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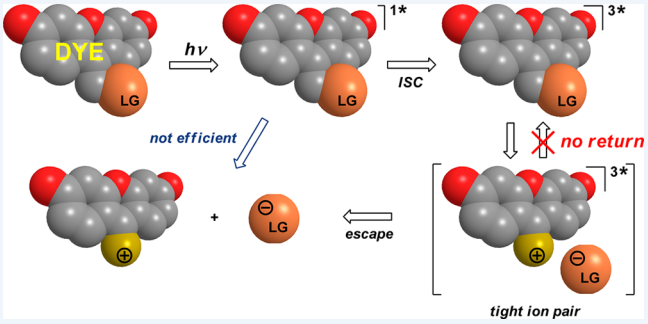
Searching for Improved Photoreleasing Abilities of Organic Molecules

Tomáš Šolomek,*,† Jakob Wirz,*,‡ and Petr Klán*,†

†Department of Chemistry and RECETOX, Masaryk University, Kamenice 5, 625 00 Brno, Czech Republic

‡Department of Chemistry, University of Basel, Klingelbergstrasse 80, CH-4056 Basel, Switzerland

CONSPECTUS: Photoremovable protecting groups (PPGs) are chemical auxiliaries that provide spatial and temporal control over the release of various molecules: bioagents (neurotransmitters and cell-signaling molecules, Ca^{2+} ions), acids, bases, oxidants, insecticides, pheromones, fragrances, etc. A major challenge for the improvement of PPGs lies in the development of organic chromophores that release the desired bioagents upon continuous irradiation at wavelengths above 650 nm, that is, in the tissue-transparent window. Understanding of the photorelease reaction mechanisms, investigated by laser flash photolysis and rationalized with the aid of quantum chemical calculations, allows for achieving this goal.



In particular, simple Hückel calculations provide useful guidelines for designing new PPGs, because both the lowest excited singlet and triplet states of conjugated systems can be reasonably well described by a single electronic configuration formed by promotion of a single electron from the highest occupied molecular orbital (HOMO) to the lowest unoccupied MO (LUMO) of the ground state configuration. Here we show that Hückel calculations permit rapid identification of common features in the nodal properties of the frontier orbitals of various chromophores that can be classified into distinct chromophore families. If the electronic excitation involves a substantial electron density transfer to an sp^2 carbon atom at which HOMO and LUMO are nearly disjoint, for example, by virtue of symmetry, favorable photoheterolysis can be expected when the corresponding atom carries a leaving group at the α-position. We show examples of photoheterolytic reactions that indicate that the efficiency of photoheterolysis diminishes for chromophores absorbing in the NIR region. We provide a rationale for more efficient photoheterolytic reactions occurring via the triplet state, and we demonstrate the advantages of this mechanistic pathway. Analogies in the structure−reactivity relationships of PPGs can therefore lead to new strategies for the development of more efficient NIR-absorbing photoremovable protecting groups.

INTRODUCTION

G. N. Lewis' structures, combined with the formalism of pushing "curly" arrows that goes back to Sir Robert Robinson, form the indispensable language of chemists to visualize organic compounds and their reactions in simple terms. Arrow pushing indicates how positive and negative charges are distributed in organic molecules through resonance. These methods had essentially been derived from the intuition of gifted chemists rather than from any solid physical background, but it was later shown that they can be mathematically related to molecular orbital (MO) theory. Unfortunately, Lewis structures are inadequate to describe the electronic structures of excited molecules and their reactivities. In fact, it is frequently found that the rules for excited state reactivity are *opposite* to those valid for the ground state; well-known examples are the Woodward−Hoffmann rules and Zimmerman's *meta*-effect.[1,2] To deal with excited molecules, we can make some predictions using suitable empirical models of photochemical reactions,[1,3] such as Dauben, Salem and Turro's reaction classifications,[4] El Sayed rules,[5] or Wagner's guidelines for estimating the type II photoreaction efficiencies of phenyl ketones.[6]

Modern quantum chemical methods provide both structures and remarkably accurate energies of electronically excited molecules and can offer valuable predictions of their reactivity. While these methods may be able to answer a given question, they are black boxes that hardly provide any guidelines for the chemist's intuition to ask the right questions. The mathematical simplicity of the Hückel MO (HMO) method has become largely immaterial thanks to the ubiquitous availability of extensive computing power, but it does keep its value for predicting trends using perturbation theory[1] and for the interpretation of and extrapolation from the results from more elaborate calculations. HMO programs are freely available on the Internet.[7] The HMO method deals only with the π systems of conjugated compounds. In most cases, both the S_1 and T_1 states of conjugated systems are reasonably well described by a single excited configuration formed by promotion of an electron from the HOMO to the LUMO of the ground state configuration. In this Account, we describe

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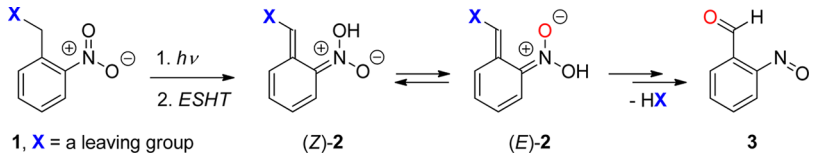
Scheme 1. Photochemistry of the 2-Nitrobenzyl Chromophore



several examples of how simple quantum chemical methods have guided us to design new photoactivatable compounds. The chromophores absorbing in the UV region are introduced first, and then we discuss strategies to design the chemical systems activatable by visible to NIR light.

■ PHOTOREMOVABLE PROTECTING GROUPS

Photoremovable protecting groups (PPGs) are chemical auxiliaries that provide spatial and temporal control over the release of molecules.[8] The release from PPGs can be triggered by one- or two-photon direct excitation, by sensitization, or by photoinduced electron transfer (PET). The design of a new PPG demands that numerous requirements are fulfilled according to the specific needs of a given application. In particular, the PPGs should absorb at sufficiently long wavelengths to avoid excitation of other (bio)molecules, and the photoreaction should be clean and efficient.[8] 2-Nitrobenzyl (oNB, **1**) derivatives[9] were introduced among the first PPGs and are the most widely used due to their robust photochemistry (Scheme 1). The *aci*-nitro intermediate **2**, from which the leaving group (LG) is released after a cascade of irreversible steps, is initially formed via an intramolecular excited-state hydrogen-atom transfer (ESHT) in the singlet or triplet excited state of **1**.[10−12] The formation of toxic nitroso byproducts, such as **3**, that absorb strongly at the wavelengths where parent **1** can be excited, thus creating an internal filter, represents one of the major drawbacks of oNB PPGs.

Photorelease by UV Light

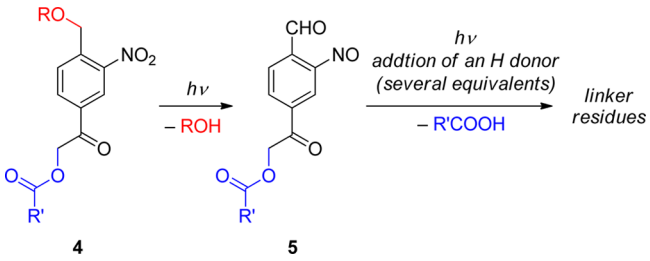
PPGs are commonly used to protect/deprotect (i.e., lock/unlock) the activities of molecules through only one functional group. Our first example is a photocleavable monochromophoric 4-acetyl-2-nitrobenzyl (ANB, **4**) linker, in which we combined the properties of oNB and phenacyl (PA) chromophores to connect two molecules through different functionalities that can be selectively disconnected in sequence upon irradiation (Scheme 2).[13] This allows for releasing a molecule attached to a support in solid-state synthesis or for drug delivery in a controlled manner.

The presence of two photoactive groups in a single chromophore raises the concern of regioselectivity of the initial photochemical step. We used a HMO calculation to predict that the LUMO of ANB is essentially a nitro-group-localized MO. Promotion of an electron to the LUMO increases the electron density on the oNB moiety of ANB in both the lowest singlet and triplet excited states, and this moiety undergoes the initial photochemical reaction releasing the first leaving group (LG). As a result, the nitro group is reduced to a nitroso group to give **5**. The PA moiety requires that a hydrogen donor, such as propan-2-ol, is present to reduce the carbonyl group in its ^{3}n,π^* state in order to release the second LG.[14] A HMO calculation shows that the LUMO in **5** is localized on the nitroso group, which must therefore be chemically reduced prior to the PA carbonyl group. Indeed, at least 2 mol equiv of a H atom donor was necessary to accomplish complete photorelease of the second protected substrate.

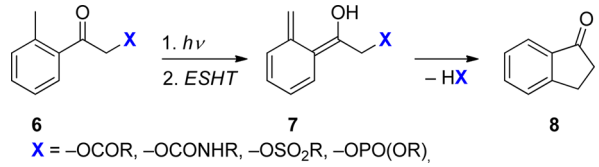
Many alternative PPGs have been developed that overcome some of the disadvantages of oNB PPGs, but so far none of them gained a comparably broad interest. For example, the 2-alkylphenacyl PPG **6** (Scheme 3) was introduced and studied in our laboratories since 2000.[15−19] Various LGs on the α-carbon are efficiently released upon irradiation via short-lived xylylenol intermediates **7**, forming the nonreactive indanone side-product **8**.

We aimed at extending the versatility of the 2-methylphenacyl chromophore for synthetic applications by coupling the photoenolization with concomitant epoxide ring-opening in 2,5-dimethylbenzoyl oxiranes **9** (Scheme 4).[20] Irradiation of **9** (R^1 = H, R^2 = CH_3) leads to intramolecular ESHT in the ^{3}n,π^*

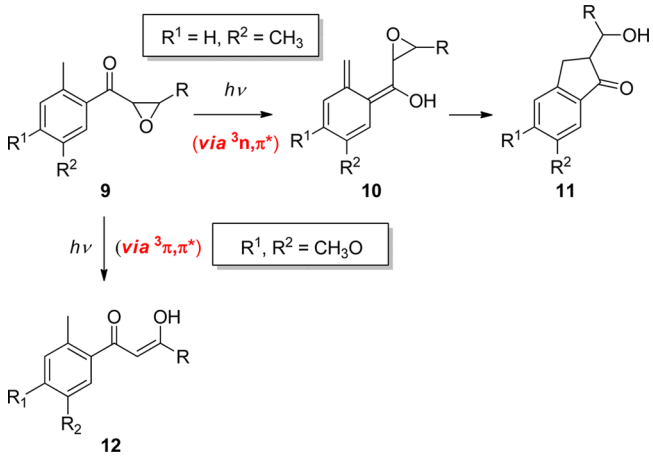
Scheme 2. Photocleavable Monochromophoric Linker Carrying Two Different Leaving Groups



Scheme 3. Photochemistry of 2-Alkylphenacyl PPGs



Scheme 4. Photochemistry of 2-Methylbenzoyl Oxiranes 9



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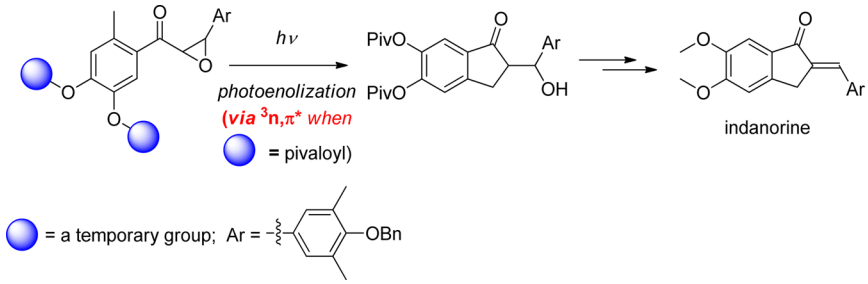
Scheme 5. Strategy of an Electronic-State "Protection" in the Synthesis of Indanorine



excited state via xylylenols **10** to give hydroxymethylindanone **11**. Unfortunately, the reaction persisted only with weakly donating alkyl groups on the aromatic ring. When more strongly electron-donating methoxy substituents, which are frequently encountered in a number of pharmaceutically interesting indanones such as donepezil,[21] were attached to the chromophore **9**, the course of the photoreaction was altered, and homolytic ring-opening resulted in the formation of the unwanted photoproduct **12** (Scheme 4).

It is well-known that electron donors in the *para* position of phenyl ketones stabilize the $^3\pi,\pi^*$ excited state.[22] Thus, we assumed that the lowest excited triplet had been switched from the productive ^{3}n,π^* to a $^3\pi,\pi^*$ state. A "protection" of the ^{3}n,π^* state was therefore needed to retain the selectivity of this photoreaction. This can be achieved by introduction of temporary "dummy" groups (Scheme 5). However, only the experimental rate constants for bimolecular ESHT of monosubstituted acetophenones were available,[22] and just a few of them have been determined for bi- and multiply substituted acetophenones. It was therefore difficult to predict on an empirical basis which temporary groups could be employed to preserve the desired ^{3}n,π^* lowest state. Quantum chemical calculations allowed us to avoid excessive trial-and-error experiments. In this case, the HMO method would not help and a calculation that goes beyond the MOs of π symmetry was required. We chose a suitable group from a small library generated by DFT calculations.[23] The selected substrate was synthesized and the desired selectivity was indeed retained; the target indanone derivative was formed as the sole photoproduct (Scheme 5).

Although the DFT calculation is a black box in this case, valuable insight can be obtained by inspecting the geometries optimized for differently substituted triplet-excited molecules **9**. Two adjacent bulky groups (R^1, R^2 = acyloxy) impose a considerable steric hindrance, and as a result, both rotate out of the plane of the benzene ring, which reduces the conjugation so that the group in the *para* position acts as a hyperconjugative σ-acceptor.[24]

Photorelease by Visible Light

Short-wavelength UV radiation is not compatible with many applications, especially in biology and medicine, because it can induce adverse side reactions in other molecules. Three general strategies that profit from visible light activation to overcome this obstacle are available: (1) direct excitation by visible light, (2) photosensitization via energy or electron transfer from a sensitizer, and (3) two-photon excitation-induced release using pulsed long-wavelength radiation. Here we discuss the first two approaches.

Only a few known PPGs can be activated directly by visible light. Yet, photorelease induced by light of wavelengths above 650 nm (the region of 650−950 nm is called a phototherapeutic or tissue-transparent window)[25] is most desired in biological and medical applications. A measure of the photorelease efficiency is given by the product of the quantum yield and the decadic molar absorption coefficient, $\Phi\varepsilon(\lambda_{irr})$, sometimes called the *uncaging cross section*.[8] For example, a common UV-light absorbing PPG may release a LG with a quantum yield of Φ_{rel} = 0.1−0.5 at 350−400 nm, but the ε values often do not exceed 100 M^{-1} cm^{-1}. Hence $\Phi_{rel}\varepsilon(\lambda_{irr})$ is in the range of 10−50 M^{-1} cm^{-1}. On the other hand, if the $\varepsilon(\lambda_{irr})$ value of a visible-light-absorbing PPG is large, for example, ∼5 × 10^4 M^{-1} cm^{-1}, Φ_{rel} may be below 10^{-3} yet providing a comparable uncaging cross section. Moreover, working with a PPG with strong absorbance in the visible region that releases a LG more efficiently would be difficult under ambient light.

Heterolytic photodissociation is facilitated when the electronic excitation to the lowest singlet excited state involves a substantial transfer of electron density to the sp^2 carbon atom of the chromophore that carries a LG in the α-position, whose σ-antibonding orbital is mixed with the chromophore's LUMO. This is the basis of Zimmerman's *meta*-effect in the photosolvolysis of methoxybenzyl acetates (Figure 1).[2] A related

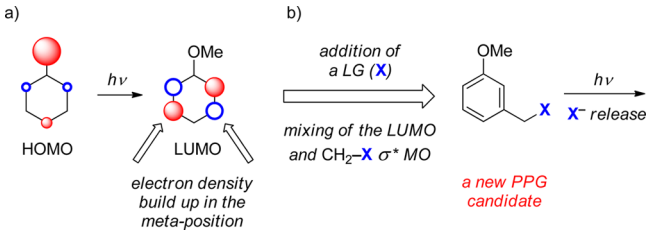


Figure 1. (a) Rationalization of Zimmerman's *meta*-effect and (b) its use in the design of a PPG candidate.

example is given by the observed rate constants for fluoride elimination, k_{-F}, from eight isomers of singlet excited trifluoromethylnaphthols; $\log(k_{-F}/s^{-1})$ increases linearly with the calculated excited state charge density q^* at the CF_3-substituted carbon atom: $\log(k_{-F}/s^{-1}) = (-5.2 \pm 1.3) + (11.7 \pm 1.1)q^*$, $R^2 = 0.95$.[26]

The same principle explains the photochemical activity of coumarinyl-4-methyl PPGs with the α-carbon bearing a LG positioned where the coumarin has the largest coefficient in the LUMO but a negligible contribution to the HOMO (Figure 2a). Promotion of an electron from the HOMO to the LUMO weakens the C−LG bond and induces rapid heterolytic dissociation with release rate constants on the order of $k_{rel} \approx 10^9$−10^{10} s^{-1}.[27,28] Coumarins have found a number of applications in biological and material chemistry as PPGs,

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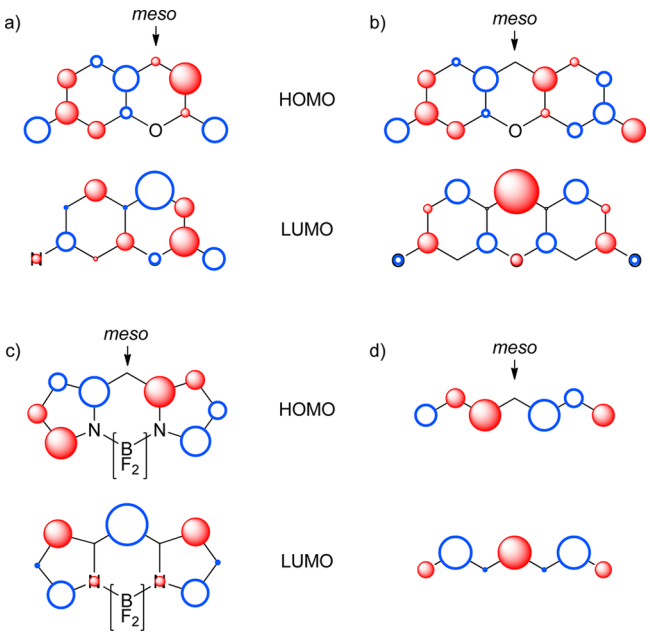


Figure 2. Hückel HOMO (top) and LUMO (bottom) of π-systems of (a) coumarin, (b) xanthene, (c) BODIPY, and (d) trimethine cyanine chromophores. The following heteroparameters were used: $h_{O(exocyclic)} = 1.5$, $k_{CO(exocyclic)} = 0.9$; $h_O = 2.0$, $k_{CO} = 0.66$; $h_N = 1.75$, $k_{CN} = 0.9$; the saturated $[-BF_2-]^-$ moiety was ignored.

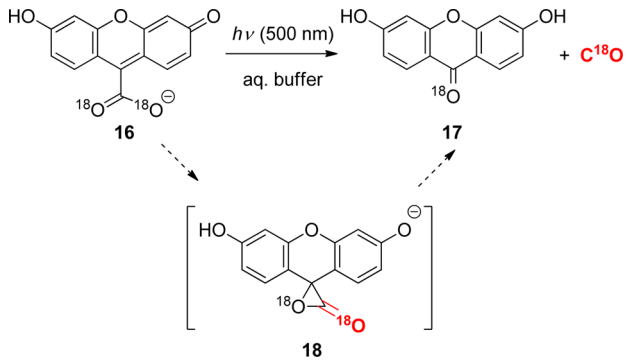
and their reactivity and photophysics are well-understood.[28−30] Although the absorption of some derivatives extends to the visible region, no coumarin can be photoactivated directly by irradiation above 450 nm.[8,27]

Fusion of another aromatic ring to the coumarin chromophore leads to a xanthene dye and shifts the absorption well into the visible region. The HMO method reveals that the favorable nodal properties of the frontier MOs of coumarins are preserved, with the HOMO and LUMO *disjoint* at the *meso*-position (Figure 2b). As a result, fluorescein features an increase in negative charge of $c_{meso,LU}^2 - c_{meso,HO}^2 = 0.37$ at the *meso* carbon atom upon HOMO−LUMO excitation. We expected that a LG attached to this position through an α-carbon should be heterolytically released.

We tested this hypothesis by synthesizing the (6-hydroxy-3-oxo-3*H*-xanthen-9-yl)methyl derivatives **13a,b** (Scheme 6).[31] Most xanthene derivatives, such as fluorescein, have an aromatic substituent at position C9. Attempts to install a saturated oxymethyl linker to this position, as well as many alternative synthetic procedures, were not successful. Only 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was a sufficiently strong agent to oxidize 9*H*-xanthene-3,6-diol derivatives as synthetic precursors to **13a,b** in the last step. However, only 1:1 complexes with DDQ (**13a,b**·DDQ) were obtained that could not be separated from DDQ. These compounds released the LGs (*O,O*-diethyl phosphate or acetate) upon irradiation in almost quantitative chemical yields in aqueous media, and the chromophore thus became the first transition-metal-free PPG that absorbed over 500 nm. The disappearance quantum yields were relatively low (~0.01) but, owing to the large molar absorption coefficients of ~4 × 10^4 M^{-1} cm^{-1} at 520 nm, the uncaging cross sections were satisfactory, $\Phi\varepsilon(\lambda_{irr}) \approx 100$ M^{-1} cm^{-1}.

Surprisingly, we found that 6-hydroxy-3-oxo-3*H*-xanthene-9-carboxylic acid (**14**, Scheme 6) is the side-product formed by release of the leaving group from **13a,b**·DDQ, presumably by oxidation of the anticipated primary product 6-hydroxy-9-hydroxymethyl-3*H*-xanthen-3-one (**15**, Scheme 6) by DDQ present in the solution. We noticed that **14** and its isotopomer **16** were photochemically active; irradiation of **16** at 500 nm in phosphate buffer at pH 7.4 gave 3,6-dihydroxy-9*H*-xanthen-9-one (**17**, Scheme 7) exclusively with a quantum yield Φ of

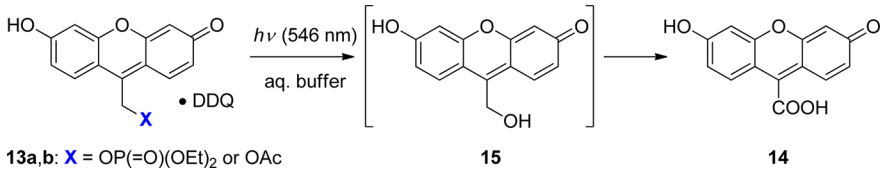
Scheme 7. Photochemistry of Isotopically Labeled 16



(6.8 ± 3.0) × 10^{-4}. A 6-fold increase in the quantum yield was obtained at pH = 5.7, at which **16** and its conjugate base possess equal absorbances at the excitation wavelength. The $\Phi\varepsilon(\lambda_{irr})$ was then on the order of 10 M^{-1} cm^{-1} at $\lambda_{irr} \approx 500$ nm and pH = 7.

The concomitant release of carbon monoxide was the most exciting feature of this transformation. Various carbon monoxide-releasing molecules (CORMs) are available to study the biological effects and therapeutic potential of CO.[32,33] With the exception of unsaturated cyclic α-diketones,[34] only transition-metal containing photochemical CO-releasing molecules (photoCORMs) had been reported to be triggered by visible light by 2014.[32,33] The simultaneous irradiation of **16** and uncomplexed methemoglobin (MetHb, Fe^{II}) in an aqueous solution at 503 nm led to the formation of carbonylhemoglobin (COHb) that was detected spectroscopically at 440 nm (Figure 3).[35] The distinct absorption bands of all species involved, **16**, MetHb, and COHb, provided the means for the simultaneous observation of CO complexation. Compound **16** with $\Phi\varepsilon(\lambda_{irr})$ = 10 M^{-1} cm^{-1} therefore represented a new generation of organic photoCORMs that efficiently release CO.

Scheme 6. Photochemistry of 13a,b·DDQ



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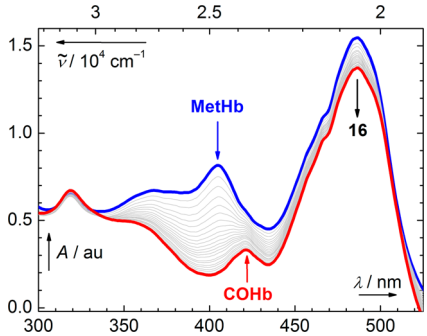


Figure 3. Absorption spectra measured following irradiation of **16** (black arrow) in the presence of methemoglobin (MetHb, blue arrow) and $Na_2S_2O_4$ in degassed aqueous phosphate buffer at pH = 7.4 at 503 nm.[35] The initial (blue bold line) and final (red bold line) spectra are highlighted. The rise of a band due to the product COHb is marked by the red arrow.

The reaction of the isotopically labeled **16** suggested that the α-lactone **18** is formed upon irradiation, possibly involving a photoinduced intramolecular electron transfer (see the BODIPY derivatives below), which decarbonylates to form **17**. It is known that oxiranones are short-lived reactive compounds that efficiently undergo decarbonylation.[36]

A different approach involved a 1,3-dithian-2-yl substituent at the *meso*-position of pyronin (**19**, Scheme 8).[37] This compound exhibits strong absorption ($\lambda_{max} \approx 580$ nm) and emission ($\lambda_{max} \approx 610$ nm) in aqueous solutions, and irradiation at the major absorption band leads ($\Phi \approx 0.03\%$) to a stable photoproduct, xanthenone **20**, that absorbs below 430 nm. Electron transfer or direct thiolate release could lead to C−C bond cleavage in the pyronin chromophore. The mechanism is still under investigation in our laboratory.

Because the syntheses of compounds **13** and **14** are cumbersome and we could not find alternative pathways to produce them in sufficient quantities that would allow us to modify the xanthene chromophore properties and shift its absorption to still longer wavelengths, we decided to look for an alternative chromophore exhibiting similar photoreactivity that could be easily prepared and modified.

By analogy to the xanthene derivatives, we searched for chromophores that would possess equivalent nodal characteristics of their frontier MOs using HMO calculations. We found that coumarin, xanthene, dipyrromethene, and cyanine dyes share the same features in their frontier MOs (Figure 2) and can, therefore, be considered as a single family of chromophores. Since the syntheses and photophysics of many of these dyes are well established, our finding offered potential for the development of new photoactivatable compounds that absorb light in the visible or NIR region. A few examples that confirm this concept are discussed below.

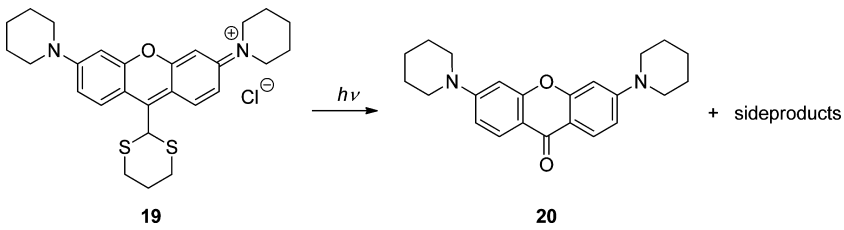
Boron-dipyrromethene (BODIPY) is a popular dye that has received considerable attention in the past decade due to its distinctive and easily tunable optical properties as well as a number of applications. As xanthene, BODIPY shows an antisymmetric HOMO with a nodal plane at the *meso* position, where it possesses the largest coefficient in the LUMO (Figure 2c). A charge increase of $c_{meso,LU}^2 - c_{meso,HO}^2 = 0.30$ at the *meso* carbon atom upon HOMO−LUMO excitation was obtained by a HMO calculation, and therefore we decided to test the corresponding BODIPY derivatives as photoCORMs and PPGs.

The *meso*-carboxy BODIPY (COR-BDP) derivatives **21a,b** (Scheme 9) were synthesized and tested for their photochemical release of CO in both *in vitro* and *in vivo* experiments.[38] This new generation of purely organic photoCORMs was found to be thermally stable but activatable by irradiation with visible-to-NIR light in aqueous buffer (pH = 7.4) solutions. COR-BDPs **21a,b** undergo decarbonylation upon irradiation in degassed solutions with quantum yields of 2.7×10^{-4} and 1.2×10^{-5} and corresponding $\Phi_{rel}\varepsilon(\lambda_{irr})$ values on the order of approximately 10 and 1 M^{-1} cm^{-1}, respectively. Compound **21b** releases CO not only upon excitation at its major absorption maxima (368 and 652 nm) but also at the absorption tail in the near-infrared region (732 nm) (Figure 4). To our knowledge, the derivative **21b** is the first caged transition-metal-free compound that efficiently releases a molecule upon one-photon excitation with near-infrared photons.

Steady-state and transient spectroscopy experiments and DFT calculations were performed to study the CO-release mechanism from COR-BDPs. Our results provided evidence that an electron is transferred from the carboxylate moiety reducing the BODIPY chromophore in the triplet state. An oxyallyl-type triplet diradical **22** (Scheme 9) that would be formed by such a process must then decay by intersystem crossing (ISC) to the singlet ground state where it forms the α-lactone **23**, which releases CO, analogously to **16**.[35] The fate of the triplet diradical **22** has striking similarities with that appearing in the photo-Favorskii rearrangement of *p*-hydroxyphenacyl[39,40] (pHP) PPGs and demonstrates the importance of the nodal properties of the chromophore's frontier MOs (see Figure 2 and Schemes 9 and 11).

To show that BODIPY can be used as a PPG, we prepared the *meso*-oxymethyl BODIPY derivatives **24** (Figure 2; Scheme 10).[41] The synthesis was easy in this case, and the compounds released a carboxylate as a LG in aqueous solutions upon irradiation at $\lambda_{irr} \approx 500$ nm with efficiencies comparable to that of **13**. However, before we finished this work, two excellent papers by the independent research groups of Weinstein[42] and of Winter appeared,[43] reporting photorelease from the same type of the BODIPY cages. The QYs of the release of

Scheme 8. Photochemistry of 19



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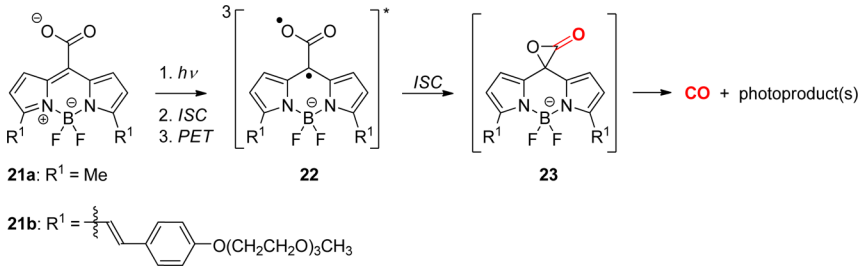
Scheme 9. Photochemistry of 21



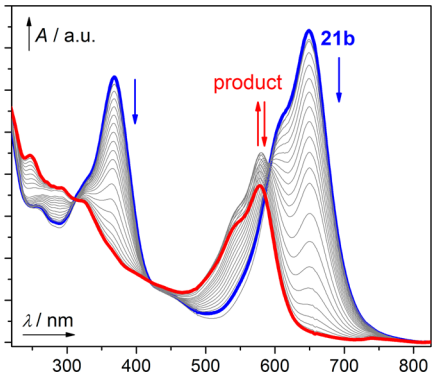
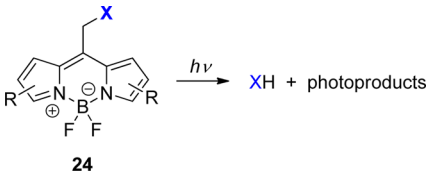


Figure 4. Irradiation of **21b** at 625 nm at pH = 7.4.[38] The spectra before (blue line) and after (red line; the photoproduct initially formed degrades upon prolonged irradiation) irradiation are highlighted.

Scheme 10. Photochemistry of 24



carboxylates are low, but the corresponding $\Phi_{rel}\varepsilon(\lambda_{irr})$ values ($\leq$117) at $\lambda_{irr} \approx$ 500−550 nm are encouraging.

The successful release of both CO and carboxylates from the BODIPY derivatives adds more credibility to our hypothesis that the design of new photoactivatable compounds can be predicted simply by analyzing the frontier MOs of various chromophores using HMO calculations. The Φ_{rel} in the new BODIPY PPGs and COR-BDPs are somewhat lower than those reported for the xanthene analogues, and the values are expected to decrease further for derivatives that possess markedly red-shifted absorption[44] (e.g., compare Φ of COR-BDPs **21a** and **21b**). Unfortunately, the corresponding $\varepsilon(\lambda_{irr})$ values do not sufficiently compensate for the decrease of Φ_{rel}, and the product $\Phi_{rel}\varepsilon(\lambda_{irr})$ diminishes as well when the energy of the lowest excited state is lowered. A major challenge is thus to achieve a relatively efficient photoactivation, especially for derivatives that absorb NIR photons, by increasing the Φ_{rel}. Here, we propose a strategy based on our experience with UV-light absorbing PPGs to achieve this goal.

It has been previously shown that the elevated ground-state energy surfaces resulting from the generation of destabilized cations derived from, for example, coumarins or xanthenes, in conjunction with stabilized excited-state surfaces, can lead to productive conical intersections (CIs) along the heterolysis reaction coordinate.[45] The similarity of the nodal properties of the frontier MOs of dipyrromethenes and cyanines suggests that PPGs derived from them will share similar features in their heterolytic photodissociation. The excited-state heterolysis rate constants of different LGs from coumarins exhibit a Brønsted linear free-energy relationship showing that a barrier is encountered before the CI, at which the photoexcited system returns to the ground state.[27] For excellent nucleofuges, most of the singlet excited state molecules follow the productive pathway to the primary ground state tight ion-pair with >90% efficiency,[28] that is, the branching ratio at the CI largely favors heterolysis with only small losses due to regeneration of the starting material. There are three major processes that decrease the overall quantum yield, for mediocre LGs in particular. Two of them, fluorescence and internal conversion (IC), take place before the excited molecule overcomes the reaction barrier in the excited state, while the strongly exothermic ion-pair recombination competes with the escape of the ions from the solvent cage. The corresponding processes with their associated potential energy surfaces are depicted in Figure 5.

This scenario resembles a seemingly unrelated photoreaction, the ESHT in oNB compounds (Scheme 1). There, the Φ_{rel} of different LGs depend markedly on the type of the LG at the benzylic position, albeit in an inverted fashion, with good LGs being responsible for low Φ_{rel}.[12,46] The reason is a different stabilization of the radical center, which emerges in the benzylic position along the ESHT reaction coordinate, by different LGs. The compounds with LGs that are good radical stabilizers have earlier transition states with a lower energy and undergo more efficient ESHT to form the *aci*-nitro intermediates **2** with higher Φ_{rel}. Calculation of the corresponding excited state energy surfaces for a series of oNB systems revealed that their shapes change according to the Bell−Evans−Polanyi principle as shown in Figure 6.[12] Besides fluorescence and IC, the most important process that depletes the population of the S_1 state is a rapid spin−orbit-coupling-driven ISC populating the triplet state. Both the lowest excited singlet and triplet states in oNBs can be described by a single n,π^* configuration, where an electron is promoted from a nonbonding orbital in the nitro group to an antibonding π-orbital. These states differ by the spin of one electron but their corresponding energy surfaces are similar with nearly the same barriers to ESHT. Although the surfaces are similar, there are significant differences that offer a valuable lesson to learn.

Lifetimes of molecules in their triplet state are usually much longer than those of molecules in the singlet excited state because emission and radiationless processes are spin-forbidden. Specifically, no rapid population transfer occurs at crossings of a triplet and a singlet surface unlike at a crossing between two singlet surfaces. Therefore, a molecule that faces an impenetrable barrier on the singlet excited surface, and eventually is deactivated by IC or fluorescence, has much longer

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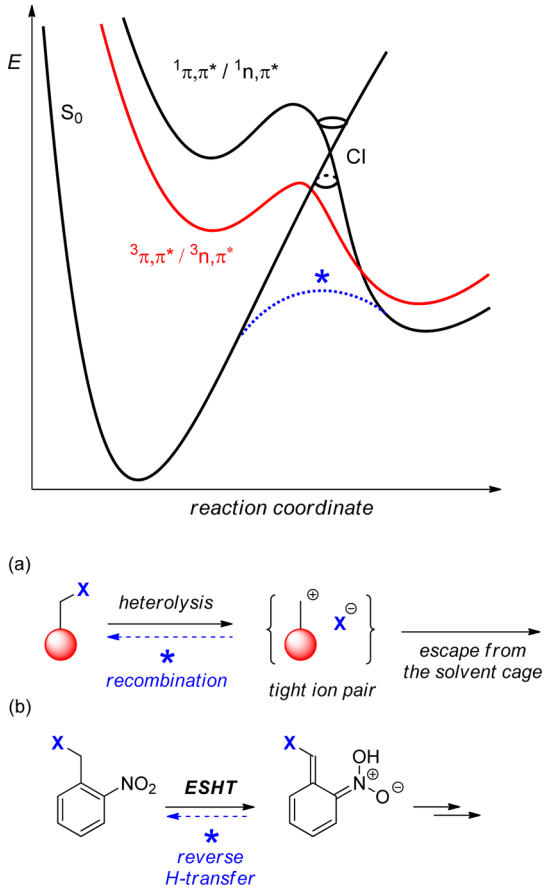

Figure 5. Potential energy surfaces for (a) photochemical heterolysis or (b) excited state hydrogen transfer in the lowest excited singlet (black line) and triplet (red line) states.

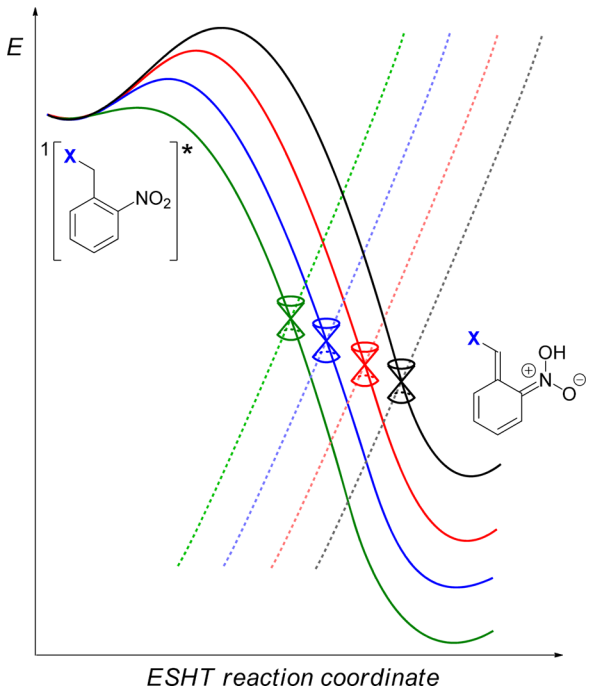

Figure 6. Demonstration of the Bell–Evans–Polanyi principle in the ESHT in oNB with different LGs providing different stabilization (decreasing from green to black) to the nascent benzylic radical center along the ESHT reaction coordinate.

time to surpass a comparable barrier in the triplet state. This can be demonstrated on oNB derivatives **1** with different LGs.[12,46] An oNB with an excellent radical-stabilizing LG, such as an amino group, was predicted to undergo essentially barrierless ESHT in the singlet excited state, and its Φ_{rel} is determined by the branching ratio at the S_1/S_0 CI. On the other hand, a molecule with a moderate radical-stabilizing group, such as an alkoxy group, encounters a barrier that is difficult to overcome within the ultrashort lifetime of oNB in its S_1 state. Deactivation of the S_1 state by rapid ISC thus transfers most of the population to the triplet state with nearly the same ESHT barrier, and with a lifetime that would be longer by 2 orders of magnitude if the ESHT was absent. Note that a triplet molecule "ignores" the triplet/singlet crossings along the triplet ESHT coordinate. As a result, all triplet molecules undergo efficient ESHT, and the overall Φ_{rel} is higher for the latter LG, though the ESHT faces a higher reaction barrier. This scenario, suggested by calculations,[12] was in good agreement with experimental observations,[13,46] and it offers a strategy to design NIR-light-absorbing PPGs that efficiently release the LG by heterolytic photodissociation in the triplet state.

Indeed, efficient triplet state heterolysis has precedent in two examples studied previously in our laboratories, the benzoin[47,48] and *p*-hydroxyphenacyl[39] (pHP) PPGs. Both compounds are derived from the phenacyl chromophore which is known to undergo rapid ISC because the singlet n,π* and triplet π,π* states are close in energy.[49] Photoheterolysis in the pHP analogues **25** (Scheme 11) formally leads to a triplet cation that stabilizes itself considerably by instantaneous ejection of the phenolic proton to form a triplet oxyallyl-type diradical **26**.[39,40,50] The release rates and the quantum yields reported for pHPs are among the highest of photoheterolytic reactions[8,27,51] and demonstrate the favorable photophysical features of the productive triplet state where recombination of the triplet tight ion pair is prohibitively endothermic (Figure 5).

A HMO calculation reveals that the oxyallyl diradical **26** is isolobal with the destabilized cations that were found by Winter and collaborators to have a nearby CI along the heterolysis reaction coordinate.[45,52] As a matter of fact, the phenacyl chromophore (Scheme 11b) belongs to the same family of chromophores as those depicted in Figure 2 in terms of the nodal properties of the frontier MOs. This suggests a similar scenario for their triplet heterolysis provided that their corresponding oxyallyl-derived cations are stable enough to avoid homolysis.[44]

The chromophores absorbing visible or NIR light unfortunately display low ISC rates that result from small spin–orbit coupling because their lowest $^1\pi,\pi^*$ state lies well below any ^{3}n,π* state. A considerable amount of work is thus needed to improve the existing visible-light-absorbing chromophores to enhance their ISC rates. Strategies overcoming this obstacle employing heavy-atom-effect mediators[53] or chromophore dimers[54] to increase the spin–orbit coupling are already emerging in the literature.

■ CONCLUSIONS

Recent advances to improve properties of PPGs using various experimental strategies and quantum chemical calculations are described in this Account. Several organic chromophores absorbing at the red edge of the visible region with satisfactory uncaging cross sections were discovered, and a strategy for the design of more efficient heterolysis via the triplet state is proposed.

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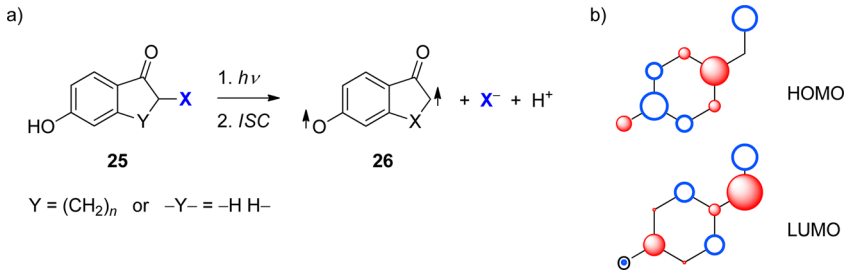
Scheme 11. (a) Photoheterolysis of LGs from pHP-based PPGs and (b) HOMO and LUMO of a phenacyl chromophore



■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: tom.solomek@gmail.com.
*E-mail: j.wirz@unibas.ch.
*E-mail: klan@sci.muni.cz.

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Notes

The authors declare no competing financial interest.

Biographies

Tomáš Šolomek obtained his Ph. D. jointly at Masaryk University and University of Fribourg with Prof. Petr Klán and Prof. Thomas Bally. He was a postdoctoral fellow with Dr. Michal Juríček at University of Basel and is currently on his move to Northwestern University (Prof. Michael Wasielewski). His research focuses on anything that is fun to learn.

Jakob Wirz studied chemistry at the ETH Zurich and obtained his Ph.D. with Prof. E. Heilbronner. He is Emeritus Professor of chemistry from the University of Basel. His work centered on photochemistry and spectroscopy, laser flash photolysis, reaction mechanisms, and photoremovable protecting groups.

Petr Klán obtained his Ph.D. at Michigan State University under the supervision of Professor Peter J. Wagner. He is Professor at Masaryk University, Brno, Czech Republic. His current research focuses on photochemistry, mechanisms of organic reactions, photoremovable protecting groups and fluorophores, and environmental photochemistry.

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