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Using DNA Origami Nanostructures To Determine Absolute Cross Sections for UV Photon-Induced DNA Strand Breakage

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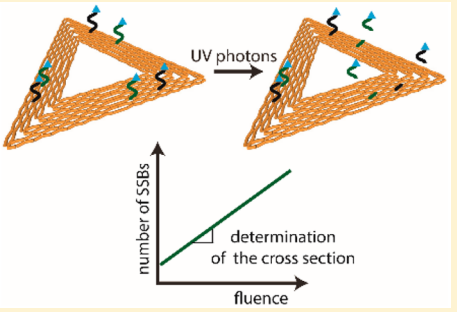
Supporting Information

ABSTRACT: We have characterized ultraviolet (UV) photon-induced DNA strand break processes by determination of absolute cross sections for photoabsorption and for sequence-specific DNA single strand breakage induced by photons in an energy range from 6.50 to 8.94 eV. These represent the lowest-energy photons able to induce DNA strand breaks. Oligonucleotide targets are immobilized on a UV transparent substrate in controlled quantities through attachment to DNA origami templates. Photon-induced dissociation of single DNA strands is visualized and quantified using atomic force microscopy. The obtained quantum yields for strand breakage vary between 0.06 and 0.5, indicating highly efficient DNA strand breakage by UV photons, which is clearly dependent on the photon energy. Above the ionization threshold strand breakage becomes clearly the dominant form of DNA radiation damage, which is then also dependent on the nucleotide sequence.



The susceptibility of the DNA molecule to energetic photons, particularly to the ubiquitous ultraviolet (UV) radiation, is the subject of an immense and long-standing research.[1] Because DNA is the carrier of genetic information, any radiation-induced alteration or degradation of its structure directly leads to drastic vital effects such as cell death or tumor genesis.[2,3] It has been shown that absorption in the UV range around 4.7 eV (260 nm), corresponding to resonant $^1\pi\pi^*$ excitation in the nucleobases,[1,4] mainly leads to rapid population of the electronic ground state via conical intersections and to a small extent to nucleobase modifications such as cyclobutane pyrimidine dimers.[1] At higher photon energies (>6 eV) DNA strand breaks become the dominant form of radiation damage.[5,6] To reach a profound understanding of photoinduced DNA strand breakage, which allows modeling the irradiation effects on a macroscopic level, absolute cross sections for a specific DNA damage are needed, particularly their dependence on both the photon energy and the molecular structure.

There has been a persistent effort to quantify the DNA damage induced by vacuum ultraviolet (VUV) irradiation (see refs 5, 7, and 8 and references therein); however, so far the investigations have been typically performed on plasmid DNA, in which the induced damage, such as single and double strand breaks (SSBs and DSBs, respectively), can be recorded by gel electrophoresis. The obtained results indeed provided valuable information about the yields of SSBs and DSBs as a function of both the irradiation dose and the photon energy, which were important to understand, and model biological effects induced by ionizing radiation.[7] Nevertheless, the quantification of SSBs by gel electrophoresis is error prone,[6] and from the experiments performed on plasmid DNA it remains unknown in which part of the DNA the actual damage occurs and what the influence of both the primary and the secondary structure on the DNA damage is. It has been reported that stacking interactions between the DNA nucleobases lead to a strong modification of their electronic properties and hence their photoinduced fragmentation dynamics.[9] In early attempts to understand the mechanism of UV-induced DNA strand breakage it was already suggested that it depends on the nucleotide sequence. In these experiments chromatographic methods were used to analyze the damage to dinucleotides;[10] however, as was demonstrated recently with low-energy electrons, chromatographic methods fail for the analysis of longer DNA sequences,[11] in which sequence-dependent effects are actually expected to be the most relevant. Consequently, to the best of our knowledge, absolute cross sections for VUV-induced sequence-specific

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DNA strand breakage of oligonucleotides have not yet been reported.

Furthermore, the results measured for plasmid DNA may depend markedly on the experimental procedure. For example, it has been suggested that variation of the plasmid damage reported by different authors may be due to different sample preparation conditions and different structure of the DNA as a result of different residual water containment by the dried plasmid DNA.[5] It has been also pointed out recently that the film thickness can strongly influence the radiation damage by modifying both the molecular structure of the material and the deposition process.[12] Finally, possible effects from either secondary electrons produced in the substrate or an indirect damage cannot be absolutely excluded.[5] Therefore, it appears that there is a serious constraint in the research on UV damage to DNA. On the one hand the photophysics of basic DNA components (e.g., nucelobases or nucleotides) can be studied under well-defined conditions but cannot be simply extrapolated to quantify the damage of the DNA molecule, as the sequence and structure contributions are not taken into consideration. On the other hand, the quantification of degradation of a macroscopic DNA sample cannot be scaled down to unambiguously determine the absolute cross section for the VUV-induced damage of a single DNA molecule with defined sequence.

In the following, we report an unprecedented study on sequence-specific DNA damage induced by VUV photons on the single-molecule level. By using DNA origami-based DNA nanoarrays, we are able to visualize the dissociation of single chemical bonds by atomic force microscopy (AFM)[13−15] and determine the absolute cross sections for strand breakage (σ_{SSB}) in specific oligonucleotides at various photon energies. The basic experimental procedure is illustrated in Figure 1a.

Triangular DNA origami substrates are used due to their rigidity and their low tendency to form clusters. Because the target sequences are arranged in a pattern recognizable in AFM images, two target sequences can be studied simultaneously within one irradiation experiment. The samples are deposited on a UV transparent CaF_2 substrate to avoid any secondary effects due to absorption by the substrate and are irradiated under normal atmospheric pressure in a transparent Ar atmosphere. Under the dry conditions the direct interaction of VUV photons with DNA is probed and the contribution of OH radical-induced DNA damage can be ruled out. The target sequences are modified with a biotin marker on the 5′ end. After irradiation the DNA nanoarrays on the CaF_2 substrates are treated with a solution of streptavidin (SAv), which binds to the biotin markers of the intact target oligonucleotides. The SAv can then be easily recognized in AFM images and thus the number and position of damaged target oligonucleotides can be determined. The method is intrinsically digital regarding the information on both the strand breakage and the target sequence; therefore, it allows fast and parallel determination of σ_{SSB} with unprecedented control over the DNA's primary and also secondary structure.[16,17] The σ_{SSB} values have been determined by measuring dose−response curves.[18] The results clearly indicate a dependence of σ_{SSB} on the photon energy and to some extent also on the sequence. By measuring the photon absorption cross sections (σ_{PA}) of the same target sequences at the same photon energies, we additionally obtain the quantum yield of DNA strand breakage.

DNA origami nanostructures were prepared from the M13mp18 scaffold strand and a set of 208 short oligonucleotides according to a well-established procedure.[13,19] In brief, the DNA strands are mixed in TAE buffer with 10 mM $MgCl_2$ and annealed from 80 °C to room temperature within 4−6 h, and the nonassembled excess strands are removed by spin-filtering. The assembled structures are deposited in 1× TAE buffer with 10 mM $MgCl_2$ on CaF_2 substrates for 2 min. The excess solution is removed by washing with 4 mL of ethanol/water (1/1) mixture, and subsequently the sample is dried with a blow of nitrogen. Then, the samples are transferred into the irradiation chamber and exposed to VUV photons. After irradiation the samples are rinsed again with ethanol/water to remove fragmentation products and then incubated in a 50 nM solution of streptavidin (SAv) for 2 min, washed again, and dried. Then, the samples are analyzed with AFM (Figure 1b). Within the accuracy of the experiment the strand break cross section is independent of the position of target strands on the DNA origami template. Compared with isolated oligonucleotides the target sequences in the present experiment are attached to the DNA origami template and have thus one more potential site that can be broken to be detected as a strand break. A schematic view of the experimental setup is given in Figure 1c. The irradiation chamber has been connected to the APEX branch of the DISCO beamline[20] of the SOLEIL synchrotron facility (France) and filled with argon gas under normal atmospheric pressure through the differential pumping stage of the branch.[21] For the present energy range, the second-order light has been filtered off by a MgF_2 window mounted on the window valve isolating the differential pumping. Because CaF_2 holders are used any secondary effects that could result from substrate irradiation (secondary electrons, heating, etc.) are practically excluded. Because we are working on a single-molecule level the photon irradiation above the ionization

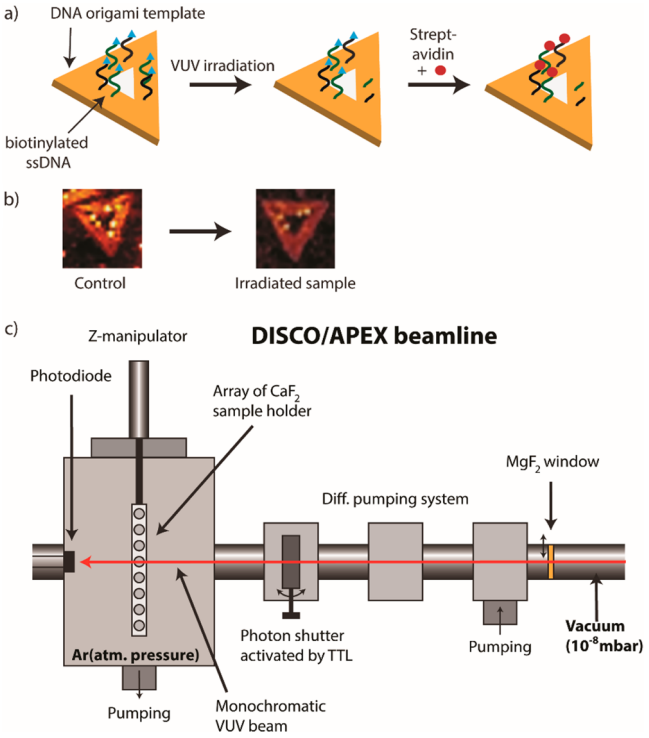

Figure 1. (a) Scheme of the DNA origami triangles which serve as a support of the oligonucleotide target structures. (b) Typical AFM images of a nonirradiated control sample (left) and a sample irradiated with VUV light (right). (c) Schematic view of the experimental setup.

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threshold of DNA is not expected to modify the strand breakage or to lead to significant charging of the DNA. The samples are inserted in front of the VUV beam by using a Z-manipulator and irradiated for a defined period. The beam diameter is larger than the exposed sample and the photon flux is measured only for the exposed, active sample area. The irradiation time was controlled by using a rotatable shutter activated by a TTL signal. The photon flux has been constantly monitored during the irradiation period by using a calibrated photodiode (AXUV 100, International Radiation Detectors) placed downstream the sample holder. The photon flux used to evaluate the absolute cross sections has been measured with the sample holder pulled out. A series of samples was irradiated with different photon fluence at a fixed photon energy. The relative number of strand breaks N_{SSB} was extracted from AFM images by comparing the number of specifically bound SAv on irradiated and nonirradiated triangular DNA origami structures with the expected maximum coverage. For each irradiated sample, about ten AFM images, that is, 500−1000 DNA origami structures, have been recorded and analyzed.

The fluence (Φ) dependence of N_{SSB} at 8.44 eV photon energy is shown in Figure 2. It shows a linear increase of N_{SSB} until a saturation is reached at ~1.3×10^{15} cm^{-2}. The DNA origami structures are modified with two different oligonucleotide sequences ($TT(ATA)_3TT$ and $TT(CTC)_3TT$), which can be independently analyzed by AFM. From the slope of the linear fit in the low fluence regime σ_{SSB} is determined: $N_{SSB} = \sigma_{SSB} \cdot \Phi$.[15,18] The strand break cross sections for the two different DNA sequences at four different photon energies are summarized in Supplementary Table 1 and displayed in Figure 3. They vary between 0.9×10^{-16} and 6.9×10^{-16} cm^2 depending on the photon energy and the oligonucleotide sequence.

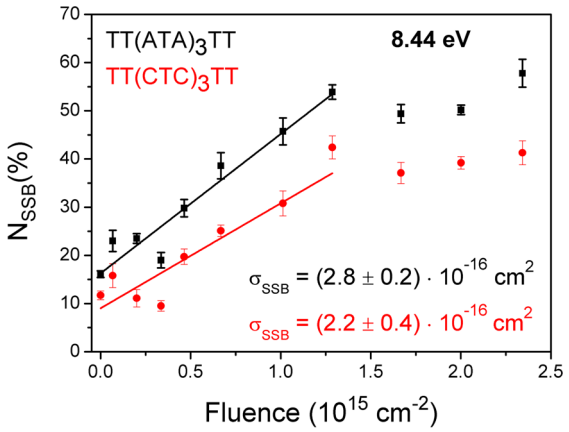

Figure 2. Relative number of strand breaks plotted as a function of the photon fluence at 8.44 eV. From the slopes of the linear fits in the low-fluence regime the absolute cross sections for strand breakage are extracted.

Photoabsorption cross sections (σ_{PA}) for the oligonucleotides have been measured in solution from 350 (3.54 eV) to 190 nm (6.52 eV) using both a double spectrophotometer and the synchrotron radiation circular dichroism branch of the DISCO beamline.[22] Absorption measurements have been carried out on thin films of oligonucleotides deposited on CaF_2 windows to reach for shorter wavelengths. The condensed phase measurements have been scaled to absolute cross sections obtained from the solution phase. Although UV spectroscopy is known to be indicative of higher order structure of biological polymers, the effect of the physical state on the absorption cross sections is not drastic and both measurements can be compared, as previously done for other biomolecules.[23] The procedure is described in detail in the Supporting Information.

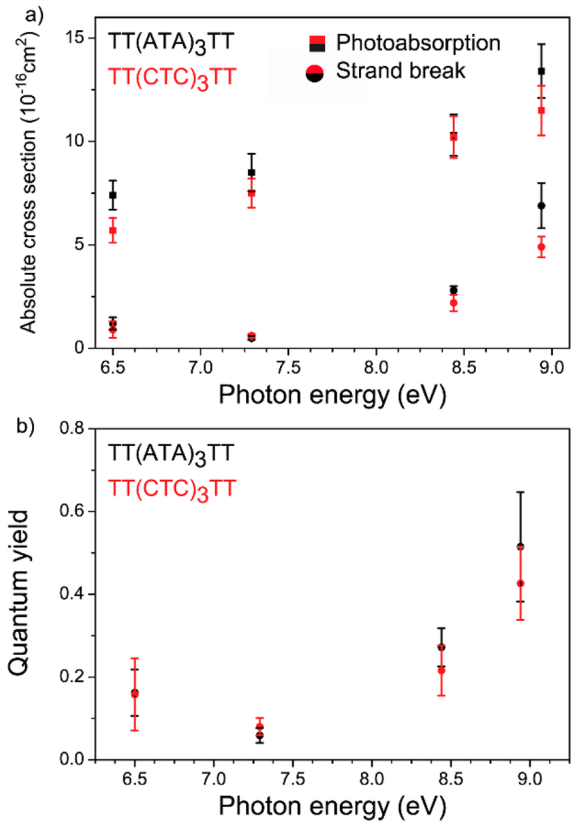

Figure 3. (a) Absolute cross sections for DNA photoabsorption (open symbols) and strand breakage (full symbols) for two different oligonucleotides determined at four different photon energies. (b) Quantum yield for strand breaks for the two oligonucleotides obtained from the data in panel a.

The photon energy dependence of σ_{SSB} is displayed in Figure 3a (circles) and shows a minimum around 7.29 eV. At lower energy (6.50 eV) σ_{SSB} is slightly larger, and toward higher energies σ_{SSB} rises steeply. The slight increase in σ_{SSB} at 6.50 eV indicates a resonant process and contrasts with the σ_{PA}, which increases monotonically from 6.5 to 8.94 eV, as shown in the top of Figure 3a (square symbols). The excitation in the 6.3 to 6.5 eV range is ascribed to a $\pi-\pi^*$ transition within the nucleobases.[24] In recent tandem mass spectrometric experiments using protonated adenine-5′-monophosphate stored in an ion trap and irradiated with VUV photons, a resonant fragmentation around 6.50 eV was found resulting in the formation of protonated adenine due to an N-glycosidic bond cleavage.[4] The current data show that the $\pi-\pi^*$ transition at 6.50 eV results not only in base abstraction but also in a more efficient DNA strand breakage, that is, a bond cleavage within the sugar−phosphate backbone.

At the higher energies investigated here the oligonucleotides can be ionized at the nucleobases because the vertical ionization energy (IE) of isolated A is 8.44 eV and the vertical IE of C is 8.94 eV.[25] The IEs of stacked nucleobases are slightly lower[15] and the ionization threshold of the DNA sugar 2′-deoxy-D-ribose was recently found to be 9.4 eV,[26] which is clearly above

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the energies considered here. σ_{SSB} increases steeply at these energies, indicating more efficient strand breakage from ionized DNA compared with the strand breakage from electronically excited states. In a previous study on single strand breakage in plasmid DNA by 8.3 eV photons a cross section of 8.1×10^{-15} cm^2 was found.[27] The lower values of σ_{SSB} found in the present study are ascribed to the fact that we have used 13mer oligonucleotides compared with the plasmid DNA used by Hieda et al., which consists of several thousand base pairs. At higher photon energy of 26.5 eV an SSB cross section of (2 to 3) $\times 10^{-13}$ cm^{-2} was recently reported.[28] In previous experiments using low-energy electrons, strand break cross sections on the order 10^{-14} cm^2 have been reported for both plasmid DNA[18,29] and oligonucleotides.[15] Such high damage cross sections are due to the dissociative electron attachment mechanism, which proceeds through a transient anionic state and is very efficient at low electron energies.[30,31]

The two different oligonucleotide sequences investigated here ($TT(ATA)_3TT$ and $TT(CTC)_3TT$) exhibit very similar properties, but distinct differences appear for σ_{SSB} at higher energies (8.44 and 8.94 eV, see Figure 3a). That is, σ_{SSB} is higher for the $TT(ATA)_3TT$ sequence than for the $TT(CTC)_3TT$ sequence by a factor of 1.3 at 8.44 eV and by a factor of 1.4 at 8.94 eV. The comparison with the absorption cross section of the two oligonucleotides (Figure 3a, square symbols) indicates that the higher sensitivity of the A-containing sequence can partly be attributed to a higher photoabsorption. Nevertheless, a very recent study found that the energy threshold for DNA photo damage at the sugar-phospate backbone is considerably lower (4.2 eV) than that for damage at the nucleobases (6.9 eV).[32] Such low-energy thresholds might be associated with low ionization energies that have been reported for the negatively charged phosphate in DNA.[33] Thus, the strand breakage at low energies proceeds most likely via the DNA backbone, and at higher energies fragmentation pathways involving the nucleobases start to be operative, resulting in more distinct values of σ_{SSB} for the two different sequences. At 8.44 and 8.94 eV a radical cation might be formed on one the nucleobases. Previously, it was shown that excited nucleobase radical cations are transferred into sugar radicals through a hole and proton transfer.[34−36] These sugar radicals represent important precursors for DNA strand breakage, and they might be formed more efficiently in the A containing sequence than in the C containing sequence.

The energy dependence of the strand break quantum yield is presented in Figure 3b. For both molecules, the yields range from 16% at 6.5 eV to 40−50% at 8.94 eV, with a minimum at 7.29 eV of 6−8%. Interestingly, the minimum at 7.24 eV observed in Figure 3b indicates that a relaxation mechanism other than strand breakages becomes predominant at 7.24 eV. Nevertheless, the quantum yields demonstrate the extremely high efficiency of DNA strand breakage upon absorption of UV photons. Thus, the strand breakage is most likely a direct result of the excitation/ionization either of the DNA backbone or the nucleobases and is not due to a combined process such as the production of secondary low-energy electrons, which then react with the target sequence. Furthermore, the quantum yields indicate that strand breakage is the dominant decay channel after photon absorption at energies above the ionization threshold.

In conclusion, we present for the first time absolute cross sections and quantum yields for the strand breakage of specific oligonucleotide sequences ($TT(ATA)_3TT$ and $TT(CTC)_3TT$) induced by VUV photons with energies around the ionization threshold (6.50, 7.29, 8.44, and 8.94 eV). The strand break cross sections vary between 0.9×10^{-16} and 6.9×10^{-16} cm^2 depending on both the oligonucleotide sequence and the photon energy. DNA strand breakage takes place both from the $\pi-\pi^*$ transition at 6.50 eV and presumably from ionized states accessed at higher photon energies. The strand breakage is highly efficient, which is reflected by quantum yields ranging from 6 to 50%. The sequence dependence of σ_{SSB} is most pronounced at the higher energies investigated here and is reflected in a higher sensitivity of the A-containing sequence, which could be due to a stronger delocalization of excited/ionized stats in stacked A bases. The present experiments are based on a novel DNA origami technique, which allows us to determine absolute cross sections for strand breakage in well-defined oligonucleotide sequences. This is the basis for a thorough and comprehensive investigation of photoinduced DNA strand break mechanisms.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jpclett.5b02238.

Additional AFM images of DNA nanostructures irradiated on CaF_2, additional measurements indicating the biotin stability, dose−response curves for the irradiation energies 6.50, 7.29, and 8.94 eV, detailed information about the measurements of the photoabsorption cross sections of the different DNA sequences, and complete refs 20−22. (PDF)

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Notes

The authors declare no competing financial interest.

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