

When inflexibility is counterproductive: Mechanism of UV-induced DNA Dewar lesion revealed

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Excessive exposure to ultraviolet (UV) radiation of sunlight can result in skin damage and may even induce skin cancers. Irradiation with UV light causes mutations in the DNA, which can interfere with or even inhibit the read-out of genetic information and hence affect the cell function. The Dewar lesion is one of the major UV-induced reaction products, which can itself generate mutations. Understanding the mechanism that leads to the formation of the Dewar lesion is therefore of great interest.

Researchers from Ludwig-Maximilians-Universitaet (LMU) in Munich have now shown that the [DNA backbone](#) (the double-stranded scaffold which bears the subunits that encode the [genetic information](#)) plays a decisive role in the process. The Dewar lesion can be generated only if the backbone of the DNA is intact. If the [DNA strand](#) itself is broken, and therefore more flexible, the Dewar reaction will not take place. The process reveals a surprisingly paradoxical facet of the [DNA structure](#). On the one hand, an unbroken backbone is a prerequisite for DNA function and for [cell survival](#); on the other, the intact backbone favors the formation of Dewar lesions upon exposure to UV, and so facilitates UV-induced mutagenesis. ([Angewandte Chemie](#), 23 November 2011)

[UV radiation](#) induces [molecular changes](#) in DNA structure, which can lead to [genetic mutations](#) and finally to cell death. Energetic UV light primarily produces two types of photochemical damage in the subunits

of the DNA - cyclobutane pyrimidine dimers (CPDs) and (6-4) photoproducts. Both types of lesion are due to cross-linking of adjacent pyrimidine bases on the same DNA strand. Continued exposure to UV light transforms the (6-4) photoproduct into a Dewar lesion by inducing further structural changes. Dewar lesions are stable end-products of continuous exposure to sunlight. Moreover, they are highly mutagenic, i.e. they can themselves induce a range of further mutations. "While the [chemical changes](#) that give rise to CPDs and (6-4) photoproducts are already well understood, this is not true for the Dewar lesion," says LMU chemist Professor Thomas Carell, who is also a member of the Center for Integrated Protein Science Munich (CiPSM), one of the Clusters of Excellence at LMU.

In a joint project within the SFB749 initiative Carells group together with research teams led by LMU physicist Professor Wolfgang Zinth (CiPSM) and Regina de Vivie-Riedle of the Department of Chemistry, could show that the backbone of the DNA plays a crucial role in the formation of the Dewar lesion. The backbone consists of repeating units made up of sugars and phosphates, which link the succession of bases that represent the protein-coding information in the DNA. "To our surprise, we found that the Dewar lesion can be generated only if the backbone in the affected region is intact," Carell explains. "If the continuity of the backbone is interrupted, or if the cross-linked base-pairs alone are exposed to sunlight, the Dewar structure fails to form." Thus, an interdisciplinary cooperation, which included chemists, physicists and theorists has, for the first time, been able to dissect the photochemical formation of the Dewar lesion at the atomic level. "Our results also show that the process is remarkably effective; indeed, this is one of the most efficient light-induced reactions known to occur within the DNA," says physicist Wolfgang Zinth.

Theoretical considerations yielded further insights into the details of the Dewar isomerization. "To follow the photochemical reaction dynamics

on a high level of theory we came up with a hybrid method that separates the molecular system into subsystems treated on different quantum mechanical levels. This hierarchic strategy allows us to evaluate the dynamics of the complete system," says de Vivie-Riedle. Based on these calculations, the researchers were able precisely to define the role of the DNA backbone in the formation of the Dewar lesion. Cleavage of the backbone makes the molecule more flexible. Under these conditions, the (6-4) lesion will be protected and the system returns via a photophysical pathway back to its initial state. In contrast, an intact backbone keeps the molecule rigid, and strains the pyrimidine ring structure. The result is that only those atoms that must rearrange to form the Dewar isomer remain mobile, which favors the reaction that leads to the stable Dewar lesion.

More information: Mechanism of UV-Induced DNA Dewar-Lesion Formation, Karin Haiser, Benjamin P. Fingerhut, Korbinian Heil, Andreas Glas, Teja T. Herzog, Bert M. Pilles, Wolfgang J. Schreier, Wolfgang Zinth, Regina de Vivie-Riedle, Thomas Carell, *Angewandte Chemie*. Article first published online: 23. Nov. 2011; [DOI: 10.1002/ang.201106231](https://doi.org/10.1002/ang.201106231)

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