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[17] Initial synthesis of **1**: A solution of 1,3,5-tris(diphenylphosphanyl)-benzene (**L**; 63 mg, 0.1 mmol) in CH_2Cl_2 (3 mL) was added to a solution of AgOTf (38.5 mg, 0.15 mmol) in CH_3NO_2 (1 mL). Diffusion of diethyl ether vapor into the resulting solution over one week gave colorless hexagonal crystals of **1** in 10% yield, together with powdery amorphous material. Higher yield synthesis: 1,3,5-tris(diphenylphosphanyl)benzene (**L**; 31.5 mg, 0.05 mmol) and AgOTf (17.0 mg, 0.067 mmol) were dissolved in a mixture of ethanol (7 mL) and nitromethane (3 mL), placed in a loosely stoppered polypropylene flask and partially evaporated at 88 °C overnight. Block and hexagonal colorless crystals were manually separated from the powdery amorphous byproduct. Yield: 50–80%; elemental analysis calcd (%) for $[Ag_4\mathbf{L}_3(OTf)_4]\cdot CH_3NO_2$: C 52.79, H 3.42; found: C 52.55, H 3.32.
[18] X-ray data were collected on a BrukerAXS SMART diffractometer using the SAINT-NT[26] software with omega/phi scans. A crystal was mounted on to the diffractometer under dinitrogen at approximately 120 K. The structure was solved using direct methods with the SHELXTL program package.[27] Crystal Data for the hexagonal plate crystals $\{C_{130}H_{99}F_{12}Ag_4P_9S_4O_{12}\}_n$ (**1**): $M = 2919.54$, hexagonal, space group $P\bar{3}c$, $a = 29.949(8)$, $c = 25.929(10)$ Å, $V = 20141(11)$ Å^{-3}, $Z = 4$, $\mu = 0.545$ mm^{-1}. A total of 39337 reflections were measured for the angle range $4 < 2\theta < 45$ and 8797 independent reflections were used in the refinement. The final parameters were $wR2 = 0.3009$ and $R1 = 0.0906$ [$I > 2\sigma I$]. Cell parameters for the block crystals $[\{C_{130}H_{99}F_{12}Ag_4P_9S_4O_{12}\}_n]$ (**1′**)[23]: $M = 2919.54$, hexagonal, space group $P\bar{3}c$, $a = 30.076(1)$, $c = 25.791(1)$ Å, $V = 20204(1)$ Å^{-3}. The residual densities (< 1 electron Å^{-3}) associated with the voids indicate small amounts of very diffuse solvent molecules. Consequently, the nature of the solvent could not be determined using X-ray diffraction methods. Powder diffraction measurements were performed on a Siemens D5000 powder diffractometer in continuous mode with step size of 0.02° and step time of 20 s. ^{31}P NMR spectra were obtained at 121 MHz and 25 °C and are referenced to external 85% phosphoric acid ($\delta = 0$). CCDC 170632 (**1**) and 176871 (**1′**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
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[23] A cell check was undertaken on a crystal from a batch that had been washed with ethanol and dried in air for 2 days which gave cell parameters $a = b = 30.076(2)$, $c = 12.8958(8)$ Å $\gamma = 120°$ indicating the presence of a possible polymorph with a *c* axis half that of the original cell. The data was collected and processed using these cell parameters, however, subsequent attempts at structure determination in this cell were unsuccessful. Thus we concluded the apparent halving of the *c* axis in this crystal was incorrect and after transformation to the larger cell $a = b = 30$, $c = 25$ Å, $\gamma = 120°$ the structure was shown to be the same as previously determined with a $wR2 = 0.22$ and $R1 = 0.0632$.
[24] This ignores the effect of curvature within the cavities, which would place slightly more stringent limits on *p* and *w* for a given cavity size.
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A (6-4) Photolyase Model: Repair of DNA (6-4) Lesions Requires a Reduced and Deprotonated Flavin**

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Ultraviolet irradiation of cells causes the formation of a variety of DNA lesions with known mutagenic, carcinogenic, and lethal effects.[1, 2] The main UV lesions are cyclobutane–pyrimidine dimers (CPD lesions) formed in a photochemically allowed $[2\pi + 2\pi]$ cycloaddition and (6-4) photoadducts; the latter are presumably more mutagenic.[3, 4] The highly mutagenic (6-4) lesions are believed to be formed in a Paternó-Büchi reaction between two adjacent pyrimidines in the DNA duplex to give initially an oxetane intermediate, which rearranges above −80 °C to the (6-4) photoadduct by a proton shift and a C–O bond scission (Scheme 1).[5] Both types of DNA lesions are repaired in many organisms by a special class of repair enzymes, namely DNA photolyases, which cleave both lesions back into the monomers in a light-dependent, single electron transfer based repair reaction.[6] In the last decade, crystallographic,[7, 8] enzymatic,[9, 10] and model compound studies[11–14] showed that the photolyases,[15] which are responsible for the repair of CPD lesions, contain a

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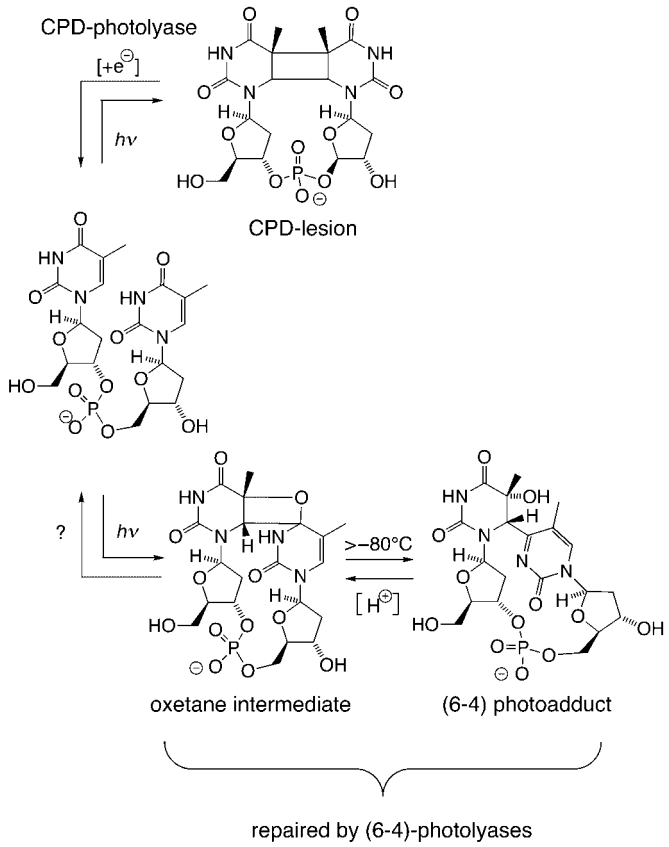


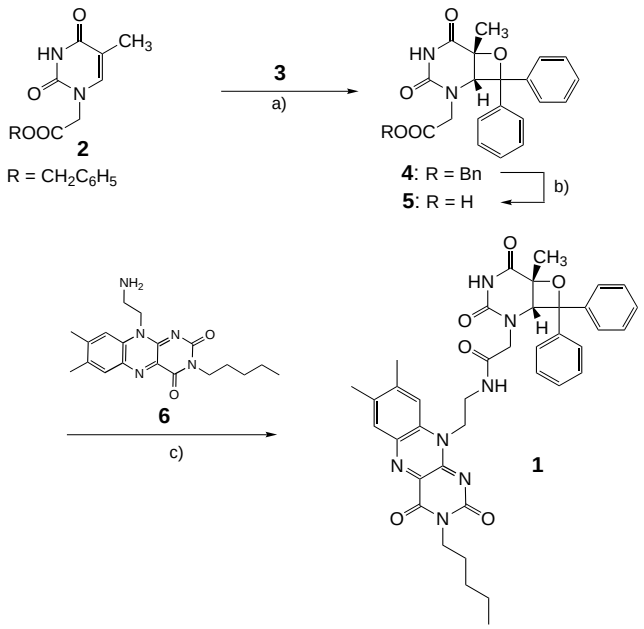
Scheme 1. Depiction of the formation and repair of the mutagenic cyclobutane pyrimidine dimer lesion (CPD lesion) and of the (6-4) photoadduct via the key oxetane intermediate.

reduced and deprotonated flavin ($FADH^-$),[13, 16] which upon excitation by light, donates one electron to the CPD dimer. This cleaves (cycloreverts) spontaneously into its radical anion. In contrast, the (6-4) photolyases,[17, 18] which exclusively repair (6-4) lesions,[19] are less well characterized, and the repair mechanism is currently not understood.[20, 21]

Based on the sequence homology between CPD and (6-4) photolyases and because both repair enzymes contain an FAD coenzyme, Kim et al. proposed a repair mechanism.[18] Their model postulates that binding of the (6-4) lesion induces a back rearrangement of the (6-4) photoadduct into the oxetane.[22] Calculations predict that this rearrangement could be energetically too costly to proceed spontaneously within the active site of the enzyme.[23] Recently, however, two histidine residues that catalyze the putative oxetane formation were identified.[22] The key premise of the mechanism proposed by Kim et al. is the rapid cleavage of the oxetane intermediate by a light-induced electron transfer. Quantum chemical calculations (in the gas phase) predict that oxetanes cleave spontaneously after single electron donation or after single electron abstraction.[24] Laser flash photolysis experiments by Falvey and co-workers[25] and Miranda et al.[26] recently provided experimental evidence that oxetanes do indeed split in the presence of various electron donors and acceptors in a light-dependent reaction.[27] So far, experiments which could clarify the function of the flavin coenzyme in (6-4) photolyases and in particular the direction of the electron transfer within the enzyme active site are not reported. A preliminary study by Falvey and coworkers, however, provided evidence that a light-induced oxetane cleavage could be possible with a reduced and also with an oxidized flavin, although these studies were hampered by decomposition of the flavin.[28] For a deeper understanding of one of nature's most important genome-repair processes, the direction of the electron transfer needs to be clarified.

Herein we report for the first time about flavin-induced oxetane-splitting experiments that use the covalently linked flavin- and oxetane-containing model compound **1** (Scheme 2). We found that **1** is able to mimic the critical putative cycloreversion step catalyzed by DNA (6-4) photolyases with a high quantum yield. We show that the flavin-induced splitting of the oxetane is only possible through the reductive pathway. The cycloreversion is induced by single electron donation to the oxetane and strictly requires the flavin in its reduced and deprotonated state. The results prove a close mechanistic relationship between CPD and (6-4) photolyases.[29]

The synthesis of the (6-4) photolyase model compound **1** required for this study and the chemistry of the cleavage reaction is depicted in Schemes 2 and 3. Irradiation of **2** in the presence of benzophenone (**3**) furnished the stable oxetane **4**, which was isolated by flash chromatography. This oxetane is supposed to model the unstable putative oxetane intermediate. Hydrogenolytic cleavage of the benzyl ester and condensation of the obtained oxetane acid **5** with 10-aminoethylflavin **6** furnished model compound **1** after flash chromatography as a yellow powder ready for mechanistic studies.



Scheme 2. Synthesis of (6-4) model compound **1**. a) benzophenone (**3**), *hν*, acetonitrile, 6 h, 18%; b) Pd/C, acetic acid, room temperature, 3 h, 57%; c) HOBT, TBTU, DMF, room temperature, 2 h, 92%. HOBT = 1-hydroxy-1*H*-benzotriazole; TBTU = 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate; DMF = *N*,*N*-dimethylformamide.

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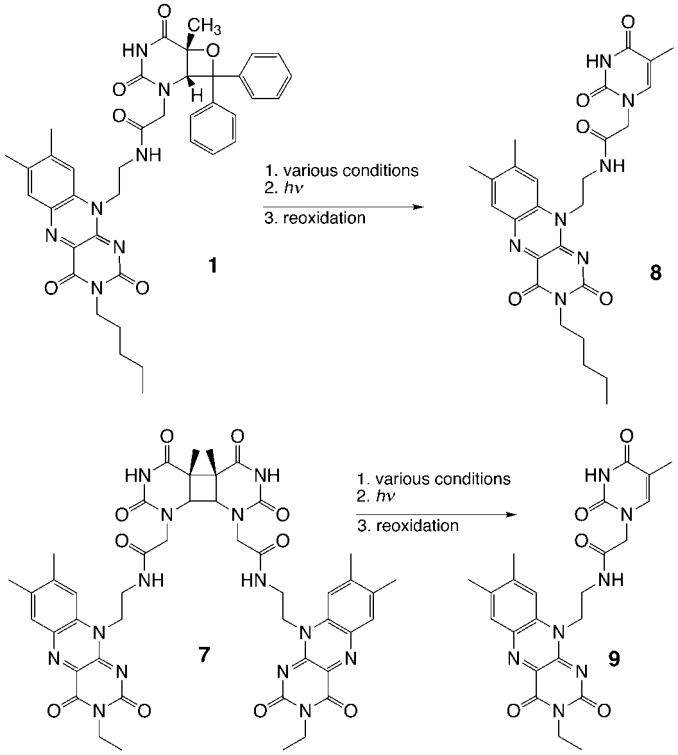
To uncover directly potential mechanistic similarities or differences between (6-4) and CPD photolyases, we performed most of our studies with a 1:1 mixture of the (6-4) model compound **1** and the well-studied CPD photolyase model compound **7**[30] under direct competition conditions (Scheme 3). To allow rapid separation by HPLC of the model compounds **1** and **7** and of the cleavage products **8** and **9**, the flavins in **7** and **9** contain an ethyl side chain at N3, and the flavins in **1** and **8** possess a pentyl side chain at N3.



Scheme 3. Cleavage reaction of **1** and **7** to form **8** and **9**, respectively.

To investigate whether oxetane splitting is possible by an oxidized flavin, a solution of both model compounds **1** and **7** in ethylene glycol (10^{-5} M – 10^{-6} M) was prepared and irradiated with monochromatic light (366 nm) in a fluorimeter. We performed these experiments twice: once under anaerobic and once under aerobic reaction conditions. The results were, however, the same. During the irradiation experiments, samples were taken from the assay solution after defined time intervals with the help of a microsyringe and analyzed by reversed-phase HPLC. The results of all the experiments are summarized in Figure 1. Chromatogram 1 (Figure 1) shows the elution profile of the model compound mixture (**1** + **7**) after 0 min of irradiation. The oxetane model compounds **1** and the CPD model compound **7** elute with very different retention times at 22.7 min and at 9.1 min, respectively. Chromatogram 2 (Figure 1) was obtained after irradiation of the mixture for more than 1 h. None of the two expected reaction products **8** and **9** were detected, showing that the oxidized flavin is unable to initiate the splitting of the oxetane and of the CPD lesion. Since the reduction potential of the

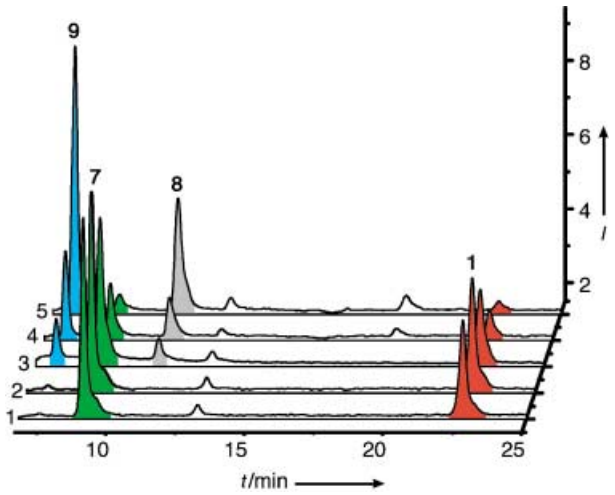


Figure 1. Chromatograms (HPLC) obtained during the various irradiation experiments. Elution times **9**: 7.4 min, **7**: 9.1 min, **8**: 11.3 min, **1**: 22.7 min. Conditions: Nucleosil C18-column (5 × 250 mm), detection at 450 nm, gradient: A = water, B = acetonitrile, 60% A to 30% A in 25 min, flow rate: 0.7 mL min^{-1}.

light-excited flavin is about $E^*_{red} = 1.7$ V, the results show that the oxidation potential of the oxetane could be $E_{ox} > 1.7$ V.

To investigate the possibility of splitting the oxetane reductively, we stoppered another assay solution that contained a mixture of **1** and **7** with a rubber septum, and purged the solution intensively with nitrogen for 20 min to establish anaerobic conditions. Upon addition of a reducing sodium dithionite solution, the flavin fluorescence vanished. The UV spectrum of the sample proved the presence of the reduced flavin under these conditions. The solution was again irradiated at 366 nm. The HPLC chromatogram of a sample taken after 1 h of irradiation and subsequent rigorous reoxidation of the flavin through shaking exposed to air for about 12 h is depicted in Figure 1 (trace 3). To our surprise, only a small amount of the expected cleavage products **8** and **9**, which separate well (11.3 min and 7.4 min), were formed, which shows that the reduced flavin coenzyme is also almost inactive as a photosensitizer. Independent irradiation studies of both model compounds confirm that the oxetane and the CPD dimer do not cleave efficiently under these "just-reductive" conditions. For the CPD photolyases, it was shown that efficient dimer splitting strictly requires deprotonation of the reduced flavin.[13, 16] To investigate how flavin deprotonation affects the critical oxetane cycloreversion, we added triethylamine to the assay solution to ensure deprotonation of the N1-H ($pK_a \sim 6.5$)[31] of the reduced flavin. Within a few minutes of irradiation of the assay solution under these basic reaction conditions, both model compounds **1** and **7** had been converted significantly into the cleaved products **8** and **9**. Trace 4 (Figure 1) depicts the result obtained after irradiation for 20 min. Trace 5 (Figure 1) represents the reaction mixture after 60 min of irradiation. An independent study of the oxetane model compound **1** shows that under these conditions, oxetane cleavage proceeds with a half-life of about 20 min. When the same solution was kept in the dark, no oxetane cleavage occurred, which proves that the cycloreversion is, indeed, a light-induced process. Addition of

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acetic acid to the assay solution stops the cycloreversion reaction immediately, thus underlining the strict requirement for basic conditions. Irradiation of oxetane **4** in the presence of flavin **6** under otherwise identical conditions does not result in any oxetane cleavage, which clearly shows that the splitting reaction is an intramolecular reaction.

To determine the efficiency of the oxetane and CPD model compounds, we determined the quantum yields for the model repair reaction (Figure 2). Cleavage of the oxetane proceeds with a quantum yield of 0.3% under neutral conditions (Figure 2, bar 4) and not at all in the presence of acid (Figure 2, bar 5). Under basic conditions, however, oxetane splitting is twice as efficient ($\phi = 2.3\%$, Figure 2, bars 1 and 3) as CPD cleavage ($\phi = 1\%$, Figure 2, bar 2). This high quantum efficiency is in full agreement with a recent laser flash photolysis experiment by Falvey and co-workers which shows that oxetane ring opening is faster than CPD cleavage.[25] The quantum yield of 2.5% for a model compound compares well with the photolyase repair quantum yield of approximately 50%, which shows that our new model compound **1** mimics the repair reaction remarkably well.

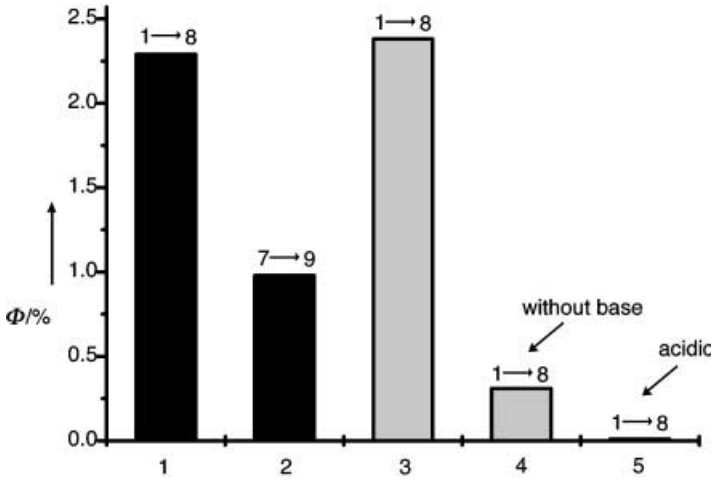

Figure 2. Bar graph of the measured quantum yields. Black bars (one experiment): results from the direct competition experiment **1** + **7** to give **8** + **9**. Grey bars: results from independent studies as indicated above the graphs. Conditions: ethylene glycol solutions. Bar 1: oxetane model **1** ($c = 4 \times 10^{-6}$ M); Bar 2: CPD model **7** ($c = 2 \times 10^{-6}$ M); Bars 3–5: **1** + **7** ($c = 1.0 \times 10^{-4}$ M).

In summary, we prepared and investigated the first covalently linked model compound for the DNA (6-4) photolyase. We showed that the oxidized flavin and the reduced, but not deprotonated, flavin are unable to repair efficiently. Oxetane splitting clearly requires the reduced and deprotonated flavin. The result suggests that, in agreement with the mechanism proposed by Kim and co-workers, electron transfer proceeds from the flavin to the oxetane as the key step of the repair reaction. The strict requirement to deprotonate the flavin suggests that an electron transfer from the neutral FlH_2 to the oxetane is either not possible or provides a zwitterionic intermediate $FlH_2^{\bullet+}$ – oxetane$^{\bullet-}$, which is too short-lived to allow oxetane cleavage to compete with back electron transfer. Instead, deprotonation furnishs a more potent flavin donor FlH^-, which gives a charge-shift intermediate $FlH^{\bullet+}$ – oxetane$^{\bullet-}$ after electron transfer. The lifetimes of this intermediate now needs to be measured to gain further insight into one of nature's most important genome repair processes. The important fact that the cleavage of the CPD dimer in model compound **7** and oxetane splitting in model compound **1** proceed fastest under identical conditions (reduced and deprotonated flavin coenzyme) provides strong support for a very similar mechanism.

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