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VIP *Very Important Paper*

Remote Photodamaging of DNA by Photoinduced Energy Transport

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Local DNA photodamaging by light is well-studied and leads to a number of structurally identified direct damage, in particular cyclobutane pyrimidine dimers, and indirect oxidatively generated damage, such as 8-oxo-7,8-hydroxyguanine. Similar damages have now been found at remote sites, at least more than 105 Å (30 base pairs) away from the site of photoexcitation. In contrast to the established mechanisms of local DNA photodamaging, the processes of remote photodamage are only partially understood. Known pathways include those to remote oxidatively generated DNA photodamages, which were elucidated by studying electron hole transport through the DNA about 20 years ago. Recent studies with DNA photosensitizers and mechanistic proposals on photoinduced DNA-mediated energy transport are summarized in this minireview. These new mechanisms to a new type of remote DNA photodamaging provide an important extension to our general understanding to light-induced DNA damage and their mutations.

1. Introduction

DNA is the biopolymer used by all living organisms for the storage of their genetic information as encoded by the sequence. Exposure of DNA to solar light, in particular energy-rich UV light, is as frequent and serious threat for the integrity of the genetic information. UV light induces different types of photodamages[1] that cause mutations,[2] and, in the worst case, cancer.[3] Therefore, the understanding of excited state dynamics in DNA is fundamentally important to unravel the different pathways to DNA photodamages. In general, UV light is divided into UV-A light (400 nm–320 nm), UV-B light (320 nm–280 nm) and UV-C light (280 nm–100 nm). UV-C light is efficiently absorbed by the ozone layer in the stratosphere and thus not considered as threat to organisms on earth. UV-B light is directly absorbed by the heterocyclic and aromatic components of DNA, which are T, A, C and G, the four letters of the genetic alphabet. The relaxation pathways of their excited states are extremely fast, typically on the ps timescale, and can be elucidated only by ultrafast time-resolved lase spectroscopy.[4] Such studies revealed that the fate of excitation energy by UV-B light is governed by the base stacking inside double-helical DNA.[5] The excitons decay rapidly (<1 ps) into charge-separated states (exciplexes and excimers) with charges delocalized over several base pairs. They are relatively long-lived in the stacked situation in double-stranded DNA, and decay by charge recombination to the ground state occurs in a few hundred ps.

This combination of fast photophysical processes in stacked ensembles of DNA bases protect DNA from UV-B damage. This is an important photochemical feature of the natural DNA components.

On the other hand, pyrimidines, particularly thymines, form a singlet state ($^1\pi\pi^*$) upon UV-B excitation that decays also in a few hundred ps. However, if two thymines are adjacent to each other in the DNA sequence, a cyclobutane pyrimidine dimer (CPD) is formed from the thymine singlet state in less than 1 ps by a nearly barrierless $[2\pi+2\pi]$-cycloaddition between the two C5–C6 double bonds.[6] CPDs are the main photodamages in DNA and considered as a molecular origin of skin cancer.[3b,7] They are preferably formed between T and T, but also formed in combination with 5-methyl-C,[8] which is an important epigenetic marker,[9] but are not formed between C and C; mixed TC and CT dimers are formed in lower yields than TT dimers.[10]

In comparison to UV-B light, UV-A light is only weakly absorbed by DNA. However, analysis of photodamaged DNA by UV-A light reveals also CPDs as the major lesion (Figure 1).[11] Remarkably, this pathway does not require any photosensitizer because the molar extinction of double-stranded DNA consisting of A and T at 350 nm is significantly higher than a comparable mixture of both nucleosides. Obviously, CDPs are formed via longer living excitonic states which can only be formed in stacked ensembles in double-stranded DNA.[12] Additionally, base pairing enhances DNA fluorescence and facilitates also CPD formation by UV-A excitation as another pathway to DNA photodamaging;[13] and of course, triplet sensitizers, like ketoprofen[14] and other phenones[15] also induce the formation of CPDs. These pathways to CPDs are typically induced by UV-A light due to the n-π^* transition of the photosensitizers that is selectively excited. 5-Formyluracil (fU) is a suggested epigenetic marker that is generated with low efficiency by enzymatic oxidation of T and its carbonyl group enables this modification also as triplet DNA photosensitizer and thereby CPD formation.[16]

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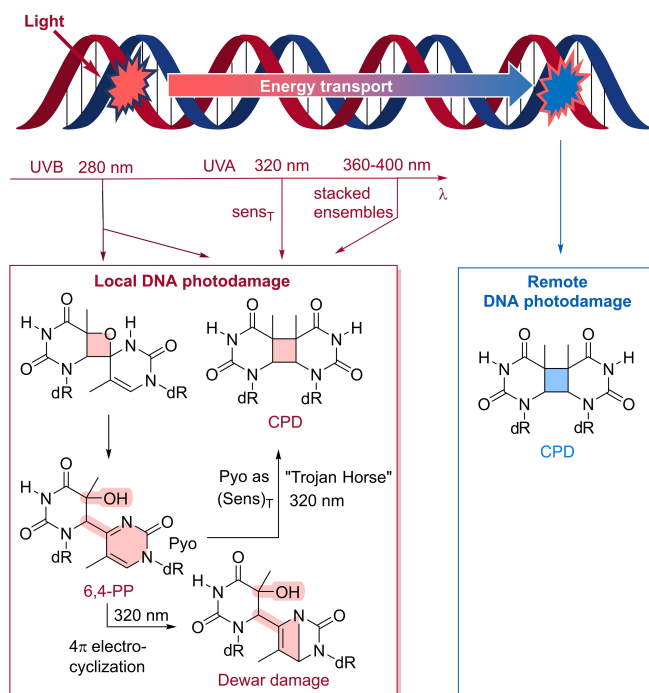European Chemical
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Figure 1. Local DNA photodamages, including the cyclobutane pyrimidine dimer (CPD), the 6,4-photoproduct (6,4-PP) and the Dewar damage, and remote DNA photodamaging mediated by energy transport through the DNA (sens$_T$: triplet photosensitizer, see Figure 3).

The 6–4-photolesions (6,4-PP) are also formed by a $[2\pi+2\pi]$ cycloaddition as the CPDs, however between the C5-C6 double bound of the nucleoside on the 5'-side with the C4 carbonyl bond of the nucleoside on the 3'-side. In organic-chemical synthesis, this reaction is called a Paternó-Büchi reaction and forms an oxetane. In contrast to the cyclobutane of a CPD, the oxetane of the primary photoproduct is unstable und undergoes a ring opening to the final 6,4-PP. In contrast to CPDs, 6,4-PPs are more efficiently formed between T and C rather than T and T. In this case, the imine tautomer of the C on the 3'-side reacts to an azetidine that converts into the corresponding 6,4-PP. The 6,4-PP acts as "Trojan Horse" in DNA, because it is able to photosensitize DNA triplet states by the pyrimidone at the 5'-side.[17] This induces additional CPD

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damaging by excitation with UV-A light and triplet-triplet energy transfer to adjacent pyrimidines.[17] Upon excitation with UV-A light, the 6,4-PPs undergo an $[4\pi]$-aza-electrocyclization and yield the Dewar photoproducts[18] which are more abundant in DNA of cells that were irradiated by light.[19]

Before the latter types of UV-A-induced photodamages were identified it was concluded that UV-A-dependent DNA damages must be depending on the reaction with oxygen (Figure 2).[20] Accordingly, UV-A light is a source for oxidative stress to biological cells.[7] Two major types of pathways were elucidated for oxygen-dependent DNA photodamaging.[8] Type I describes a photoinduced electron transfer between a cofactor chromophore and DNA bases yielding the G radical cation as an intermediate. G has the lowest oxidation potential among the natural DNA components.[21] Further reaction of the G radical cation with oxygen or reactive oxygen species (ROS) gives 8-oxo-7,8-hydroxyguanines (8-oxo-G)[22] and Fapy-dG[23] as the most "prominent" DNA damages of a variety of structurally different oxidatively generated G damages.[24] The 8-hydroxy-7,8-dihydroguanyl radical that is formed by hydration of the G radical cation[25] could be further oxidized by oxygen to 8-oxo-G, or reduced to 2,6-diamino-4-hydroxy-5-formamido-pyrimidine (Fapy-G). The G radical cation reacts also with nucleophiles, such as ε-amino groups of lysines in proteins, and forms DNA-protein crosslinks.[26] The deprotonation of the G radical cation is significant at neutral pH and generates a G radical that efficiently reacts with the superoxide radical anion to 2,2,4-triamino-5(2H)-oxazolone as another G oxidation product.[27]
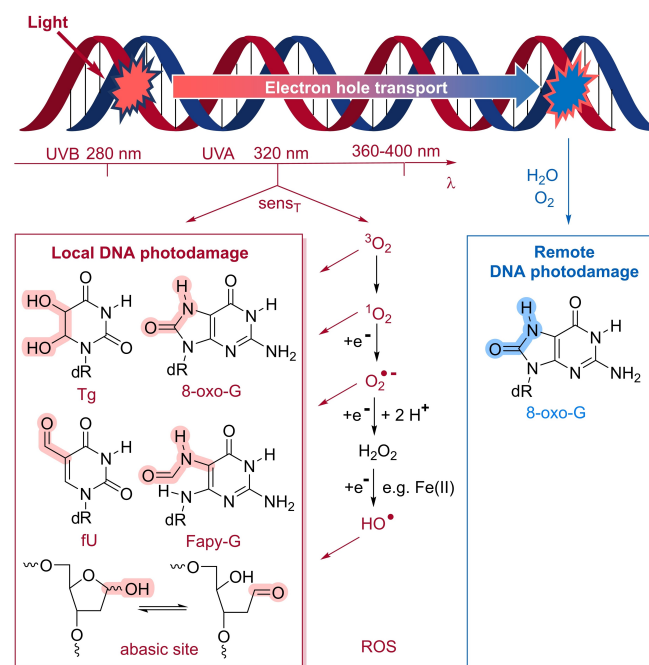

Figure 2. Local oxidatively generated DNA photodamages, including thymine glycol (Tg), 8-oxo-7,8-dihydroguanine (8-oxo-G), 5-formyl-uracil (fU), 2,6-diamino-4-hydroxy-5-formamidopyrimidine guanine (Fapy-G) and the abasic site, caused by reactive oxygen species (ROS), and remote DNA photodamaging mediated by electron hole transport (sens$_T$: triplet photosensitizer, see Figure 3).

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Flavins[28] and pterins[29] are typical biological photosensitizers that damage DNA by the type I mechanism. There is also knowledge about the type I reactivity of the higher energy pyrimidine radical cations.[30] The hydration of the T radical cation gives the 6-hydroxy-5,6-dihydrothym-5-yl radical that reacts with oxygen to peroxy radicals as precursors of monomeric or tandem T lesions in DNA. The deprotonation of the methyl group of the T radical cation generates the 5-(uracilyl)methyl radical that reacts with oxygen to 5-hydroxylmethyluracil and fU. The typical oxidatively generated pyrimidine damages, like the thymidine glycol, are formed indirectly by participation of intermediate A radicals.[31] Type II DNA photodamage is caused by singlet oxygen and subsequently formed reactive oxygen species (ROS). The $[4+2]$ cycloaddition between G and singlet oxygen leads to 8-oxo-G by high selectivity.[32] It was claimed that natural components (e.g. flavins and porphyrins) inside cells serve as chromophores and triplet photosensitizers for singlet oxygen and redox activity for the other ROS. Accordingly, the formation of the superoxide radical anion was initially categorized as a type-II process. A recent review by Baptista et al. classifies the formation of the superoxide radical anion as a type I process since it involves an electron abstraction from DNA, mainly guanine, by triplet photosensitizers. In a subsequent step, the electron is transferred from photosensitizer radical anion to oxygen.[33] Fenton chemistry produces the hydroxy radical which is often mentioned as the most powerful ROS and toxic oxidant for cells.[34] Hydroxyl radicals are responsible for many oxidatively generated DNA damages, including single strand breaks, abasic sites, and oxidatively generated DNA base damages, in particular thymine glycol, 8-oxo-G and Fapy-G are generated in approximate similar yields.[35]

In contrast to these established mechanisms of DNA photochemistry and the corresponding damages, the possibility to observe such damages far, meaning more than 5 base pairs away from the site of photoexcitation has only partially explored and understood. In the late 1990s and early 2000s, the pathways of remote or "long-range" oxidatively generated DNA damages have been extensively studied within the research field of DNA-mediated electron hole transport.[36] Recently, singlet and triplet energy transport over long ranges in DNA have also emerged as a pathway of DNA photodamaging, because both types of photochemical pathways do form CPDs.[37] There are proposals on the mechanisms available in literature. The unifying question for both types of DNA transport processes, electron hole and energy, is how far they may occur in DNA from the initial site of light excitation to the remote site of damaging. This minireview summarizes the current literature on remote DNA photodamaging and focuses on DNA-mediated energy transport (part 1), and subsequently compares the knowledge briefly with the well-studied DNA-mediated electron hole transport to remote oxidatively generated damages (part 2).

2. Photosensitization of DNA and Remote Photodamage by Energy Transport

Although the cancerogenic potential of the direct absorption of UV-A and UV-B light by DNA is well understood, as described above for the local DNA photodamages, UV light may also interact indirectly with DNA through photosensitization by endogenous or exogenous chromophores. Photosensitizers can extend the dangerous fraction of the solar light spectrum to the UV-A range and beyond into the visible (Vis) range. Thereby, the probability for DNA photodamages as early skin cancer events increases upon exposure to sunlight. The question is, how DNA triplet states are induced in DNA. The triplet state energies (T_1) of the isolated nucleotide monophosphates lie in the range between $E_T = 310$ kJ/mol (for TMP) and $E_T = 321$ kJ/mol (for CMP).[38] These energies are significantly influenced by base pairing and stacking interactions in double-stranded DNA. Although not every influence has been characterized so far, it is evident that stacked T pairs in DNA have the lowest triplet state of $E_T = 270$ kJ/mol (Figure 3)[14b] which makes them to preferred energy traps resulting in the chemical formation of T–T dimers. To selectively sensitize the formation of CPD damages and induce triplet energy transport in DNA the T_1 state of the photosensitizer needs to be higher than 270 kJ/mol, and the excitation coefficient ε should be outside the nucleic absorption, preferably in the UV-A range, and must be sufficiently high.

There are four major classes of triplet photosensitizers that were applied for sensitizing DNA photodamages: (i) benzophenones (Bp), (ii) xanthones (Xt), (iii) acetophenones (Ap) and (iv) transition metal complexes, such as $[Ru(bpy)_3]^{2+}$. (i) Benzophenones are widely used in organic photochemistry as photosensitizers due to their quantitative intersystem crossing. Benzophenone (Bp, E_{T1}287 kJ/mol)[39] and its derivatives were also extensively studied by Miranda et al. to elucidate the photochemical pathways to local photosensitized DNA damage,[14a] including damaging by photoinduced electron transfer, hydrogen abstraction, generation of reactive oxygen species (ROS) and triplet-triplet energy transfer. Interestingly, the derivatives of benzophenones with oxy- and methoxy-substituted are applied as UV-A absorbing components in sunscreens[40] that are supposed to protect the human skin from the biological responses to DNA photodamages by the sun.[41] The T_1 energies of benzophenones with electron-donating substituents, in particular 4-methoxybenzophenone (BpOMe, $E_T = 290$ kJ/mol),[39a] 4-methylbenzophenone (BpMe, $E_T = 289$ kJ/mol)[39b] and 4-aminobenzophenone (BpNH$_2$, $E_T = 280$ kJ/mol),[39a,42] are still sufficiently high to photosensitize T in DNA and promote DNA photodamaging. Moreover, these benzophenone derivatives show a significant amount of UV-A extinction which we have used for an intramolecular $[2\pi+2\pi]$ cycloaddition of an organic substrate in aqueous solution.[43] In comparison to benzophenone, anthraquinone has a very low T_1 energy (Aq, $E_T = 261$ kJ/mol),[44] not sufficient for triplet energy transfer to DNA. Instead, it has been used to study electron hole transport through DNA mainly by Schuster et al.[45] (ii)
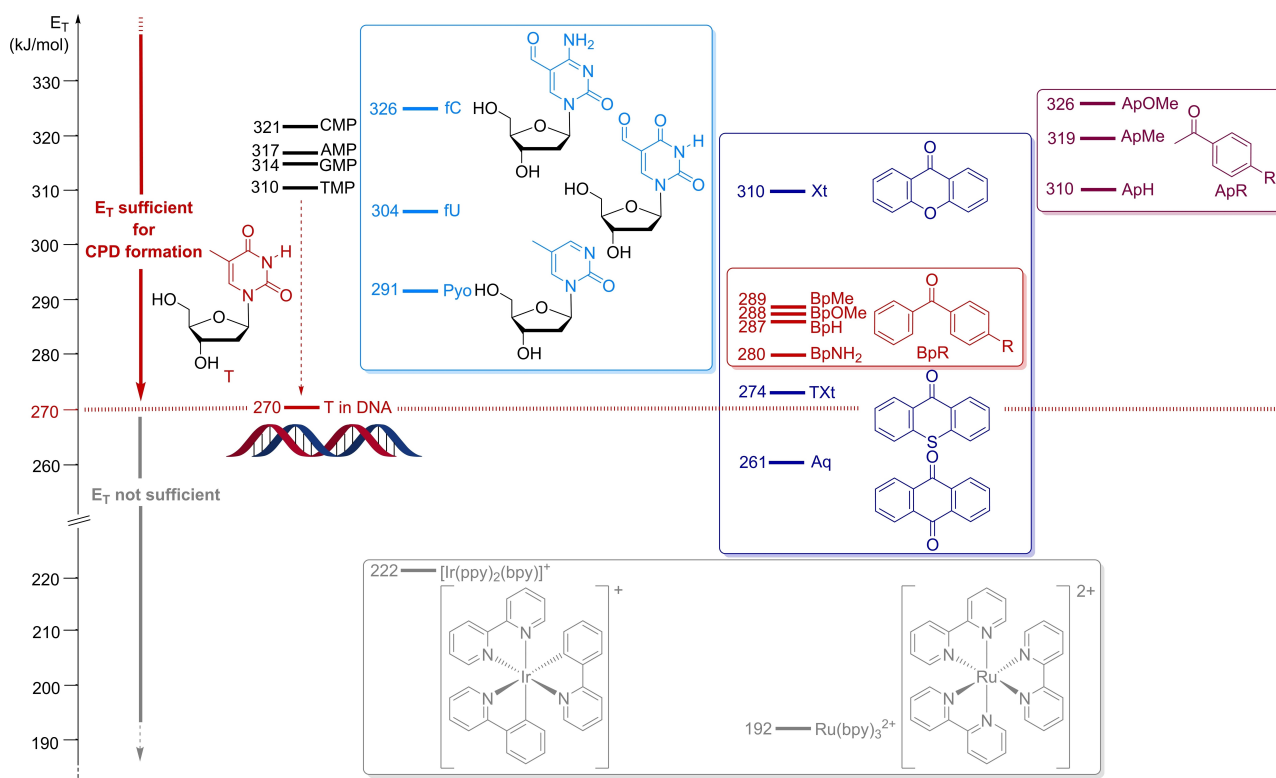
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Figure 3. Triplet energies E_T in kJ/mol of the nucleoside monophosphates (black), the natural or natural-like DNA modifications 5-formyl-cytosine (fC), 5-formyl-uracil (fU) and the nucleoside of 5-methyl-2-pyrimidone from the 6,4-PP (Pyo, red box) and the artificial DNA photosensitizers (sens$_T$) xanthone (Xt), thioxanthone (TXt) and anthraquinone (Aq, dark blue box), benzophenones (Bp, light blue box), acetophenones (Ap, purple box), and ruthenium and Iridium complexes ([Ru(bpy)$_3$]$^{2+}$ and [Ir(ppy)$_2$)bpy)]$^+$, grey box). It is a prerequisite for CPD formation that the triplet energy E_T must be higher than that of T in DNA (270 kJ/mol).

Xanthone has a high T_1 energy (Xt, $E_T = 310$ kJ/mol),[44] whereas thioxanthone has a very low one (SXt, $E_T = 274$ kJ/mol),[44] the latter just sufficiently high to photosensitize Ts in DNA. Similar to unsubstituted benzophenone, as further discussed below, unsubstituted xanthone is oxidizing guanine and thereby sensitizes mainly oxidatively damaged guanine damage.[46] (iii) The corresponding ketones with one phenyl group less are the acetophenones, with triplet energies ranging from $E_T = 310$ kJ/mol[39b] for unsubstituted acetophenone (Ap) over $E_T = 319$ kJ/mol[39b] for 4-methylacetophenone (ApMe) to $E_T = 326$ kJ/mol)[39b] for 4-methoxyacetophenone (ApOMe). In contrast to benzophenones, these organic chromophores are not only able to photosensitize stacked T in DNA but also single nucleotides. Accordingly, recent studies by Zinth et al. showed by time-resolved measurements that 4-methoxyacetophenone is an efficient photosensitizer for CPD formation on the dinucleotide level.[47] (iv) Finally, transition metal complexes mainly of ruthenium and iridium are broadly used photocatalysts in organic chemistry, both by photoinduced electron/hole transfer and by triplet energy transfer.[48] In particular, [Ru(bpy)$_3$]$_{2+}$ differs from the aforementioned organic chromophores since the mainly used transition is a d-π^* MLCT transition that is excited in the visible range of light followed by quantitative intersystem crossing to the T_1 state. However, the triplet energies of [Ru(bpy)$_3$]$^{2+}$ ($E_T = 192$ kJ/mol)[48] and also of [Ir-

(ppy)$_2$(bpy)]$^+$ ($E_T = 222$ kJ/mol)[48] are not sufficient to induce DNA photodamaging by sensitization and triplet energy transfer. Instead, ruthenium complexes with intercalating ligands were used to study photoinduced electron hole transport through DNA mainly by Barton et al.[49]

There are at least three interesting naturally occurring modified nucleosides that are able to induce DNA photodamaging by sensitization. The aforementioned 6,4-PP contains the 5-methyl-2-pyrimidone (Pyo) whose T_1 energy is sufficiently high to sensitize Ts in DNA ($E_T = 291$ kJ/mol).[17b] Miranda et al. elucidated that the 6,4-PP acts as "Trojan Horse" by its rather strong UV-A extinction. This chromophore as part of the 6,4-PP promotes further DNA photodamaging mainly by the formation of CPDs. However, it was recently demonstrated by Douki et al. that the 6,4-PP is not an efficient Trojan horse for generating CPDs since the predominant photoreaction of the 6,4-PP in DNA is its conversion into the related Dewar damage.[50] 5-Formyl-C (fC) and fU are two proposed epigenetic markers[51] with a carbonyl group enabling these modified nucleosides for n-π^* transition. There T_1 energies lie in the range between $E_T = 304$-314 kJ/mol (fU)[16,52] and $E_T = 326$ kJ/mol (fC)[52] which makes obvious that they are comparable to the organic chromophores xanthone and acetophenones. Although their UV-A extinction might by very low, Miranda et al. recently showed that fU is able to photoinduce T—T dimerization in model compounds by

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triplet energy transfer.[16] In contrast to xanthone and acetophenone, they do not oxidize G by photoinduced electron transfer. It is important to mention here that the levels of fC and fU are low and reach a maximum of a few modifications per 10^5 pyrimidine bases in DNA. Thus, it is very unlikely that fC and fU contribute significantly to photosensitized CPD formation in cells.[53]

In contrast to the extensive studies of DNA-mediated charge transport in the 1990s and early 2000s, there are only few experimental studies on the question if DNA transports the triplet energy over long distances. This lack of knowledge is surprising because DNA-mediated triplet energy transport opens an important pathway to DNA photodamages, like CPDs, occurring at remote sites and not locally at the site of excitation by light. Although these distances might be small with regard to a whole gene, the proposal that another site might be damaged than the site of initial photoexcitation is important to the understanding of mutations that are caused by CPDs by their deamination.[54]

In 1998, Barton et al. studied long-range triplet energy transfer in DNA by two transition metal complexes that were attached to the opposite 5'-termini of a piece of double-stranded DNA, like **DNA1** (Figure 4). The first ruthenium complex shows luminescence upon DNA binding. This luminescence is quenched by the second Osmium complex at the other end. The distance dependence over 30–44 Å was very shallow with a characteristic γ value of 0.1 Å^{-1}. The γ value was typically adapted from the β value describing the principal exponential distance (r) dependence of electron transfer rates and triplet energy transfer rates according to $k \sim \exp(-\beta \cdot r)$, when only luminescence quenching or product yields are used, and not kinetic data was obtained. The experimentally determined shallow distance dependence is surprising regarding the low-lying triplet state of such ruthenium complexes in comparison to the lowest triplet state in DNA (T). Thus, a triplet energy
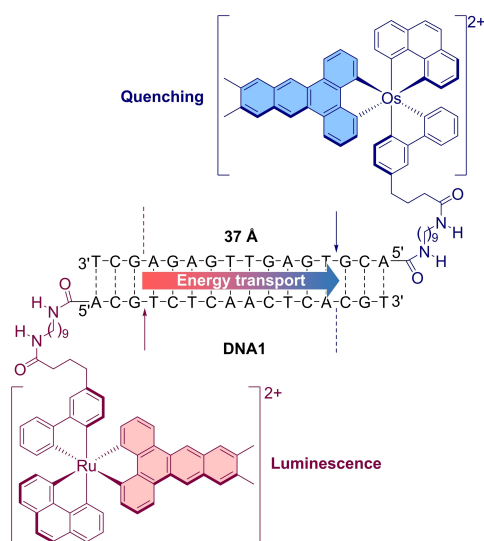
hopping process can completely be excluded since the triplet energy of the ruthenium complex cannot be transferred to any of the intervening DNA components. This makes a one-step transfer of the triplet energy from the ruthenium to the osmium complex the only plausible mechanistic pathway, which, on the other hand, looks very unlikely with respect to the rather long distances of up to 44 Å in these experiments and the typical exponential distance dependence of such processes. Unfortunately, there was no further insight into the energy transfer mechanism in these DNA architectures.

As seen in previous example, the exact definition of the site of photoexcitation as energy donor and the site of energy acceptor is an important prerequisite for the experimental study of triplet energy transport in DNA. We followed this principle and constructed a new type of DNA architecture that allowed us to determine the distance dependence of triplet energy transport through DNA directly by the formation of CPDs as the most important DNA photodamage (Figure 5). We used benzophenones, acetophenone and xanthones as photosensitizers (sens$_T$). They were placed as artificial C-nucleosides **X** into the DNA architectures and serve as energy donors. Their synthetic incorporation at distinct sites in the DNA sequence fixes the photosensitizer and defines the site of photoexcitation. The C-nucleoside of benzophenone photoinduces a range of electron transfer processes in DNA; in particular it oxidizes G to the radical cation.[55] Similar photoinduced oxidation was described
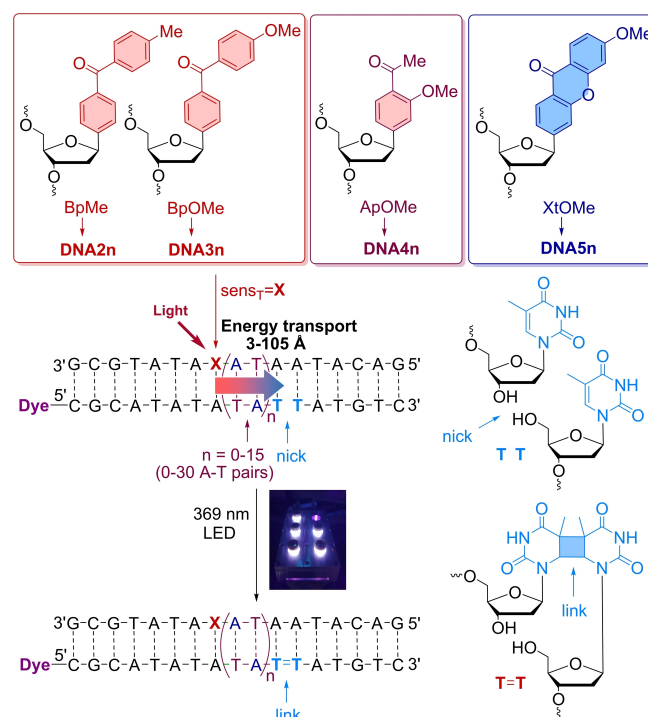

Figure 4. DNA-mediated triplet energy transfer probed by a combination of two intercalating Ru and Os complexes as 5'-modifications of **DNA1**. The Os complex quenches the luminescence of the Ru complex.

Figure 5. Three-component DNA architectures **DNA2-DNA5** for the distance dependent formation of CPD damages. The photosensitizers sens$_T$ were **X** = BpMe, BpOMe, ApOMe and XtOMe were incorporated as C-nucleosides into oligonucleotides. These were annealed with two separate pieces of counterstrands such that the phosphodiester bridge is lacking between the two adjacent Ts. The CPD formation links the two oligonucleotide pieces which can be analyzed by PAGE.

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for xanthone.[46] In order to reduce the oxidative properties of the benzophenone we used the C-nucleoside of benzophenones and xanthones with electron donating groups; BpMe as internal photosensitizer in **DNA2n**, BpOMe in **DNA3n**, ApOMe in **DNA4n** and XtOMe in **DNA5n**. Furthermore, the sequences of these synthetic DNA architectures were designed such that there was only one single site in the sequence where two Ts were placed adjacent to each other. The phosphodiester bond between these two Ts is lacking. Instead, two separate oligonucleotide pieces were annealed with the counterstrand bearing the photosensitizer and serving as a template for annealing of the ternary construct. The formation of the CPD after triplet energy transport glues the two oligonucleotide pieces together. One of the two oligonucleotide pieces was marked with a fluorescent dye at the 5'-terminus (either fluorescein or the photostable Atto dye). This allows the analysis and quantification of the CPD formation by PAGE.

Since both the site of photosensitization and the site of CPD formation are well defined in the DNA sequence, our DNA architecture allowed to study the distance dependence of the photodamaging over n double A−T pairs, ranging from n = 0 (direct neighborhood) to n = 15 (30 intervening base pairs). This works only if we assume that the energy transport through the DNA is the rate-limiting step and the CPD formation is a fast process. This assumption is based on published singlet chemistry, for which the CPD formation was described as an essentially barrierless reaction from the initial $\pi\pi^*$ state and an ultrafast process to the CPD product with a rate on the femtosecond timescale.[6] The CPD formation serves as kinetic trap for the triplet energy transport through the DNA. This assumption allowed us to elucidate the distance dependence of triplet energy transport by the quantification of CPD yields after identical irradiation times. We obtained with the benzophenone and acetophenone photosensitizers in **DNA2n**, **DNA3n** and **DNA4n** obvious exponential, but very shallow distance dependencies for the CPD yields, with γ values in the range between 0.13 Å^{-1} and 0.34 Å^{-1} over distances of up to 37 Å. At first glance, these values are similar to the aforementioned Barton studies. The mechanism for triplet energy transport, however, in our experiments must be different, since all three photosensitizers provide T_1 energies well above the T_1 energy of T inside DNA. Thus, an energy transport by hopping from A−T pair to A−T pair is more likely. This means that the triplet energy is transported stepwise over the DNA base pairs until it is kinetically trapped by the CPD formation. This multi-step mechanism contradicts Barton's triplet energy transfer below the triplet energy of DNA, but is consistent with theoretical models on exciton localization. Recent theoretical calculations by Voityuk et al.[56] suggest that the experimentally observed exponential distance dependence with a low γ value can be best explained by a stepwise intrastrand energy transport (Figure 6) between the individual Ts over the alternating A−T sequence between energy donor (photosensitizer X) and energy acceptor (T T). In an earlier study by the same authors, it was proposed that triplet energy transport in DNA is a process on the nanosecond time scale.[57] In principal, an energy transfer with exponential distance dependence could also be explained
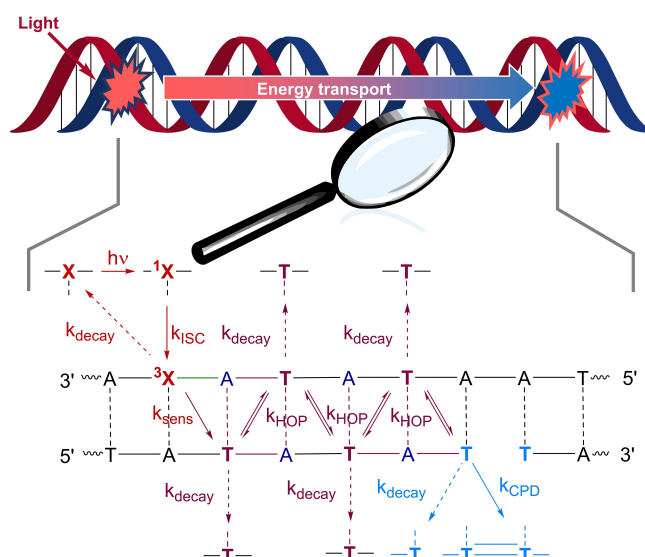

Figure 6. Proposed hopping mechanism of triplet energy transport from the photosensitizer (sens_T) **X** as energy donor through DNA (**DNA22**, **DNA32** or **DNA42**) to the site of CPD formation as energy trap; individual rates k for decay, intersystem crossing (ISC), hopping (HOP) and CDP formation (CPD).

as a single step process, but earlier calculations showed that triplet energies persist for 0.80 ns in A stacks and 6.35 ns in T stacks with very little delocalization, n = 1.03 in A stacks and 1.01 in T stacks. This means that the triplet energy is localized on single base (or base pairs) which supports the energy hopping model and stands clearly in contrast to the short ps lifetimes of singlet excited states in single- and double-stranded DNA and their delocalization over several base pairs. In our experiments with **DNA2n**, **DNA3n** and **DNA4n** the triplet energy transport was limited to a distance of 37 Å due to the detection limit of the PAGE analysis.

In the most recent experiments with **DNA5n**, we used 3-methoxyxanthone as photosensitizer (sens_T) and C-nucleoside **X** in the DNA architecture. In contrast to the benzophenones, 3-methoxyxanthone shows strong fluorescence, has a S_1 energy of $E_S = 332$ kJ/mol and does not show significant triplet photochemistry.[58] Thus, we assume that the photochemistry in **DNA5n** is dominated by singlet chemistry. As a result, we elucidated a completely different distance dependence. Instead of the exponential distance dependence typical for the triplet energy transport, a sigmoidal distance dependence was observed, similar to a Förster-type energy transfer. The sigmoidal transition was assigned to a mechanistic change observed at 24–31 Å (6–8 base pairs). At shorter distances than 25 Å, a coherent energy transfer with little distance dependence was observed. Above 25 Å, CPD formation was observed over distances of up to 105 Å (30 A−T pairs) which could only be explained by a singlet energy hopping process that might work more efficiently than the triplet energy hopping induced by the benzophenones. According to theoretical calculations by Frank, the formation of a CPD damage is only possible if the exciton is located on the site of damage.[59] Such a localized exciton yields a dimer only between a well-stacked pair of Ts (with a closed

distance between them). The final distance limit for such remote CPD formation may still not be discovered since the current experimental limit of 105 Å was set by the photo-stability of the applied Atto dye marker over the applied long irradiation time.

3. Comparison with Remote Oxidatively Generated DNA Damage by Photoinduced Electron Hole Transport

In the 1960s, Eley and Spivey published the first remarks and the basic idea that double-helical DNA might be able to transport electrons over longer distances.[60] It took about 20 years, until Barton et al. published the experimental observation of DNA-mediated electron transfer between DNA-bound metallointercalators.[61] Since then, the question of DNA-mediated electron or electron hole transport was extensively studied with very controversial results mainly in the 1990s and early 2000s. There are numerous reviews available on this subject and is of course not the scope of this minireview to recall all details of these studies.[36,49,62] Instead, a few major results should supplement the question of remote photodamaging of DNA by energy transport, as described in the previous section, with some obvious similarities between photoinduced energy transport and photoinduced electron hole transport in DNA, when they are observed over long distances.

The extremely controversial results from experimental work on DNA-mediated electron hole transport focused on the distance dependence as the most critical parameter. The controversy was finally solved for photoexcited electron transport in DNA by a unifying picture and explained by a mechanistic change between coherent superexchange over short ranges and an incoherent hopping over long ranges.[63] To be more precise, the mechanistic change between the DNA-mediated coherent electron hole transfer and long-range incoherent electron hole transport by hopping occurs somewhere between 14–20 Å (3-5 base pairs, vide infra). This was first evidenced in 2001 by Giese et al. using the yields of oxidatively generated G damage (mainly 8-oxo-G) determined from PAGE and HPLC analysis.[64] Five years later, a mechanistic transition at similar distances was verified by time-resolved spectroscopy in modified DNA hairpins by the groups of Lewis and Wasielewski.[65] In 2013, these results were finally supported by theoretical calculations by Ratner et al.[66] For DNA-mediated energy transfer, the mechanistic change between a short-range energy transfer and incoherent energy hopping over long distances was observed at 24–31 Å (6-8 base pairs), as mentioned above.[67] This makes obvious, that there is a high similarity between both processes, energy transfer and electron hole transfer in DNA, which further supports the possibility and occurrence of energy transport over long distances.

Photoinduced remote G damaging is also a well-studied phenomenon.[62a,68] The electron hole transport occurs via G radical cations as intermediates and the G radical cation is the charged precursor for oxidatively generated G damages. It was further shown that the reaction of the hydrated G radical with oxygen,

the so-called "water reaction", serves finally as charge trap and forms 8-oxo-G as primary G damage (Figure 7).[69] High-intensity UV lase photolysis of DNA generates both purine and pyrimidine radical cations.[70] In native DNA, such experiments preferentially yield G oxidation products (like 8-oxo-G and Fapy-G) over T oxidation products (like Tg and fU), while in denatured DNA the product distribution differs and G oxidation products are decreased. This is an important support for the evidence of electron hole migration in native DNA, since the initially formed T and G radical cations are preferentially trapped at remote Gs as electron hole sinks. Interestingly, such evidence for electron hole transfer and remote oxidatively generated G damage was provided also for cellular DNA.[71] A possible role of long-range electron hole transport through DNA is discussed for sensing DNA damage by redox-active proteins.[72] For decades, it was assumed that the hydroxyl radical that is formed by both photoinduced and non-photochemical pathways, as discussed above, is responsible for the formation of remote oxidatively generated DNA damage. In contrast to this previous assumption, it was shown by Meyerstein et al. that the carbonate radical anion and not the hydroxyl radical is the product of the Fenton reaction in aqueous solutions with bicarbonate.[73] As a consequence, it was proposed that the carbonate radical anion initiates the electron hole transport through DNA and leads to remote oxidatively generated
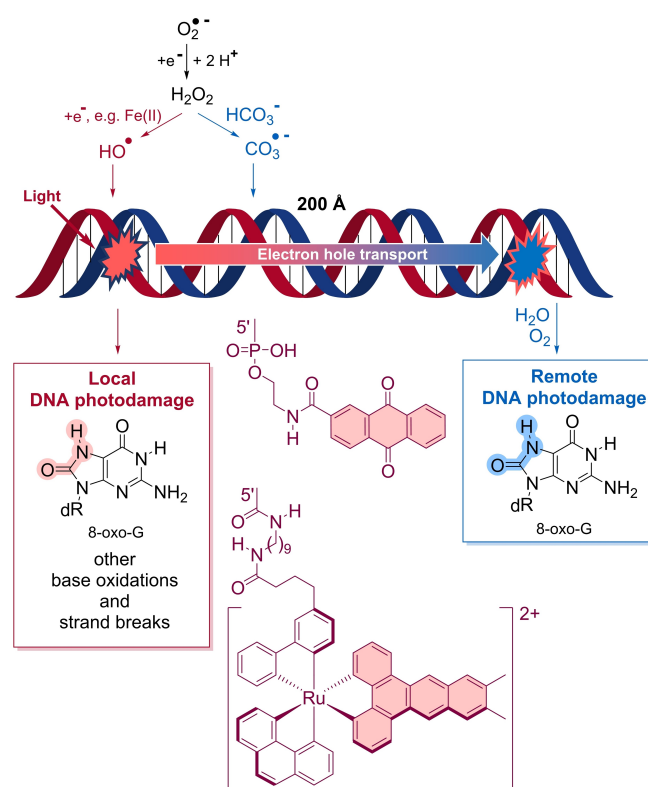

Figure 7. Photoinduced G damage reaction oxygen species (top) and by attached electron hole donors (bottom). The hydroxyl radical forms local and remote oxidatively generated DNA damages, whereas the carbonate radical anion was proposed to induce electron-hole transport and remote oxidatively generated DNA damaging. Remote DNA photodamage can also be induced by anthraquinone and ruthenium complexes attached to the 5'-terminus.

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damage according to the very recent viewpoint by Burrows et al.[74] But this seems to be speculative without further investigations; according to another recent viewpoint by Halliwell et al. the hydroxy radical is still a significant player in oxidatively generated damage in vivo.[75] A type II photosensitized oxidation pathway to remote DNA damages might be possible, because the oxidation of both isolated and cellular DNA by singlet oxygen exclusively yields 8-oxo-G with a lack of sequence dependence.[76] The current "world record" for the formation of oxidatively generated G damage by DNA-mediated electron hole transport still is the distance of 200 Å set independently by the groups of Schuster[77] and Barton.[78] DNA-mediated charge transport was measured even over 340 Å (100 base pairs) by electrochemical methods, but the charge transport mechanism might differ from hopping over Gs and may involve other base radical cations (such as A radical cations).[79] The 200 Å limit seems to be more reasonable with respect to the kinetic situation. The electron hole hopping occurs between Gs occurs with rates in the range of 10^6–$10^8 \, s^{-1}$.[80] The trapping of the G radical cation by water occurs with a rate of $10^4 \, s^{-1}$ and is the rate-limiting step.[81] Taken together, the distance over which an electron hole can be transported through DNA is likely be already reached by the experiments (200 Å). This limit is currently double as large as the experimentally determined limit of 105 Å for long-range energy transport. In the latter case, however, the final distance limit might not yet be detected, because the kinetic situation is different. The CPD formation as trapping reaction for the energy is extremely fast (ps timescale), is not the rate-limiting step and thereby does not limit the distance of energy transport. The energy transport through DNA has not yet been studied by spectroscopic methods to elucidate any rates. Thus, the distance limitation for DNA-mediated energy transport might be much larger than the distance limit for electron hole transport.

4. Conclusions

DNA photodamaging at the site of excitation by light is a well-studied process and leads to a number of characterized damages, including mainly CPDs and 6,4-PPs. Indirect oxidatively generated DNA photodamages, in particular 8-oxo-, are also locally formed by photoinduced electron transfer and reactive oxygen species. In contrast to these established mechanisms of local DNA photo-damaging, long-range processes have only partially been explored, although DNA photodamages can also be found at remote sites, which means at least more than 5 base pairs away from the site of photoexcitation. The underlying pathways to remote oxidatively generated DNA photodamages were elucidated in the 1990s and 2000s and are sufficiently described as electron hole hopping processes. The photoinduced DNA-mediated singlet and triplet energy transport to remote damaging sites are also evident and will add an important extension to our understanding of DNA photodamaging and mutations. There are a few studies and proposals on the mechanisms in literature, which were summarized in this minireview. In particular, an energy transport by hopping from base pair to base pair over long ranges of at least 105 Å has been experimentally and theoretically proposed. Since

triplet energy transport is generally considered to be a simultaneous electron transport and hole transport in opposite directions,[82] this result seems to be reasonable with regard to well-characterized long-range electron hole transport mechanisms. However, the energetic and kinetic scenario for energy transport in DNA differs from that of electron hole transport. And the final question, how far energy migrates in DNA away from the initial site of excitation, remains unanswered. Future studies should be focusing on these basic issues and deepen our general understanding of DNA photodamaging and mutations.

Conflict of Interest

The authors declare no conflict of interest.

[1] K. Heil, D. Pearson, T. Carell, *Chem. Soc. Rev.* **2011**, *40*, 4271–4278.

[2] E. Sage, P.-M. Girard, S. Francesconi, *Photochem. Photobiol. Sci.* **2012**, *11*, 74–80.

[3] a) G. P. Pfeifer, A. Besaratinia, *Photochem. Photobiol. Sci.* **2012**, *11*, 90–97; b) J. Cadet, T. Douki, *Photochem. Photobiol. Sci.* **2018**, *17*, 1816–1841; c) J.-S. Taylor, *Acc. Chem. Res.* **1994**, *27*, 76–82.

[4] a) T. Gustavsson, D. Markovitsi, *Acc. Chem. Res.* **2021**, *54*, 1226–1235; b) N. K. Schwalb, F. Temps, *Science* **2008**, *322*, 243–245; c) Y. Zhang, K. d. L. Harpe, A. A. Beckstead, R. Improta, B. Kohler, *J. Am. Chem. Soc.* **2015**, *137*, 7059–7062; d) D. B. Bucher, B. M. Pilles, T. Carell, W. Zinth, *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 4369–4374; e) I. Buchvarov, Q. Wang, M. Raytchev, A. Trifonov, T. Fiebig, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 4794–4797.

[5] C. T. Middleton, K. d. L. Harpe, C. Su, Y. K. Law, C. E. Crespo-Hernandez, B. Kohler, *Annu. Rev. Phys. Chem.* **2009**, *60*, 217–239.

[6] W. J. Schreier, T. E. Schrader, F. O. Koller, P. Gilch, C. E. Crespo-Hernandez, V. N. Swaminathan, T. Carell, W. Zinth, B. Kohler, *Science* **2007**, *315*, 625–629.

[7] S. Mouret, C. Baudouin, M. Charveron, A. Favier, J. Cadet, T. Douki, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 13765–13770.

[8] a) S. Tommasi, M. F. Denissenko, G. F. Pfeifer, *Cancer Res.* **1997**, *57*, 4727–4730; b) W. Lee, S. Matsika, *ChemPhysChem* **2018**, *19*, 1568–1571; c) X. Li, L. A. Eriksson, *Chem. Phys. Lett.* **2005**, *401*, 99–101; d) L. Esposito, A. Banyasz, T. Douki, M. Perron, D. Markovitsi, R. Improta, *J. Am. Chem. Soc.* **2014**, *136*, 10838–10841.

[9] S. Kumar, V. Chinnusamy, T. Mohapatra, *Front. Genet.* **2018**, *9*, 640.

[10] T. Douki, A. Reynaud-Angelin, J. Cadet, E. Sage, *Biochemistry* **2003**, *42*, 9221–9226.

[11] S. Mouret, C. Philippe, J. Gracia-Chantegrel, A. Banyasz, S. Karpati, D. Markovitsi, T. Douki, *Org. Biomol. Chem.* **2010**, *8*, 1706–1711.

[12] D. Markovitsi, T. Gustavsson, A. Banyasz, *Mutat. Res.* **2010**, *704*, 21–28.

[13] A. Banyasz, I. Vaya, P. Changenet-Barret, T. Gustavsson, T. Douki, D. Markovitsi, *J. Am. Chem. Soc.* **2011**, *133*, 5163–5165.

[14] a) M. C. Cuquerella, V. Lhiaubet-Vallet, J. Cadet, M. A. Miranda, *Acc. Chem. Res.* **2012**, *45*, 1558–1570; b) F. Bosca, V. Lhiaubet-Vallet, M. C. Cuquerella, J. V. Castell, M. A. Miranda, *J. Am. Chem. Soc.* **2006**, *128*, 6318–6319.

[15] L. Liu, B. M. Pilles, J. Gontcharov, D. B. Bucher, W. Zinth, *J. Phys. Chem. B* **2016**, *120*, 292–298.

[16] I. Aparici-Espert, G. Garcia-Lainez, I. Andreu, M. A. Miranda, V. Lhiaubet-Vallet, *ACS Chem. Biol.* **2018**, *13*, 542–547.

[17] a) E. Bignon, H. Gattuso, C. Morell, E. Dumont, A. Monari, *Chem. Eur. J.* **2015**, *21*, 11509–11516; b) V. Vendrell-Criado, G. M. Rodriguez-Muniz, M. C. Cuquerella, V. Lhiaubet-Vallet, M. A. Miranda, *Angew. Chem. Int. Ed.* **2013**, *52*, 6476–6479; *Angew. Chem.* **2013**, *125*, 6604–6607.

[18] K. Haiser, B. P. Fingerhut, K. Heil, A. Glas, T. T. Herzog, B. M. Pilles, W. J. Schreier, W. Zinth, R. d. Vivie-Riedle, T. Carell, *Angew. Chem. Int. Ed.* **2012**, *51*, 408–411; *Angew. Chem.* **2012**, *124*, 421–424.

[19] a) J. Cadet, E. Sage, T. Douki, *Mutat. Res.* **2005**, *571*, 3–17; b) P. H. Clingen, C. F. Arlett, L. Roza, T. Mori, O. Nikaido, M. H. L. Green, *Cancer Res.* **1995**, *55*, 2245–2248.

[20] a) B. Epe, *Photochem. Photobiol. Sci.* **2012**, *11*, 98–106; b) J. Cadet, T. Douki, J.-L. Ravanat, P. D. Mascio, *Photochem. Photobiol. Sci.* **2009**, *8*, 903–911.

[21] a) C. A. M. Seidel, A. Schulz, M. H. M. Sauer, *J. Phys. Chem.* **1996**, *100*, 5541–5553; b) S. Steenken, S. V. Jovanovic, *J. Am. Chem. Soc.* **1997**, *119*, 617–618.

[22] a) B. Matter, D. Malejka-Giganti, A. S. Csallany, N. Tretyakova, *Nucleic Acids Res.* **2006**, *34*, 5449–5460; b) K. E. McAuley-Hecht, G. A. Leonard, N. J. Gibson, J. B. Thomson, W. P. Watson, W. N. Hunter, T. Brown, *Biochemistry* **1994**, *33*, 10266–10270.

[23] M. Dizdaroglu, G. Kirkali, P. Jaruga, *Free Radical Biol. Med.* **2008**, *45*, 1610–1621.

[24] a) G. Pratviel, B. Meunier, *Chem. Eur. J.* **2006**, *12*, 6018–6030; b) E. C. Friedberg, L. D. McDaniel, R. A. Schultz, *Curr. Opin. Genet. Dev.* **2004**, *14*, 5–10; c) C. J. Burrows, J. G. Muller, *Chem. Rev.* **1998**, *98*, 1109–1151.

[25] H. Kasai, Z. Yamaizumi, *J. Am. Chem. Soc.* **1992**, *114*, 9692–9694.

[26] S. Perrier, J. Hau, D. Gasparutto, J. Cadet, A. Favier, J.-L. Ravanat, *J. Am. Chem. Soc.* **2006**, *128*, 5703–5710.

[27] a) J. Cadet, M. Berger, G. Buchko, P. C. Joshi, S. Raoul, J.-L. Ravanat, *J. Am. Chem. Soc.* **1994**, *116*, 7403–7404; b) T. Douki, J. Cadet, *Int. J. Radiat. Biol.* **1999**, *75*, 571–581.

[28] K. Ito, S. Inoue, K. Yamamoto, S. Kawanishi, *J. Biol. Chem.* **1993**, *268*, 13221–13227.

[29] a) G. Petroselli, M. L. Dantola, F. M. Cabrerizo, A. L. Capparelli, C. Lorente, E. Oliveros, A. H. Thomas, *J. Am. Chem. Soc.* **2008**, *130*, 3001–3011; b) K. Ito, S. Kawanishi, *Biochemistry* **1997**, *36*, 1774–1781.

[30] J. Cadet, K. J. A. Davies, *Free Radical Biol. Med.* **2017**, *107*, 2–12.

[31] H. Sun, L. Zheng, M. M. Greenberg, *J. Am. Chem. Soc.* **2018**, *140*, 11308–11316.

[32] J.-L. Ravanat, S. Sauvaigo, S. Caillat, G. R. Martinetz, M. H. G. Medeiros, P. D. Mascio, A. Favier, J. Cadet, *Biol. Chem.* **2004**, *385*, 17–20.

[33] M. S. Baptista, J. Cadet, P. D. Mascio, A. A. Ghogare, A. Greer, M. R. Hamblin, C. Lorente, S. C. Nunez, M. S. Ribeiro, A. H. Thomas, M. Vignoni, T. M. Yoshimura, *Photochem. Photobiol.* **2017**, *93*, 912–919.

[34] J. A. Imlay, *Annu. Rev. Microbiol.* **2003**, *57*, 395–418.

[35] J. Cadet, T. Douki, J.-L. Ravanat, *Acc. Chem. Res.* **2008**, *41*, 1075–1083.

[36] H.-A. Wagenknecht, *Nat. Prod. Rep.* **2006**, *23*, 974–1006.

[37] B. M. Pilles, D. B. Bucher, L. Liu, P. Clivio, P. Gilch, W. Zinth, W. J. Schreier, *J. Phys. Chem. Lett.* **2014**, *5*, 1616–1622.

[38] P. D. Wood, R. W. Redmond, *J. Am. Chem. Soc.* **1996**, *118*, 4256–4263.

[39] a) C. Schweitzer, Z. Mehrdad, A. Noll, E.-W. Grabner, R. Schmidt, *Helv. Chim. Acta* **2001**, *84*, 2493–2507; b) B. Wang, P. R. Ogilby, *J. Photochem. Photobiol. A* **1995**, *90*, 85–89.

[40] S. Kim, K. Choi, *Environment Int.* **2014**, *70*, 143–157.

[41] A. Fourtanier, D. Moyal, S. Seite, *Photochem. Photobiol. Sci.* **2012**, *11*, 81–89.

[42] A. K. Singh, D. K. Palit, T. Mukherjee, *J. Phys. Chem. A* **2002**, *106*, 6084–6093.

[43] N. Gaß, H.-A. Wagenknecht, *Eur. J. Org. Chem.* **2015**, 6661–6668.

[44] W. G. Herkstroeter, A. A. Lamola, G. S. Hammond, *J. Am. Chem. Soc.* **1964**, *86*, 4537–4540.

[45] G. B. Schuster, U. Landman, *Top. Curr. Chem.* **2004**, *236*, 139–161.

[46] a) R. Tang, P. Zhang, H. Liu, Y. Liu, W. Wang, *J. Photochem. Photobiol. B* **2011**, *105*, 157–161; b) Y. Hiraku, K. Ito, K. Hirakawa, S. Kawanishi, *Photochem. Photobiol.* **2007**, *83*, 205–212.

[47] L. Liu, B. M. Pilles, A. M. Reiner, J. Gontcharov, W. Zinth, *ChemPhysChem* **2015**, *16*, 3483–3487.

[48] F. Strieth-Kalthoff, M. J. James, M. Teders, L. Pitzer, F. Glorius, *Chem. Soc. Rev.* **2018**, *47*, 7190–7202.

[49] J. Genereux, J. K. Barton, *Chem. Rev.* **2010**, *110*, 1642–1662.

[50] T. Douki, *ChemPhotoChem* **2020**, *4*, 294–299.

[51] a) G. Zheng, Y. Fu, C. He, *Chem. Rev.* **2014**, *114*, 4602–4620; b) B. Steigenberger, S. Schiesser, B. Hackner, C. Brandmayr, S. K. Laube, J. Steinbacher, T. Pfaffeneder, T. Carell, *Org. Lett.* **2013**, *15*, 366–369.

[52] A. Francés-Monerris, M. Lineros-Rosa, M. A. Miranda, V. Lhiaubet-Vallet, A. Monari, *Chem. Commun.* **2020**, *56*, 4404–4407.

[53] M. S. Baptista, J. Cadet, A. Greer, A. H. Thomas, *Photochem. Photobiol.* **2021**, DOI: https://doi.org/10.1111/php.13470.

[54] J. Gontcharov, L. Liu, B. M. Pilles, T. Carell, W. J. Schreier, W. Zinth, *Chem. Eur. J.* **2019**, *25*, 15164–15172.

[55] T. Merz, M. Wenninger, M. Weinberger, E. Riedle, H.-A. Wagenknecht, M. Schütz, *Phys. Chem. Chem. Phys.* **2013**, *11*, 7458–7462.

[56] L. Blancafort, A. A. Voityuk, *Phys. Chem. Chem. Phys.* **2018**, *20*, 4997–5000.

[57] C. Curutchet, A. A. Voityuk, *Angew. Chem. Int. Ed.* **2011**, *50*, 1820–1822; *Angew. Chem.* **2011**, *123*, 1860–1862.

[58] O. S. Wolfbeis, E. Fürlinger, *J. Am. Chem. Soc.* **1982**, *104*, 4069–4072.

[59] S. Rössle, J. Friedrichs, I. Frank, *ChemPhysChem* **2010**, *11*, 2011–2015.

[60] D. D. Eley, D. I. Spivey, *Trans. Faraday Soc.* **1962**, *58*, 411–415.

[61] J. K. Barton, C. V. Kumar, N. J. Turro, *J. Am. Chem. Soc.* **1986**, *108*, 6391–6393.

[62] a) A. Joy, G. B. Schuster, *Chem. Commun.* **2005**, 2778–2784; b) F. D. Lewis, M. R. Wasielewski, *Top. Curr. Chem.* **2004**, *236*, 45–65; c) B. Giese, *Bioorg. Med. Chem.* **2006**, *14*, 6139–6143; d) C. Behrens, M. K. Cichon, F. Grolle, U. Hennecke, T. Carell, *Top. Curr. Chem.* **2004**, *236*, 187–204; e) K. Nakatani, I. Saito, *Top. Curr. Chem.* **2004**, *236*, 163–186; f) M. Fujitsuka, T. Majima, *Phys. Chem. Chem. Phys.* **2012**, *14*, 11234–11244.

[63] A. Landi, A. Capobianco, A. Peluso, *J. Phys. Chem. Lett.* **2020**, *11*, 7769–7775.

[64] B. Giese, J. Amaudrut, A.-K. Köhler, M. Spormann, S. Wessely, *Nature* **2001**, *412*, 318–320.

[65] F. D. Lewis, H. Zhu, P. Daublain, B. Cohen, M. R. Wasielewski, *Angew. Chem. Int. Ed.* **2006**, *45*, 7982–7985; *Angew. Chem.* **2006**, *118*, 8150–8153.

[66] N. Renaud, Y. A. Berlin, F. D. Lewis, M. A. Ratner, *J. Am. Chem. Soc.* **2013**, *135*, 3953–3963.

[67] A. Kuhlmann, L. Bihr, H.-A. Wagenknecht, *Angew. Chem. Int. Ed.* **2020**, *59*, 17378–17382; *Angew. Chem.* **2020**, *132*, 17530–17535.

[68] S. Delaney, J. K. Barton, *J. Org. Chem.* **2003**, *68*, 6475–6483.

[69] B. Giese, *Annu. Rev. Biochem.* **2002**, *71*, 51–70.

[70] a) D. Angelov, A. Spassky, M. Berger, J. Cadet, *J. Am. Chem. Soc.* **1997**, *119*, 11373–11380; b) T. Douki, D. Angelov, J. Cadet, *J. Am. Chem. Soc.* **2001**, *123*, 11360–11366.

[71] J. Cadet, J. R. Wagner, D. Angelov, *Photochem. Photobiol.* **2019**, *95*, 59–72.

[72] a) K. N. Schaefer, W. M. Geil, M. J. Sweredoski, A. Moradian, S. Hess, J. K. Barton, *Biochemistry* **2015**, *54*, 932–941; b) P. A. Sontz, N. B. Muren, J. K. Barton, *Acc. Chem. Res.* **2012**, *45*, 1792–1800.

[73] E. Illés, A. Mizrahi, V. Marks, D. Meyerstein, *Free Radical Biol. Med.* **2019**, *131*, 1–6.

[74] A. M. Fleming, C. J. Burrows, *Chem. Soc. Rev.* **2020**, *49*, 6524–6528.

[75] B. Halliwell, A. Adhikary, M. Dingfelder, M. Dizdaroglu, *Chem. Soc. Rev.* **2021**, *50*, 8355–8360.

[76] P. D. Mascio, G. R. Martinez, S. Miyamoto, G. E. Ronsein, M. H. G. Medeiros, J. Cadet, *Chem. Rev.* **2019**, *119*, 2043–2086.

[77] P. T. Henderson, D. Jones, G. Hampikian, Y. Kan, G. B. Schuster, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 8353–8358.

[78] M. E. Núñez, D. B. Hall, J. K. Barton, *Chem. Biol.* **1999**, *6*, 85–97.

[79] J. D. Slinker, N. B. Muren, S. E. Renfrew, J. K. Barton, *Nat. Chem.* **2011**, *3*, 228–233.

[80] F. D. Lewis, X. Liu, J. Liu, S. E. Miller, R. T. Hayes, M. R. Wasielewski, *Nature* **2000**, *406*, 51–53.

[81] B. Giese, M. Spichty, *ChemPhysChem* **2000**, *1*, 195–198.

[82] a) G. L. Closs, M. D. Johnson, J. R. Miller, P. Piotrowiak, *J. Am. Chem. Soc.* **1989**, *111*, 3751–3753; b) G. L. Closs, P. Piotrowiak, J. M. MacInnis, G. R. Fleming, *J. Am. Chem. Soc.* **1988**, *110*, 2652–2653.