. The precipitation dissolved and a deep green solution has been formed. The solvent and rests of propylamine have been evaporated to give 37 mg (97 %) of **11a**; green solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.76 (d, J = 6.7 Hz, 1H, *H*C-1), 8.99 (d, J = 2.8 Hz, 1H, *H*C-12), 8.74 (d, J = 3.0 Hz, 1H, *H*C-14), 8.43 (d, J = 7.6 Hz, 1H, *H*C-5), 7.37 (m, 2H, *H*C-6, 13), 2.96 (m, 2H, H_2C-18), 1.68 (m, 2H, H_2C-19), 0.95 (m, 3H, H_3C-20). ESI-MS (+, m/z, LR): $[M+H]^+$ 267.0, $[2MH]^+$ 451.0.

6-Amino-1,10-phenanthrolin-5(6H)-one (12): Phenanthrolinone oxime **11** (256 mg, 1.13 mmol, 1 eq.) was dissolved in 30 mL of MeOH. 1 mL of 12 M hydrochloric acid and 27 mg of Pd/C (10%) were added. The suspension was put into autoclave under 15 bars of hydrogen atmosphere. The reaction was stirred overnight. The pressure decreased to atmospheric and the suspension turned ocre. After filtration over Celite the solution was deep red and the Celite layer was greenish. The solvent was evaporated to dryness to provide 187 mg (67 %) of orange solid **12**. The product is formed as a hydrochloride. ^{1}H NMR (300 MHz, DMSO-d_6): *enol form* **12^{enol}** δ (ppm) = 10.69 (bs, 1H, -O*H*), 9.11 (pseudo-dd, J_1 = 4.9 Hz, J_2 = 1.4 Hz, 2H, *H*C-1, 12), 9.05 (pseudo-dd, J_1 = 8.5, J_2 = 1.4 Hz, 2H, *H*C-5, 14), 8.13 (pseudo-dd, J_1 = 8.5, J_2 = 4.9 Hz, 2H, *H*C-6, 13), 7.48 – 7.07 (m, J = 51 Hz, 3H, H_3N^+-). UV-Vis (H_2O, pH = 2): λ_{max} / nm (rel. intensity) = 385 (100); (H_2O, pH = 9): λ_{max} / nm (rel. intensity) = 405 (100), 675 (30).

5-Nitro-[1,10]phenanthroline (14):[21] To a stirred solution of 1,10-Phenanthroline monohydrate monohydrochloride (3.52 g, 15 mmol) in concentrated sulfuric acid (15 mL), fuming nitric acid (7.5 mL) was added dropwise at 160 °C. The reaction mixture was kept at 160 °C for three hours, and subsequently poured into ice water. Then concentrated NaOH solution was added to adjust the pH to 3. The yellow precipitate of 5-nitro-1,10-phenanthroline was filtered off, washed with water and dried in vacuum. Yield: 3.34 g (99 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.36 (dd, 1H, $^{3}J_{H9\text{-}H8}$ = 4.4 Hz, $^{4}J_{H9\text{-}H7}$ = 1.7 Hz, H9), 9.30 (dd, 1H, $^{3}J_{H2\text{-}H3}$ = 4.3 Hz, $^{4}J_{H2\text{-}H4}$ = 1.7 Hz, H2), 9.03 (dd, 1H, $^{3}J_{H4\text{-}H3}$ = 8.6 Hz, $^{4}J_{H4\text{-}H2}$ = 1.6 Hz, H4), 8.70 (s, 1H, H6), 8.43 (dd, 1H, $^{3}J_{H7\text{-}H8}$ = 8.1 Hz, $^{4}J_{H7\text{-}H9}$ = 1.8 Hz, H7), 7.83 (dd, 1H, $^{3}J_{H3\text{-}H4}$ = 8.6 Hz, $^{3}J_{H3\text{-}H2}$ = 4.2 Hz, H3), 7.79 (dd, 1H, $^{3}J_{H8\text{-}H7}$ = 8.0 Hz, $^{3}J_{H8\text{-}H9}$ = 4.3 Hz, H8). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 153.8, 151.7, 147.8, 144.9, 144.5, 138.0, 132.7, 125.7, 125.6, 124.6, 124.5, 121.2.

5-Bromo-1,10-phenanthroline (17):[19] 1.19 g (6 mmol, 1 eq.) of 1,10-phenanthroline monohydrate was put into a heavy-walled glass reaction tube with a screw top. The reaction vessel was placed to ice bath and 3.6 mL of approx. 20 % oleum and 0.18 mL (3.5 mmol, 1.16 eq.) of bromine was added. The solid did not dissolve completely. The reaction was sealed with a screw and it was slowly (in 90 minutes) heated to 135 °C. At this temperature the reaction mixture was stirred for 23 hours. The reaction mixture was poured on 30 g of ice to create yellow solution and it was neutralized with potassium carbonate to pH = 7. The resultant pink solution was extracted to 3 × 50 mL of chloroform, washed with brine and dried over magnesium sulfate. The crude product **17** was mixed with 20 mL of diethyl ether and white solid dissolved and insoluble reddish solid remained on the bottom of the flask. The solution was transferred to another flask and after 5 minutes the

product started to crystallize from the diethyl ether solution. The white flakes were filtrated and washed with ether to give 1.302 g (84 %) of **17**; white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.22 (ddd, J_1 = 4.5 Hz, J_2 =2.9 Hz, J_3 = 1.7 Hz, 2H, *H*C-1, 12), 8.69 (dd, J_1 = 8.3 Hz, J_2 = 1.6 Hz, 1H, *H*C-14), 8.20 (dd, J_1 = 8.1 Hz, J_2 = 1.7 Hz, 1H, *H*C-5), 8.16 (s, 1H, *H*C-10), 7.76 (dd, J_1 = 8.4 Hz, J_2 = 4.3 Hz, 1H, *H*C-13), 7.66 (dd, J_1 = 8.1 Hz, J_2 = 4.4 Hz, 1H, *H*C-6). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 150.98 (C-1), 150.76 (C-12), 146.68 (C-7), 145.70 (C-3), 136.00 (C-14), 135.19 (C-5), 129.73 (C-10), 128.87 (C-8), 127.96 (C-4), 123.91 (C-6), 123.74 (C-13), 120.87 (C-9). ESI-MS (+, m/z, LR): $[M+H]^+$ 259.0, 260.10.

1a,9b-Dihydrooxireno[ff]-1,10-phenanthroline (18):[20a, b] The pH of a sodium hypochlorite solution (150 mL) was carefully set to 8.5 with 6 N HCl. To this solution tetrabutylammonium hydrogen sulfate (0.83 g, 2.5 mmol, 0.5 eq) and phenanthroline monohydrate (1.00 g, 5.0 mmol, 1.0 eq) dissolved in chloroform (80 mL) were added and the reaction mixture was vigorously stirred for 3 days until the color changed from slightly green to yellow. Then the layers were separated and the water phase was extracted with chloroform (2 x 100 mL). The combined organic layers were washed with $Na_2S_2O_3$ (10% solution, 80 mL), water (3 x 80 mL) and brine (80 mL), dried with Na_2SO_4 and the solvent was removed. 5,6-Epoxy-[1,10]phenanthroline (754 mg, 3.84 mmol, 77%) was obtained as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.91 (dd, 2H, $^{3}J_{H4/7\text{-}H3/8}$ = 4.7 Hz, $^{4}J_{H4/7\text{-}H2/9}$ = 1.7 Hz, H4/7), 8.02 (dd, 2H, $^{3}J_{H2/9\text{-}H3/8}$ = 7.7 Hz, $^{4}J_{H2/9\text{-}H4/7}$ = 1.7 Hz, H2/9), 7.41 (dd, 2H, $^{3}J_{H3/8\text{-}H7/4}$ = 4.7 Hz, $^{3}J_{H3/8\text{-}H2/9}$ = 7.7 Hz, H3/8), 4.63 (s, 2H, H1a/9b). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 151.1 (2C, C4/7), 149.8 (2C, C5a/b), 138.4 (2C, C2/9), 129.3 (2C, C1b/9a), 123.9 (2C, C3/8), 55.5 (2C, C1a/9b).

N-Ethyl-1,10-phenanthrolin-5-amine (20a): Lithium aluminium hydride (38 mg, 1.00 mmol, 1.75 eq) was suspended in THF (abs.) and *N*-[1,10]phenanthrolin-5-yl-acetamide **23a** (136 mg, 0.57 mmol, 1.00 eq) was added in small portions. The color turned immediately red and the mixture was refluxed for 5 hours. After cooling to room temperature, the mixture was filtered and washed several times with CH_2Cl_2 and Et_2O. The solvents were removed from the filtrate and HCl (10%, 11 mL) was added, followed by washing with Et_2O (3 x). The water layer was set to basic pH with NaOH (15% solution, 15 mL) and again extracted with Et_2O (4 x). The organic layers were dried with Na_2SO_4 and the solvent was removed to yield the title compound (62 mg, 0.28 mmol, 49%) as greenish oil in bad yields (not determined). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.11 (dd, $^{3}J_{H9\text{-}H8}$ = 4.3 Hz, $^{4}J_{H9\text{-}H7}$ = 1.6 Hz, 1H, H9), 8.84 (dd, $^{3}J_{H2\text{-}H3}$ = 4.3 Hz, $^{4}J_{H2\text{-}H4}$ = 1.7 Hz, 1H, H2), 8.20 (dd, $^{3}J_{H4\text{-}H3}$ = 8.4 Hz, $^{4}J_{H4\text{-}H2}$ = 1.6 Hz, 1H, H4), 7.95 (dd, $^{3}J_{H7\text{-}H8}$ = 8.1 Hz, $^{4}J_{H7\text{-}H9}$ = 1.7 Hz, 1H, H7), 7.54 (dd, $^{3}J_{H3\text{-}H2}$ = 4.3 Hz, $^{3}J_{H3\text{-}H4}$ = 8.4 Hz, 1H, H3), 7.43 (dd, $^{3}J_{H8\text{-}H9}$ = 4.3 Hz, $^{4}J_{H8\text{-}H7}$ = 8.1 Hz, 1H, H8), 6.60 (s, 1H, H6), 4.28 (br s, 1H, NH), 3.33 (dq, $^{3}J_{H1'\text{-}H2'}$ = 7.1 Hz, $^{3}J_{H1'\text{-}NH}$ = 4.8 2H, CH_2), 1.41 (t, $^{3}J_{H2'\text{-}H1'}$ = 7.1 Hz, 3H, CH_3).

Octyl-[1,10]phenanthrolin-5-yl-amine (20b): Octanoic acid [1,10]phenanthrolin-5-yl-amide **23b** (500 mg, 1.56 mmol, 1.00 eq) was suspended in 20 mL THF (abs.) and lithium aluminium hydride (44 mg, 1.17 mmol, 0.75 eq) was added carefully. The mixture was stirred for 5 days and the reaction was controlled *via* TLC. After 5 days the reaction was still incomplete and was heated to reflux for 18 hours. After cooling to room temperature, 50 mL of water and 50 mL of DCM were added and the water phase was extracted another time with 50 mL DCM. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered and the solvent was evaporated to yield the product as yellow solid (468 mg, 1.52 mmol, 98%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.03-9.01 (m, 2H, H2 and H9), 8.32 (bs, 1H, NH), 8.29-8.27 (m, 1H, H4), 8.07-8.04 (m, 1H, H7), 8.02 (s, 1H, H6), 7.55-7.46 (m, 2H, H3 and H8), 2.55-2.50 (m, 2H, H1'), 1.80-1.75 (m, 2H, H2'), 1.49-1.28 (m, 10 H, H3'-H7'), 0.87 (t, $^3J_{H8'-H7'}$ = 6.7 Hz, 3H, H8'). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 150.0 (C9), 149.7 (C2), 146.3 (C_{quart}), 143.1 (C_{quart}), 136.1 (C7), 135.1 (C_{quart}), 130.9 (C_{quart}), 130.3 (C_{quart}), 128.3 (C4), 123.5 (C8), 122.8 (C3), 120.2 (C6), 37.5 (C1'), 32.8 (C6'), 31.8 (C2'), 29.4 (C4'), 29.2(C5') 25.9 (C3'), 22.7 (C7'), 14.2 (C8'). ESI-MS (+, m/z, HR): $[M+H]^+$ calcd.: 308.2121, found 308.2121.

5-Amino-[1,10]phenanthroline (22):[21] 5-Nitro-[1,10]phenanthroline **14** (1.0 g, 4.4 mmol, 1 eq) was dissolved in ethanol (20 mL), Pd/C (200 mg) was added and the reaction mixture was purged with nitrogen. Then hydrazine monohydrate (0.26 mL, 0.27 g, 5.3 mmol, 1.2 eq) was added dropwise over 5 minutes and the reaction was stirred at 70 °C for 6 hours. The catalyst was filtered off, the filtrate was concentrated in vacuo and the product precipitated over night. It was filtered and washed with a minimal amount of ethanol to give the title compound **22** as yellow solid (456 mg, 2.4 mmol, 54 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.18 (dd, 1H, $^3J_{H9-H8}$ = 4.3 Hz, $^4J_{H9-H7}$ = 1.6 Hz,H9), 8.93 (dd, 1H, $^3J_{H2-H3}$ = 4.3 Hz, $^4J_{H2-H4}$ = 1.7 Hz, H2), 8.25 (dd, 1H, $^3J_{H4-H3}$ = 8.3 Hz, $^4J_{H4-H2}$ = 1.7 Hz, H4), 7.96 (dd, 1H, $^3J_{H7-H8}$ = 8.1 Hz, $^4J_{H7-H9}$ = 1.7 Hz, H7), 7.62 (dd, 1H, $^3J_{H3-H4}$ = 8.4 Hz, $^3J_{H3-H2}$ = 4.3 Hz, H3), 7.48 (dd, 1H, $^3J_{H8-H7}$ = 8.1 Hz, $^3J_{H8-H9}$ =4.3 Hz, H8), 6.91 (s, 1H, H5), 4.27 (s, 2H, NH_2).

N-[1,10]Phenanthrolin-5-yl-acetamide (23a):[30] To a suspension of 5-Amino-[1,10]-Phenanthroline **22** (186 mg, 0.95 mmol, 1.0 eq) in 4 mL acetonitrile acetic anhydride (2.0 mL, 2.1 g, 21 mmol, 22.0 eq) was added. The mixture was heated until everything was dissolved and then stirred for 3 days. The precipitate was filtered and drying of the residue gave the product as yellow solid (154 mg, 0.65 mmol, 68%). ^{1}H-NMR (300 MHz, DMSO-d6) δ (ppm)= 10.16 (br s, 1H, NH), 9.12 (dd, 1 H, $^3J_{H9-H8}$ = 4.2 Hz, $^4J_{H9-H7}$ = 1.6 Hz, H9), 9.03 (dd, 1 H, $^3J_{H2-H3}$ =4.3 Hz, $^4J_{H2-H4}$ = 1.7 Hz, H2), 8.63 (dd, 1 H, $^3J_{H4-H3}$ =8.4 Hz, $^4J_{H4-H2}$ = 1.6 Hz, H4), 8.44 (dd, 1 H, $^3J_{H7-H8}$ = 8.2 Hz, $^4J_{H7-H9}$ = 1.7 Hz, H7), 8.18 (s, 1H, H6), 7.82 (dd, 1 H, $^3J_{H3-H2}$ = 4.3 Hz, $^3J_{H3-H4}$ = 8.4 Hz, H3), 7.73 (dd, 1 H, $^3J_{H8-H7}$ = 8.1 Hz, $^3J_{H8-H9}$ = 4.3 Hz, H8), 2.24 (s, 3 H, H2'). ESI-MS (+, m/z, HR): $[M+H]^+$ calcd.: 238.0975, found 238.0979.

Octanoic acid [1,10]phenanthrolin-5-ylamide (23b): To a suspension of 5-Amino-[1,10]-Phenanthroline **22** (585 mg, 3.00 mmol, 1.0 eq) in acetonitrile (20 mL) octanoyl chloride (1.0 mL, 976 mg, 6.00 mmol, 2.0 eq) was added. The mixture was stirred for 2 days. The precipitate was filtered and washed with acetonitrile. Drying of the residue gave the product as slightly pink powder (882 mg, 2.74 mmol, 91%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 11.15 (s, 1H, NH), 9.47 (dd, $^{4}J_{H2\text{-}H4}$ = 1.2 Hz, $^{3}J_{H2\text{-}H3}$ = 5.3 Hz, 1 H, H2), 8.94 (dd, $^{4}J_{H9\text{-}H7}$ = 1.3 Hz, $^{3}J_{H9\text{-}H8}$ = 8.6 Hz, 1 H, H9), 8.72 (dd, $^{4}J_{H4\text{-}H2}$ = 1.0 Hz, $^{3}J_{H4\text{-}H3}$ = 8.3 Hz, 1 H, H4), 8.50 (s, 1 H, H6), 8.10 (dd, $^{3}J_{H3\text{-}H2}$ = 5.3 Hz, $^{3}J_{H3\text{-}H4}$ = 8.2 Hz, 1 H, H3), 7.93 (dd, $^{3}J_{H7\text{-}H8}$ = 4.4 Hz, $^{4}J_{H7\text{-}H9}$ = 1.3 Hz, 1 H, H7), 7.02 (dd, $^{3}J_{H8\text{-}H7}$ = 4.4 Hz, $^{3}J_{H8\text{-}H9}$ = 8.5 Hz, 1 H), 2.92 (t, $^{3}J_{H2'\text{-}H3'}$ = 7.5 Hz, 2 H, H2'), 1.88-1.79 (m, 2 H, H3'), 1.51-1.24 (m, 8 H, H4',H5',H6' and H7'), 0.88 (t, $^{3}J_{H8'\text{-}H7'}$ = 6.6 Hz, 3H, H8'). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 175.0 (C1'), 148.2 (C2), 143.2 (C9), 142.8 (C5), 137.7 (C10a), 136.3 (C4), 135.2 (C7), 133.8 (C10b), 130.0 (C6a), 125.5 (C4a), 124.3 (C3), 123.9 (C8), 116.0 (C6), 37.4 (2'), 31.9 (6'), 29.4 (2C, C5',C4'), 25.8 (C3'), 22.8 (C7'), 14.3 (C8'). ESI-MS (+, m/z, HR): $[M+H]^+$ calcd.: 322.1914, found 322.1915.

***N-Octyl-1,2,3,4-tetrahydro-1,10-phenanthrolin-5-amine (24)*:** Octanoic acid [1,10]phenanthrolin-5-ylamide **23b** (442 mg, 1.38 mmol, 1.00 eq) was suspended in 30 mL THF (abs.) and lithium aluminium hydride (104 mg, 2.75 mmol, 2.0 eq) was added carefully. Then the mixture was refluxed for 5 hours. After cooling to room temperature, the mixture was allowed to stir overnight, quenched with some drops of ice water, filtered and washed THF. The solvents were removed from the filtrate to yield the crude product. Diethyl ether (100 mL) was added to the solid crude solid product to extract a mixture of different reduction products. The solvent was evaporated and the crude mixture was used for the condensation reaction with violuric acid without further purification. ESI-MS (+, m/z, HR): $[M+H]^+$ calcd.: 312.2440, found 312.2434.

9-Octyl-6,7,8,9-tetrahydropteridino[6,7-f]-1,10-phenanthroline-11,13(5H,12H)-dione (othppd) (26): The crude mixture of reduced **23b** (180 mg) was dissolved in 10 mL acetic acid and violuric acid monohydrate (217 mg, approx. 1.0 eq) was added. The mixture was heated to reflux for one hour and afterwards neutralized with saturated $NaHCO_3$ solution and extracted with dichloromethane. The combined organic phases were washed with brine, dried with Na_2SO_4, filtered and the solvent was removed. The residue was purified by column chromatography (DCM/MeOH 10:1) and additionally by preparative TLC (DCM/MeOH 10:1, R_f = 0.42) to yield a pink solid (22.1 mg, 0.05 mmol, <15%, 4% over two steps). ^{1}H-NMR (600 MHz, DMSO-d6) δ (ppm) = 10.91 (s, 1H, NH, H12), 9.21 (t, $^{3}J_{H5\text{-}H6}$ = 3.5 Hz, 1H, NH, H5), 9.07 (dd, $^{3}J_{H1\text{-}H2}$ = 8.3 Hz, $^{4}J_{H1\text{-}H3}$ = 1.6 Hz, 1H, H1), 8.96 (dd, $^{3}J_{H3\text{-}H2}$ = 4.3 Hz, $^{4}J_{H3\text{-}H1}$ = 1.6 Hz, 1H, H3), 7.87 (dd, $^{3}J_{H2\text{-}H1}$ = 8.3 Hz, $^{3}J_{H2\text{-}H3}$ = 4.3 Hz, 1H, H2), 4.78-4.64 (m, 2H, H1'), 3.63-3.61 (m, 2H, H6), 3.08 (t, $^{3}J_{H8\text{-}H7}$ = 6.0 Hz, 2H, H8), 1.92-1.88 (m, 2H, H7), 1.79-1.74 (m,

2H, H2'), 1.26-1.10 (m, 10H, H3'-H7'), 0.77 (t, $^{3}J_{H8'-H7'}$ = 7.1 Hz, 3H, H8'). ^{13}C-NMR (150 MHz, DMSO-d6) δ (ppm) = 161.1 (C_{quart}, C13), 155.9 ($C_{quart.}$, C11), 149.7 ($C_{quart.}$), 149.6 (C3), 138.5 ($C_{quart.}$), 138.4 ($C_{quart.}$), 137.3 ($C_{quart.}$), 132.1 (C1), 127.3 ($C_{quart.}$), 125.8 ($C_{quart.}$), 125.3 (C2), 124.0 ($C_{quart.}$), 102.6 ($C_{quart.}$), 49.1 (C1'), 40.6 (C6), 31.0 (C6'), 28.7 (C7'), 28.6 (C4'), 28.3 (C5'), 27.5 (C2'), 26.0 (C8), 22.0 (C3'), 20.8 (C7), 13.9 (C8'). ESI-MS (+, m/z, HR): $[M+H]^+$ calcd.: 702.1849, found: 433.2352.

Pt(othppd)Cl$_2$ (27): The ligand othppd **26** (11 mg, 0.026 mmol, 1.0 eq) and Pt(dmso)Cl_2 (11 mg, 0.026 mmol, 1.0 eq) were dissolved in ethanol (10 mL) and heated to reflux for one hour. The solvent was removed to yield a violet solid in quantitative yield (18 mg, 0.026 mmol, 99%). ESI-MS (+, m/z, HR): $[M\text{-}Cl+CH_3CN]^+$ calcd.: 702.1849, found: 702.1869; $[M\text{-}Cl+dmso]^+$ calcd.: 739.1723, found: 739.1744.

5.9. References

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6. Summary

The thesis presents new applications and improvements in flavin photocatalysis. The first chapter introduces into flavin chemistry by showing examples from the discovery of riboflavin as photocatalyst to the state of the art in chemical photocatalysis with flavins nowadays.

In the second chapter new applications of flavin photocatalysis in benzylic oxidations are presented including the functionalization of toluenes to benzaldehydes, the oxidative cleavage of styrenes and stilbenes to benzaldehyde, the decarboxylative photooxidation of phenyl acetic acid and the direct oxidation of benzyl ethers and benzylamides to the corresponding esters and imides. The mechanism of these reactions is discussed in detail. In the toluene functionalization the electron density of the arenes is crucial: electron poor and very electron rich systems could not be oxidized, the best results were obtained in the oxidation of *p*-methoxy toluene (58%). The decarboxylative oxidation of diphenylacetic acid to benzophenone was possible quantitatively within 20 minutes of irradiation.

In chapter three aggregation effects in flavin photocatalysis are discussed. 10-Arylflavins with different *ortho*-substituents were synthesized as potentially non-aggregating flavin photocatalysts by condensation of the appropriate substituted aminouracils with nitrosobenzene. They were crystallized and characterized spectroscopically and electrochemically. The new compounds were tested in photocatalysis in a model reaction showing higher efficiency compared to riboflavin tetraacetate: The product quantum yields of the reactions mediated by the new arylflavins were higher by almost one order of magnitude. The aggregation of the compounds is discussed with regard to their orientation in the crystal and their behavior in solution with aggregation numbers determined *via* DOSY-NMR spectroscopy. However, there is no simple correlation of intermolecular interaction between the flavins and their ability as photocatalyst; π-π interactions as well as hydrogen bonding have to be taken into account, moreover the photophysical properties of the flavins (singlet and triplet quantum yield and lifetime) are influenced by substitution.

In chapter four the influence of the water content in water/acetonitrile mixtures on the reaction of *p*-methoxybenzyl alcohol to *p*-methoxybenzaldehyde catalyzed by riboflavin tetraacetate is reported. It is evident from transient absorption spectra in the µs-time scale and reaction kinetic observations that a water content of the solvent mixture of more than 75 vol% is the optimum solvent for such reactions. The large effect of water is attributed to a fast protonation of the flavin anion radical and to the prolonged lifetime of the flavin triplet state in water compared to

acetonitrile resulting in an increased probability of the triplet excited state of the flavin to react with the substrate molecule.

Flavin photocatalysts with a propyl chain in position 10 and bromine or iodine substituents in position 7 were prepared. These new flavins achieve much better quantum yields than riboflavin tetraacetate, the brominated being the best catalyst for this reaction in terms of product quantum yield using the heavy atom effect to enhance the ISC in the right balance for the reaction timescale. From the synthetic point of view these analogues with improved triplet quantum yield are interesting, because they could enable the introduction of a substrate binding site. A photoreaction with the aid of a substrate binding site is not possible in the classical system, because the flavin needs time to access the triplet state before meeting a substrate molecule. The efficient ISC might help to reach the triplet state despite the small distance to the substrate in the binding site.

In chapter five a new catalyst concept is proposed: A phenanthrolin-flavin hybrid as ligand to enable reductions with flavin photocatalysis *via* oxidation of an electron donor with a subsequent dark reaction (reduction) at the metal center. Three different synthesis routes towards such a ligand were tried but none of them was leading to the desired product. Instead a tetrahydroderivative could be obtained and isolated which was then used for metal complexation and tested in photocatalysis. This new derivative has a lower reduction potential than riboflavin tetraacetate and is therefore not able to oxidize *p*-methoxybenzyl alcohol. As electron donor triethanolamine was chosen instead and the reduction of tolan to stilbene was tested as model reaction for a reduction. Unfortunately, this reaction was not possible, too. This suggests that the reduction of the new flavin derivatives is irreversible and they are therefore not useful for photocatalysis.

In conclusion the results of this work show new applications of oxidative flavin photocatalysis and improvements of the catalytic system in three different ways: By changing the aggregation properties and by the water content in the solvent as well as heavy-atom-substitution. Finally a phenanthrolin-flavin derivative and its platinum complex were synthesized and investigated regarding their applicability in photocatalysis.

7. Zusammenfassung

Diese Arbeit stellt neue Anwendungen und Verbesserungen in der Flavin-Photokatalyse vor. Im ersten Kapitel wird ein Überblick über die Flavin-Chemie gegeben, indem Beispiele von der Entdeckung von Riboflavin bis hin zum aktuellen Stand der Forschung in der chemischen Photokatalyse mit Flavinen gezeigt werden.

Im zweiten Kapitel werden neue Anwendungen der Flavin-Photokatalyse in der Oxidation von Benzylkohlenstoffen berichtet, u.a. die Funktionalisierung von Toluolen zu Benzaldehyden, die oxidative Spaltung von Styrolen und Stilbenen zu Benzaldehyden, die decarboxylierende Photooxidation von Phenylessigsäuren sowie die direkte Oxidation von Benzylethern und -amiden zu den jeweiligen Estern bzw. Imiden. Der Mechanismus dieser Reaktionen wird ausführlich diskutiert. Bei der Toluol-Funktionalisierung ist die Elektronendichte des Aromaten entscheidend: Elektronenarme und sehr elektronenreiche Systeme konnten nicht oxidiert werden, die besten Ergebnisse wurden bei der Oxidation von *p*-Methoxytoluol erreicht (58%). Die decarboxylierende Oxidation von Phenylessigsäure war in quantitativer Ausbeute innerhalb von 20 Minuten Bestrahlungszeit möglich.

In Kapitel drei werden Aggregationseffekte in der Flavin Photokatalyse diskutiert. 10-Arylflavine mit verschiedenen *ortho*-Substituenten wurden als potentiell nicht-aggregierende Flavin-Photokatalysatoren synthetisiert, indem entsprechend substituierte Aminouracile mit Nitrosobenzol kondensiert wurden. Diese neuen Flavine wurden kristallisiert und spektroskopisch so wie elektrochemisch charakterisiert und in der Photokatalyse an der aeroben Oxidation von *p*-Methoxybenzylalkohol zu *p*-Anisaldehyd getestet (Modelreaktion). Hier zeigten sie eine höhere Effizienz als Riboflavintetraacetat: Die Quantenausbeuten der Reaktionen waren um fast eine Größenordnung höher. Die Aggregation der Verbindungen wird bezüglich ihrer Ausrichtung im Kristall sowie ihrem Verhalten in Lösung diskutiert. Dazu wurden die Aggregationszahlen mittels DOSY-NMR-Spektroskopie bestimmt. Allerdings kann keine einfache Korrelation zwischen der intermolekularen Wechselwirkung zwischen den Flavinen und ihrer Fähigkeit als Photokatalysator gefunden werden; π-π-Wechselwirkungen sowie Wasserstoffbrückenbindungen müssen berücksichtigt werden, außerdem werden die photophysikalischen Eigenschaften der Flavine (wie z.B. Singulett- und Triplett-Quantenausbeute und -Lebenszeit) durch die Substitution beeinflusst.

Im vierten Kapitel wird über den Einfluss des Wassergehalts in Wasser/Acetonitril-Mischungen auf die Riboflavintetraacetat-katalysierte Reaktion von *p*-Methoxybenzylalkohol zu *p*-Anisaldehyd berichtet. Aus den Ergebnissen der transienten Absorptionsspektroskopie im µs-Bereich und aus der beobachteten Reaktionskinetik geht klar hervor, dass ein Wasseranteil des Lösungsmittels von mehr

als 75 vol% optimal für Reaktionen dieses Typs ist. Der starke Einfluss von Wasser kann einerseits der schnellen Protonierung des Flavin-Radikalanions zugeschrieben werden und zum anderen der längeren Lebenszeit des Flavin-Triplettzustands in Wasser verglichen mit Acetonitril, was zu einer erhöhten Wahrscheinlichkeit führt, dass der angeregte Triplettzustand des Flavins mit einem Substrat-Molekül reagiert. Außerdem wurden Flavin-Photokatalysatoren mit einer Propylseitenkette in Position 10 und Brom- oder Iodsubstituenten in Position 7 synthetisiert. Diese neuen Flavine erreichen wesentlich bessere Produkt-Quantenausbeuten als Riboflavintetraacetat. Dabei liefert das bromierte Derivat die besten Resultate bezüglich der Quantenausbeute, da hier der Schwer-Atom-Effekt im richtigen Maß genutzt werden kann, um das Inter-System-Crossing für die Zeitskala der Reaktion zu verbessern. Für die Synthese sind diese Derivate mit verbesserter Triplett-Quantenausbeute interessant, da sie die Einführung einer Bindungsstelle ermöglichen könnten. Eine Photoreaktion mithilfe einer Bindungsstelle ist im klassischen System nicht möglich, da das Flavin Zeit braucht, um in den Triplettzustand zu gelangen, bevor es mit dem Substrat zusammenstößt. Das effiziente Inter-System-Crossing könnte helfen, den Triplettzustand trotz geringem Abstand zum Substrat in der Bindungsstelle rechtzeitig zu erreichen.

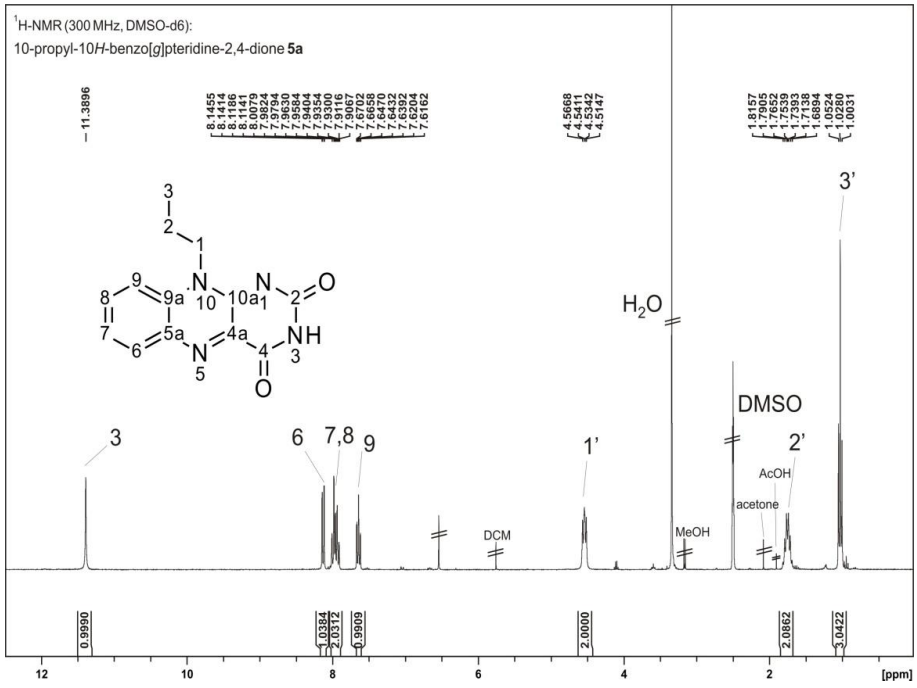
In Kapitel fünf wird ein neues Katalysator-Konzept vorgeschlagen: Ein Phenanthrolin-Flavin-Hybrid könnte als Ligand an einem Metallzentrum Reduktionen mit Flavin-Photokatalyse ermöglichen. Die Photooxidation eines Elektronendonors könnte dabei Triebkraft für eine darauffolgende Reduktion am Metallzentrum sein. Drei verschiedene Synthesewege zu einem solchen Liganden wurden untersucht, von denen keiner zum gewünschten Produkt führte. Stattdessen konnte ein Tetrahydro-Derivat erhalten und isoliert werden, welches dann zur Metallkomplexierung verwendet und in der Photokatalyse getestet wurde. Dieses neue Derivat hat ein niedrigeres Reduktionspotential als Riboflavintetraacetat und ist daher nicht geeignet, um *p*-Methoxybenzylalkohol zu oxidieren. Als Elektronendonor wurde daher Triethanolamin ausgesucht und die Reduktion von Tolan zu Stilben als Modellreaktion untersucht. Leider ergab auch diese Reaktion keinen Umsatz. Das lässt vermuten, dass die Reduktion des neuen Flavinderivats irreversibel ist und es daher nicht für die Photokatalyse geeignet ist.

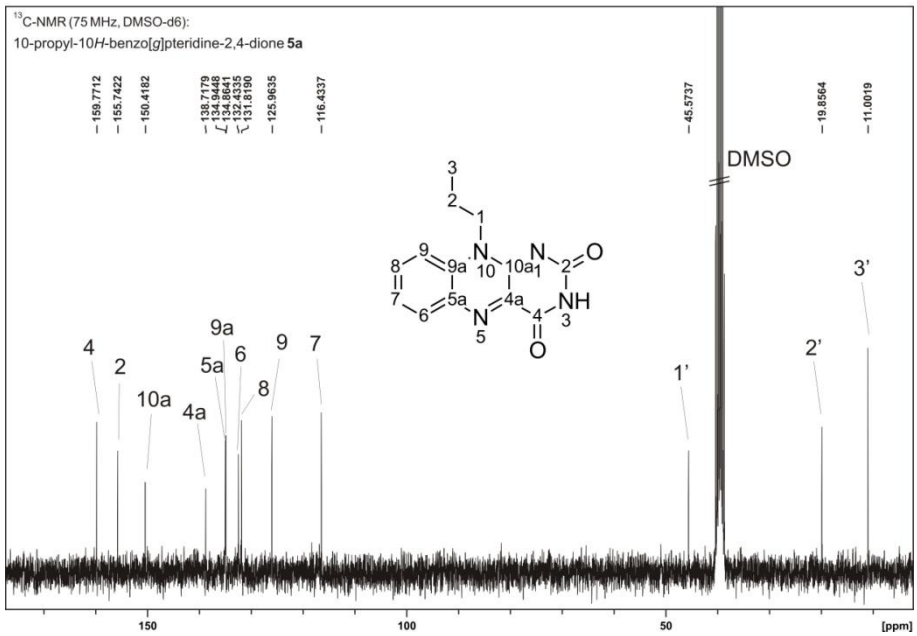
Zusammenfassend zeigt diese Arbeit neue Anwendungen der oxidativen Flavin-Photokatalyse und die Optimierung des Katalysator-System auf drei verschiedene Arten: Durch Veränderung der Aggregationseigenschaften und den Einfluss des Wasseranteils im Lösungsmittel sowie durch Schwer-Atom-Substitution. Schließlich wurde ein Phenanthrolin-Flavin-Derivat sowie sein Platinkomplex erfolgreich synthetisiert und auf seine Anwendbarkeit in der Photokatalyse untersucht.

8. Appendix

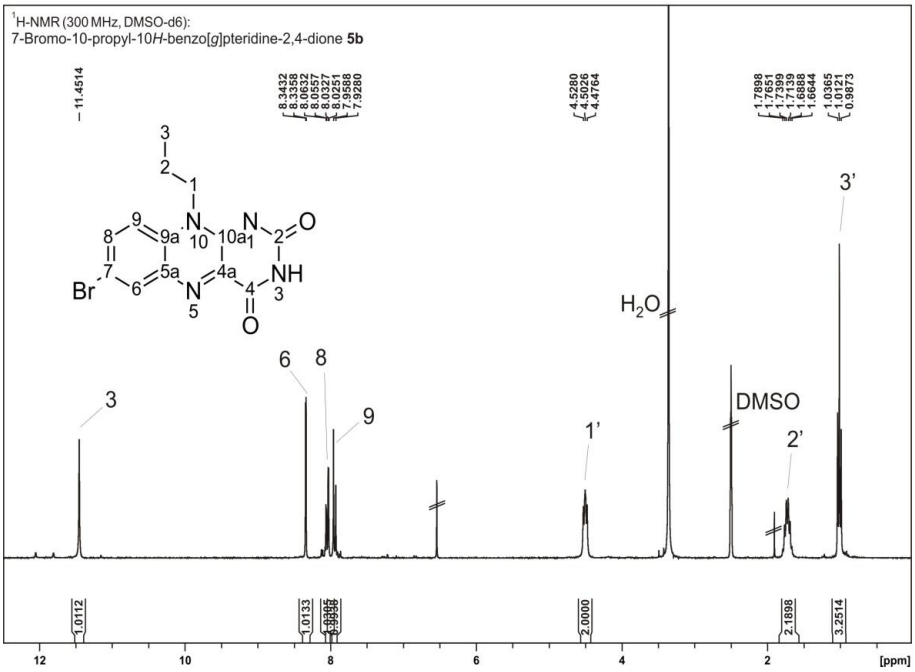
8.1. SI for Chapter 4: NMR-Spectra of New Flavins 5a-c

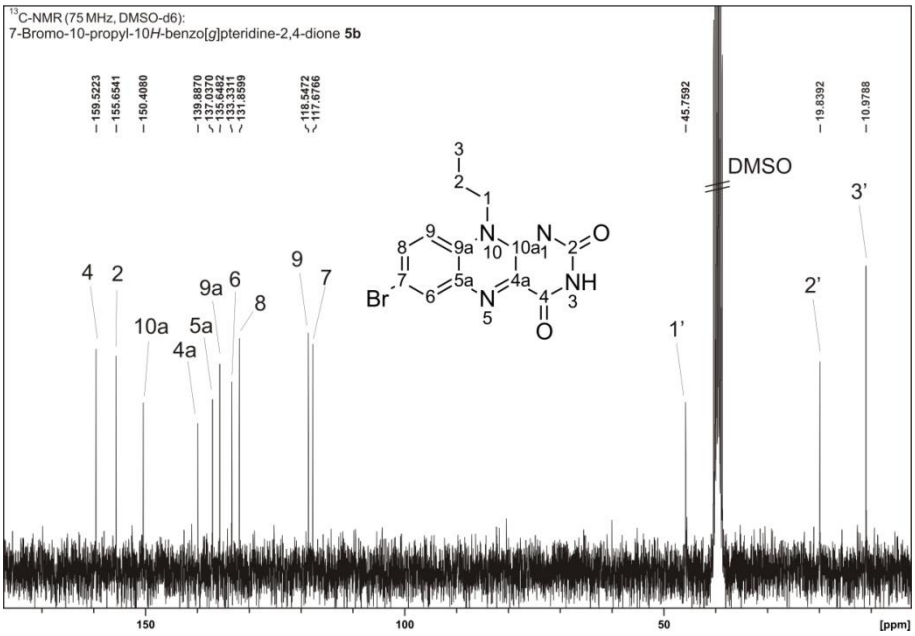
10-Propyl-10H-benzo[g]pteridine-2,4-dione 5a



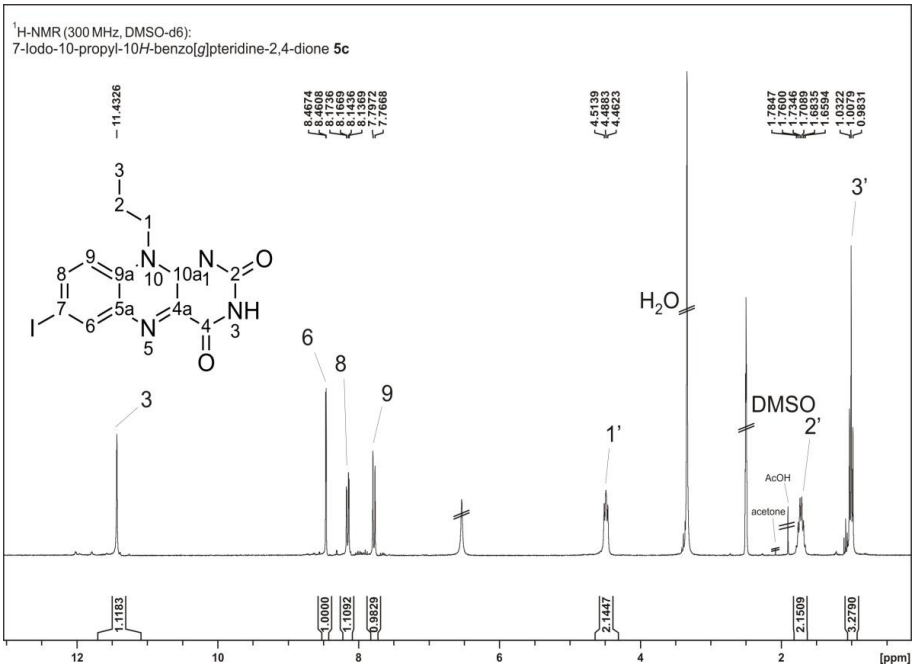


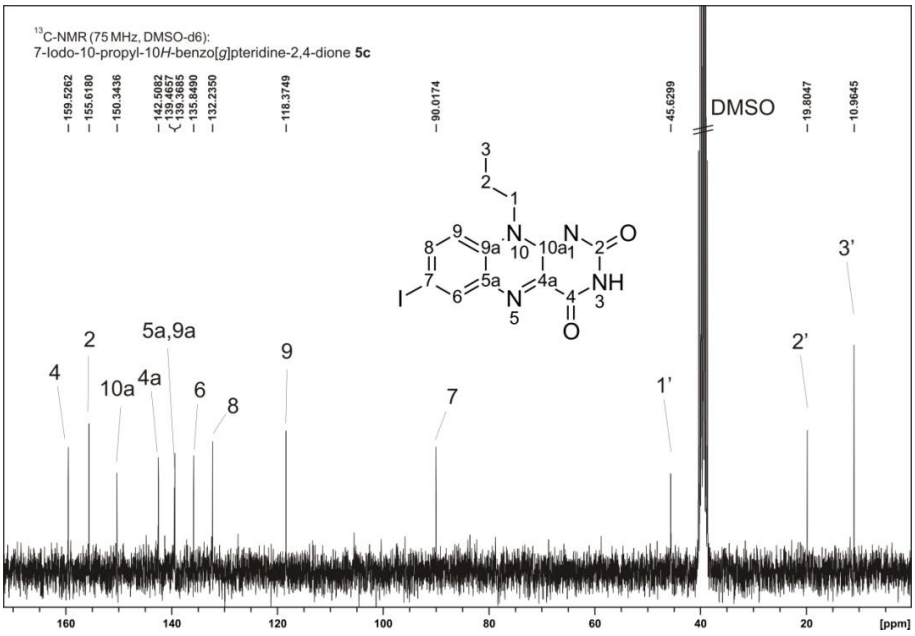
7-Bromo-10-propyl-10H-benzo[g]pteridine-2,4-dione 5b





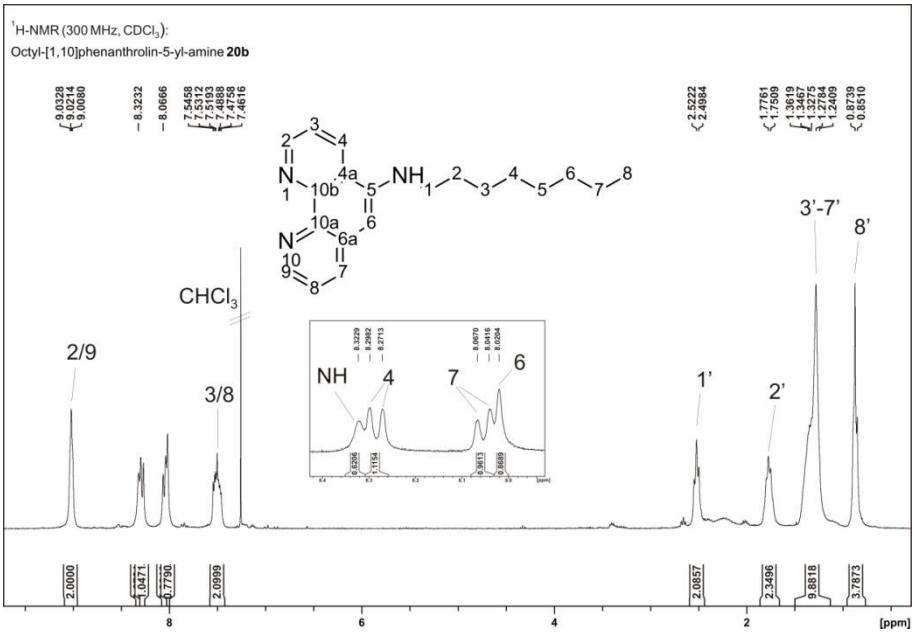
7-Iodo-10-propyl-10H-benzo[g]pteridine-2,4-dione 5c



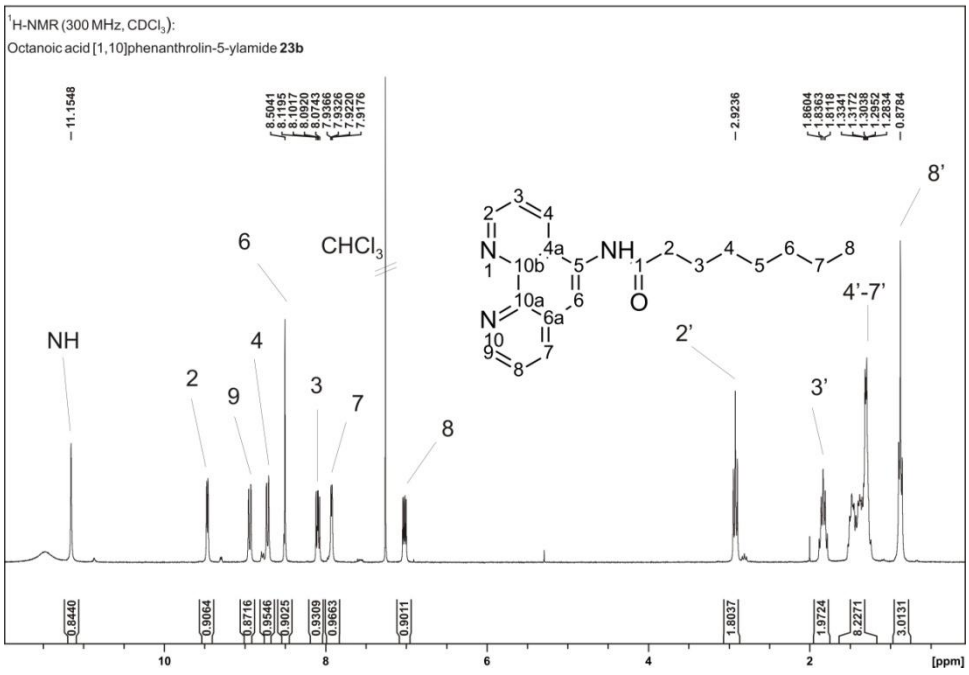


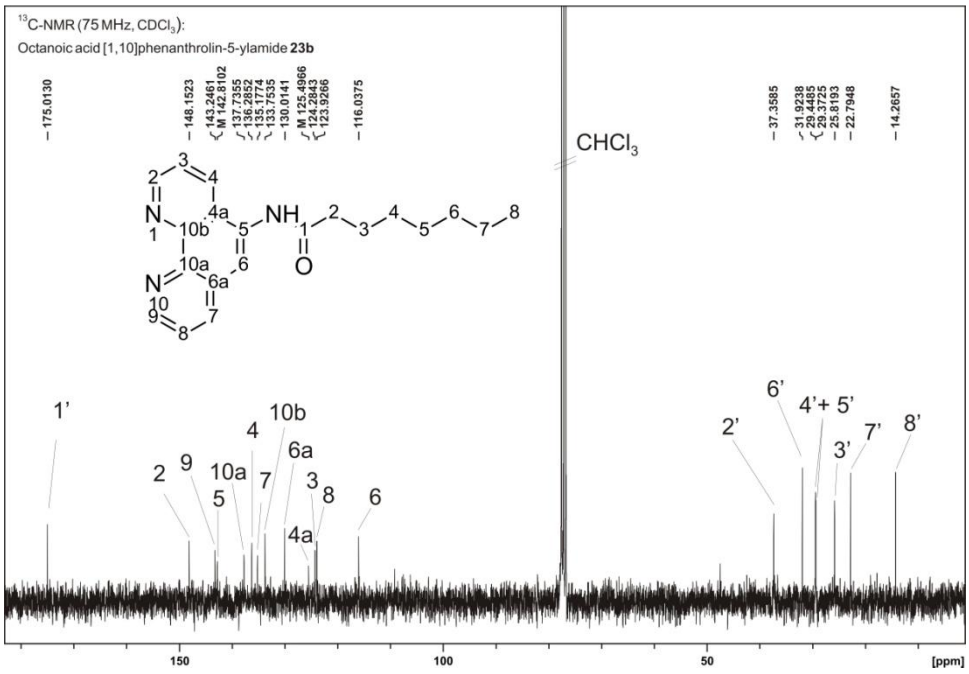
8.2. SI for Chapter 5: NMR-Spectra of New Compounds

Octyl-[1,10]phenanthrolin-5-yl-amine 20b

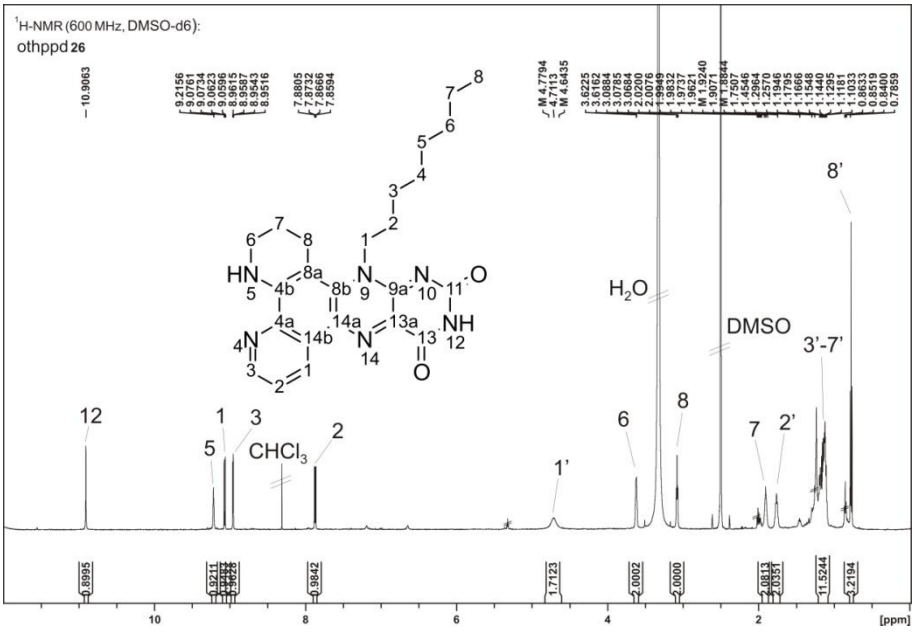


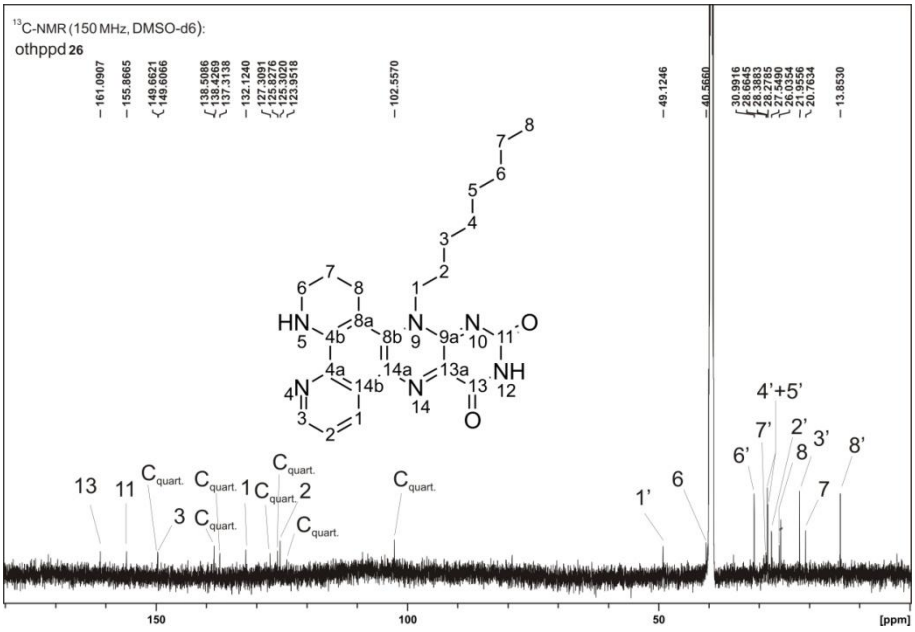
Octanoic acid [1,10]phenanthrolin-5-ylamide 23b





9-octyl-6,7,8,9-tetrahydropteridino[6,7-f]-1,10-phenanthroline-11,13(5H,12H)-dione (othppd) 26





8.3. Abbreviations

a	distance between charges (Rehm-Weller equation)
°C	degree Celsius
A	absorption
Å	Ångström
abs.	absolut
Ac	acetyl
ACN	acetonitrile
approx.	approximately
aq.	water
ATR	attenuated total reflection
b.p.	boiling point
BLUF	blue-light using FAD
Bn	benzyl
bs	broad signal (NMR)
Bu	butyl
c	concentration
c	velocity of light
ca.	approximately (lat.: *circa)*
calcd	calculated
cat.	catalytic
cf.	compare (lat.: *confer)*
cm	centimeter
d	doublet (NMR)/day
δ	chemical shift (NMR)
DADS	
dba	dibenzylidene acetone
DCM	dichloromethane
dd	double doublet (NMR)
DMA-Fl	10-(4-dimethylamino-phenyl)-isoalloxazine
dmso-d6	dimethyl sulfoxide (deuterated)
DNA	deoxyribonucleic acid
DOSY	diffusion ordered spectroscopy (NMR)
dq	double quartet (NMR)
e.g.	for example (lat.: *exempli gratia*)
E^0	standard potential
EDTA	ethylenediaminetetraacetic acid
EI	electron ionization
eq	equivalent
ESI	electrospray ionization
ESI	electronic supporting information
Et	ethyl
ET	electron transfer

et al.	and others (lat.: *et alii*, *et aliae*)
FAD	flavin adenine dinucleotide
Fc	ferrocene
Fc^+	ferrocenium
Fl	Flavin
FMN	flavin mononucleotide
fs	femtosecond
fum.	fuming
g	gramm
G	free Gibbs energy
GC	gas chromatography (FID detector)
GCMS	gas chromatography coupled with mass spectrometry
GS	
h	hour
h	Planck constant
hept	heptyl
HPLC	high performance liquid chromatography
HR	high resolution
HRMS	high resolution mass spectrometry
Hz	Hertz
I	(fluorescence) intensity
i.e.	that is (lat.: *id est*)
IR	infrared
ISC	inter system crossing
J	spin-spin coupling
K	Kelvin
k	rate constant
K_a	acid dissociation constant
kJ	kilojoule
K_s	Stern-Volmer constant
L	liter
LAH	lithium aluminium hydride
LED	light emitting diode
LOV	light, oxygen and voltage
LR	low resolution
m	mulitplet
m	molar
m.p.	Melting point
m/z	mass per charge
mA	milliampere
MBA	*para*-methoxybenzyl alcohol
MBAld	*para*-methoxybenzylaldehyde
Me	methyl
MeCN	acetonitrile

mg	milligramm
MHz	megahertz
min	minute
mL	milliliter
mm	millimeter
mmol	millimol
mOD	optical density
MS	mass spectrometry
ms	millisecond
mV	millivolt
n	normal
neg.	negative
nm	nanometer
NMR	nuclear magnetic resonance
oct	octyl
othppd	octyl tetrahydro ppd
ox	oxidized
Ph	phenyl
pos.	positiv
ppm	parts per million (NMR)
PQA	product quantum yield
PQY	product quantum yield
Pr	propyl
ps	picosecond
PT	proton tranfser
Q	quencher
q	quartet (NMR)
Q-TOF	Q – Quadrupole mass analyzer, TOF - time-of-flight mass analyzer
quant	quantitative
quart	quarternary
red	reduced
ref	reference
R_f	retention factor
RF	Riboflavin
RFTA	riboflavin tetraacetate
RT	room temperature
s	singulet (NMR)/second
SCE	saturated calomel electrode
SDS	sodium dodecyl sulfate
sec	secondary
SI	supplementary information
t	triplet (NMR)
T	temperature
T	transmission

tert	tertiary
THF	tetrahydrofuran
TLC	thin layer chromatograpghy
TMS	tetramethylsilane
TOF	turnover frequency
Tol	toluene
TON	turnover number
UHD	ultra high definition
UV	ultra violet
V	Volt
Vis	visible light
W	watt
ε	dielectric constant (Rehm-Weller equation)/extinction coefficient
λ	wavelength
λ_F	fluorescence emission wavelength
µM	micromolar
µs	microsecond
ν	frequency
τ_F	fluorescence lifetime
τ_T	triplet state lifetime
Φ	quantum yield
Φ_F	fluorescence quantum yield

9. Curriculum Vitae

Personal Details

Date and Place of Birth:	May 29th 1984, Marburg, Germany
Nationality:	German
Marital status:	single
Nationality:	German
Email:	susanne_kuemmel@gmx.de

Education

04/2009 – due 10/2012	Universität Regensburg, Faculty of Chemistry and Pharmacy, Institute for Organic Chemistry **PhD in the working group of Prof. Dr. B. König** Title: *„Chemical Photocatalysis with Flavins – New Applications and Catalyst Improvement“* Key aspects: Synthesis, characterization and development of flavin-based catalysts, reaction screening for method development Target Degree: Dr. rer. nat.
10/2003 – 02/2009	Philipps-Universität Marburg, Marburg **Chemistry Studies** Key aspects: Organic Chemistry (Diploma Thesis with Prof. Dr. A. Geyer), Theoretical/Computational Chemistry (elective subject) Diploma of Chemistry, degree: 1.3
1994 – 2003	Gymnasium Philippinum, Marburg (meanwhile: Qualification of Latin and ancient Greek) German Abitur, degree: 2.3

Work Experience

10/2011 – 04/2012	Universität Regensburg, Faculty of Chemistry and Pharmacy, **Graduate Assistant** Graduate Speaker in the DFG Graduate Collage 1626 „Chemical Photocatalysis“ (Direction and organization of seminars, coordination of the communication between graduates and professors, conceptual design and planning of research proposals)

Advancements

11/2009 – 10/2012	Deutsche Bundesstiftung Umwelt (DBU) (German Federal Environmental Foundation) **PhD Scholarship**
04/2009 – 09/2009	DFG Graduate College 640 „Photoreceptors“ **PhD Scholarship**
04/2010 – 10/2012	DFG Graduate College 1626 „Chemical Photocatalysis“ **Associated Member** (Participation in regular seminars about photochemistry and -physics, interdisciplinary cooperations in an international graduates-team)

Further Training

05/2011	Soft-Skill-Training: **Scientific Writing** Organizer: *Sprachraum*, Qualification Center LMU Munich
11/2010	Soft-Skill-Training: **Presentation Skills** Organizer: *Sprachraum*, Qualification Center LMU Munich

IT-Skills

Microsoft-Office (Excel, PowerPoint, Word), LaTeX, Origin, EndNote, Corel (Draw, Photo-Paint), ChemDraw, ACD-Labs (ChemSketch), MestReC, TopSpin, SciFinder

Languages

German	native
English	business fluent
French	basics (6 years)
Spanish	basics (2 years)

10. Publication List

10.1. Paper/Book Chapter

Robert Lechner, **Susanne Kümmel**, Burkhard König; "Visible light flavin photo-oxidation of methylbenzenes, styrenes and phenylacetic acids"; *Photochemical and Photobiological Sciences* **2010**, *9*, 1367-1377.

Maria Cherevatskaya, Matthias Neumann, Stefan Füldner, Christoph Harlander, **Susanne Kümmel**, Stephan Dankesreiter, Arno Pfitzner, Kirsten Zeitler, Burkhard König; "Visible-Light-Promoted Stereoselective Alkylation by Combining Heterogeneous Photocatalysis with Organocatalysis"; Angewandte Chemie International Edition **2012**, *51(17)*, 4062-4066; *Angewandte Chemie* **2012**, *124(17)*, 4138-4142.

Jitka Daďová, **Susanne Kümmel**, Christian Feldmeier, Jana Cibulková, Richard Pažout, Jaroslav Maixner, Ruth M. Gschwind, Burkhard König, Radek Cibulka; *Chemistry - A European Journal* **2012**, *accepted,* DOI: 10.1002/chem.201202488.

Susanne Kümmel, Radek Cibulka, Burkhard König, "Flavin Photocatalysis" in Chemical Photocatalysis, Burkhard König, ed., de Gruyter, Berlin **2013**, *submitted*.

10.2. Lecture

Susanne Kümmel, "*Vitamins for Syntheses: Photocatalysis with Flavins",* INDIGO – Indian-German Graduate School of Advanced Organic Syntheses for a Sustainable Future – PhD Research Conference and Intensive Course, February 12th-16th 2012 in Chennai (India).

10.3. Posters

Susanne Kümmel, Robert Lechner, Burkhard König, Catalysis and Photochemistry for Energy Technologies, June 29th – July 1st 2010 in Rostock (Germany).

Susanne Kümmel, Robert Lechner, Burkhard König, 3rd EuCheMS Chemistry Congress, August 29th – September 2nd 2010 in Nuremberg (Germany).

Susanne Kümmel, Robert Lechner, Burkhard König, ORCHEM, September 13th – 15th 2010 in Weimar (Germany).

Susanne Kümmel, Robert Lechner, Burkhard König, Lecture Conference of the GDCh Devision Photochemistry, September 27th – 29th 2010 in Erlangen (Germany).

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