DNA strand breaks: Reaction dynamics vs. electronic theory of organic chemistry

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Radiation damage in DNA is induced by direct and indirect effects of radiation. The number of DNA strand breaks caused by radioactive decays or X-rays can be experimentally determined. It has been reported for single-strand DNAs [1] that the cleavage of the sugar-nucleobase bond (base loss) occurs followed by that of the sugar-phosphate bond (strand break) in MALDI experiments (Fig. 1). The mechanism of strand breaks however remains unclear at a molecular level. In this study, we performed molecular dynamics simulations for short strand DNAs [1, 2] using the density-functional based tight-binding (DFTB) method [3]. The dynamics of strand breaks are analyzed from the viewpoint of energy and charge transfer.

Fig. 1. Single-strand break analyzed by MALDI TOF Mass spectrometry [1]

The target DNA is assumed to be vibrationally excited up to ~1500 K through electronic relaxation after its exposure to radiation. This scenario for the direct mechanism of DNA strand break is justified by the recent XFEL experiment on heavy atom-containing molecules such as iodouracil [4]. In the absence of any surroundings such as counter cations, a single-strand break occurs via three sequential steps both for single- and double-strand DNAs:

(i) C-N bond breaking between the base and sugar of a nucleoside

(ii) Hydrogen transfer from a sugar and to an adjacent phosphate

(iii) Cleavage of the C-O bond between neighboring sugar and phosphate

The timescale up to step (iii) was ~10 ps.

To analyze the mechanism of strand breaks, we proposed to divide the potential energy into individual atomic ones $\{V_A\}$ [5]. Each atom A is then assigned to possess an atom resolved energy (ARE), i.e., K_A+V_A, where K_A is the kinetic energy of atom A. The ARE can be used to quantify the energetic dynamics of reactions. We also estimated the charge transfer by Mulliken populations to understand the reactions from the viewpoint of the electronic theory of chemistry. These analyses clearly showed that energy and charge transfer are delocalized for (iii) beyond the domains of nucleotides while they are localized in the nucleotide for (i) and (ii).

We also present the results of theoretical investigation of the strand breaks of DNAs surrounded by water molecules and counter cations. We found that DNAs are relatively stable because the counter cations suppress global charge and energy transfer in a DNA as long as the surrounding cations are hydrated. However, DNAs are subject to a different mechanism of strand break if cations go out of the hydration pockets to approach a DNA.

[1] L. Zhu e thymine t al., J. Am. Chem. Soc. **117**, 6048 (1995).

[2] 4−6 base pairs of adenine and. See M. McCullagh et al., J. Phys. Chem. B **112**, 11415 (2008).

[3] The DFTB has been applied to large molecules. See, e.g., our work on the dynamics of C_{60}: N. Niitsu et al., J. Chem. Phys. 136, 164304 (2012).

[4] K. Nagaya et al., Phys. Rev. X, **6**(2), 021035(2016); K. Nagaya et al., Faraday Discussions (2016).

[5] This idea originates from the division of the time-dependent total electronic energy of a molecule in a laser field into electron configurational energies. See S. Ohmura et al., J. Ch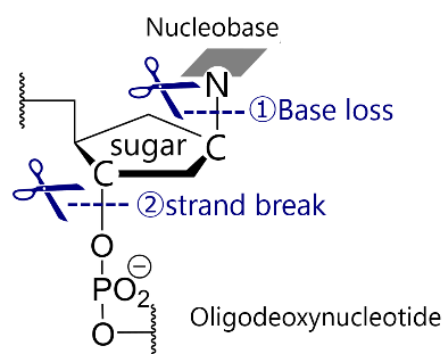em. Phys. **141**, 114105 (2014).