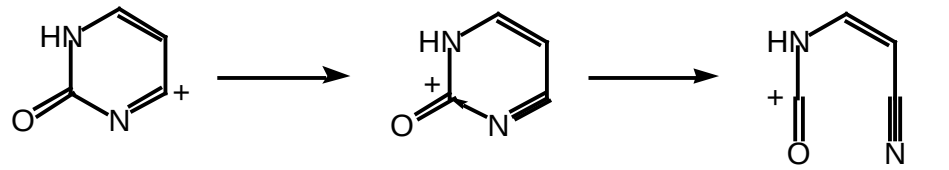
NITROSATIVE CYTOSINE DEAMINATION: A NOVEL MECHANISM OF MUTAGENESIS

*Sundeep Rayat and Rainer Glaser**
Department of Chemistry, University of Missouri-Columbia, Columbia, MO 65211

The nucleobase cytosine undergoes nitrosative deamination to form uracil which represents an important mechanism of genomic alteration.[1] This deamination process is believed to involve the formation and hydrolysis of cytosinediazonium ion while the pyrimidine ring stays intact[2] although, the diazonium ions of DNA bases have never been isolated or observed experimentally. Our recent theoretical studies have shown that the dediazoniation of the cytosinediazonium ion to form the deaminated cytosine cation and free nitrogen is a very facile process.[3] We realized that the structure of deaminated cytosine cation is best represented as a cyclic nitrilium ion, as shown, with a dative bond from the nitrile group to the electron deficient carbonyl center. Our studies further revealed that the dative bond in the deaminated cytosine cation is very weak and the cation undergoes exothermic pyrimidine ring-opening with hardly any activation energy to form the acyclic cation shown.[4]



Deaminated Cytosine Cation **Cyclic Nitrilium Ion** **Ring-opened Cation**

Based on our theoretical results, we have proposed a novel mechanism of cytosine deamination involving the pyrimidine ring-opened intermediate. To test our mechanistic hypothesis, we have synthesized the derivative of the ring opened intermediate and we have achieved ring closure to form uracil. Our studies clearly reveal that the classical mechanism of cytosine to uracil mutation involving the hydrolysis of intact diazonium ion is incomplete or entirely wrong!

---

1 Duncan, B. K.; Miller, J. H. *Nature* **1980,** *287,* 560-561. (b) Viswanathan, A.; You, H. J.; Doetsch, P. W. *Science* **1999,** *284,* 159-162, and references therein.

2 (a) Shapiro, R.; Dubelman, S.; Feinberg, A, M.; Crain, P. F.; McCloskey, J. A. *J. Am. Chem. Soc.* **1977,** *99,* 302-303. (b) Dubelman, S.; Shaprio, R. *Nucleic Acid Res.* **1977,** *4,* 1815-1827. (c) Bunton, C. A.; Wolfe, B. B. *J. Am. Chem. Soc.* **1974,** *96,* 7747-7752.

3 Glaser, R.; Rayat, S.; Lewis, M.; Son, M.-S.; Meyer, S. *J. Am. Chem. Soc.* **1999**, *121,* 6108.

4 Rayat, S. and Glaser, R., submitted for publication.