Nitrosative deamination of adenine causes DNA damage

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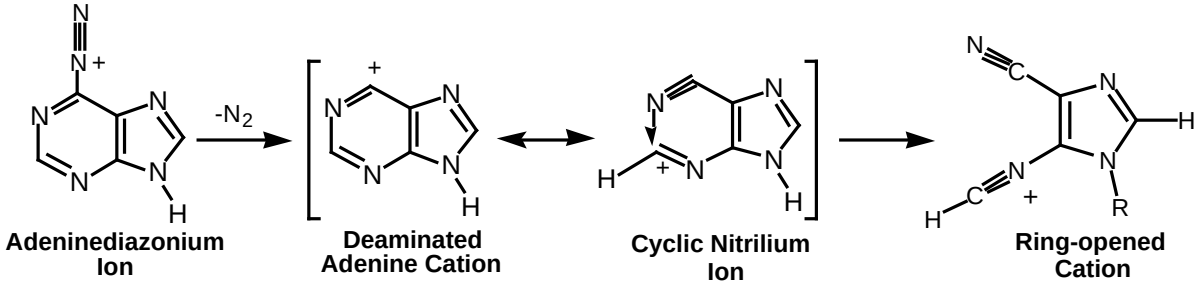
A variety of disorders in people are likely to result from DNA base deamination and interstrand cross-linking due to reactions with HNO_2 or NO. Nitric oxide is a bioregulatory agent produced in the body, and certain nitrates are used in the process of curing meat products. Because of the considerable exposure of the human body to oxides of nitrogen there has been a wide interest in studying these deamination related processes. The nucleobases adenine, cytosine, and guanine undergo deamination in the presence of HNO_2 or NO to form hypoxanthine, uracil, and xanthine. The deamination of these nucleobases is thought to occur through the formation of diazonium ions that undergo nucleophilic substitution by water or other available nucleophiles. The crosslink formation is thought to occur if the amino group of a neighboring DNA base acts as that nucleophile.



We now report the results of high level ab initio molecular orbital study conducted at the MP2(full) level of theory on the adeninediazonium ion. We found that the cyclic cation formed by the dediazoniation of the adeninediazonium ion does exist. This cation stabilizes itself via hyperconjugation by the β, γ-N-C σ-bond.[1] We found that hyperconjugation in the cyclic cation leads to a nitrile group and a dative bond. While searching the potential energy surface of this cation we unexpectedly found that a pyrimidine ring-opened cation structure *also* exists and that it is a stable minimum. Our studies further revealed that the dative bond in the deaminated adenine cation is very weak. The cyclic cation undergoes a ring opening that is thermodynamically favored and kinetically hardly hindered.[2] At the MP2(full) level of optimization, the acyclic structure is 0.81 kcal/mol more stable than the cyclic structure. Hence, we have now discovered a new and viable ring-opened cation intermediate that offers an exciting array of potential new reactions and products. The consequences and new potential products formed from this ring-opened structure of the adenine cation are now under investigation.

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[1] Glaser, R.; Rayat, S.; Lewis, M.; Son, M. -S.; Meyer, S. *J. Am. Chem. Soc.* **1999**, *121*, 6108-6119.
[2] Rayat, S. and Glaser, R., submitted for publication.