Michael Sevilla

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Radiation, free radicals and DNA

Michael Sevilla's research interests are the chemistry of free radical species produced by the high energy irradiation of DNA by gamma irradiation and ion beams. Both radiations are employed in treatment of cancer.

Ion beams are increasingly of interest to Sevilla as they can be directed to the cancer tumor and stop its growth. The principal biological effect of radiation on a cell is caused by the direct interaction of radiation with DNA, or molecules immediately surrounding the DNA, which damage the cell. Radiation induces ionizations, free electrons, or excitations in DNA that decay to a variety of free radical intermediates. These reactive species can damage DNA bases and the sugar phosphate backbone that may lead to cellular death or mutation.

Recent efforts have looked into the production of sugar radicals in DNA by high energy irradiation. These species are of critical importance to the subsequent biological damage, and, as a consequence, quantitation of the numbers of sugar radicals and their identity gives important mechanistic information. Researchers in Sevilla's lab have found that about 10 percent of all radicals produced are on the sugar phosphate backbone for gamma rays but as much as 30 percent of radicals are on the sugar phosphate backbone for ion beam irradiated DNA. This led to the hypothesis that excited states of the DNA base cation radicals may lead to damage to the sugar portion of DNA. Sevilla explains that a series of recent papers have shown this is indeed the case. "These efforts have identified the C1', C3' and C5' sites on the sugar as those that are most prone to damage by this mechanism. Sugar radicals result in DNA strand breaks and loss of DNA biological function," he says.

Sevilla also found that electrons produced by radiation also can be damaging entities while they have kinetic energy. Such species are called low energy electrons and have been recently shown to fragment the DNA strand to produce single and even double strand breaks. In addition, the Sevilla group is currently using time dependent density functional theory in the investigation of the role of excited states in the mechanisms of radiation damage. The major finding is that electronic excited states, when combined with DNA ion radicals, lead to the formation of strand breaks and DNA damage.

Representative Recent Publications

1. Adhikary A, Khanduri D, Sevilla MD. 2009. Direct observation of the hole protonation state and hole localization site in DNA-oligomers. *J Am Chem Soc* 131:8614–8619.

2. Kumar A, Sevilla MD. 2009. Role of excited states in low-energy electron (LEE) induced strand breaks in DNA model systems: Influence of aqueous environment. *Chemphyschem* 10:1426-1430

3. Becker D, Sevilla MD. 2008. Radiation damage to DNA and related biomolecules. In: *Royal Society of Chemistry Specialist Review: Electron Spin Resonance.* 21:33-56.

4. Khanduri D, Collins S, Kumar A, Adhikary A, Sevilla MD. 2008. Formation of sugar radicals in RNA model systems and oligomers via excitation of guaninecation radical. *J Phys Chem B* 112:2168-2178.

5. Kumar A, Sevilla MD. 2008. The role of πo^* excited states in electron induced DNA strand break formation: A time-dependent density functional theory study. *J Am Chem Soc* 130:2130-2131.

6. Kumar A, Sevilla MD. 2008. Radiation effects on DNA: Theoretical investigations of electron, hole and excitation pathways to DNA damage. In: *Radiation Induced Molecular Phenomena in Nucleic Acids: A Comprehensive Theoretical and Experimental Analysis*, Shukla MK, Leszcyznski J, Eds., Springer-Verlag, Berlin, 577-618.

7. Kumar A, Sevilla MD. 2007. Low-energy electron attachment to 5'-thymidine monophosphate: Modeling single strand breaks through dissociative electron attachment. *J Phys Chem B* 111:5464 -5474.

8. Li X, Sevilla MD. 2007. DFT treatment of radiation produced radicals in DNA model systems. In: *Advances in Quantum Chemistry*, Elsevier, 52:59-88.