Endogenous Nitrosation Chemistry in Carcinogenesis. Retro-Ene Reactions of Cyclic α-Hydroxynitrosamines.

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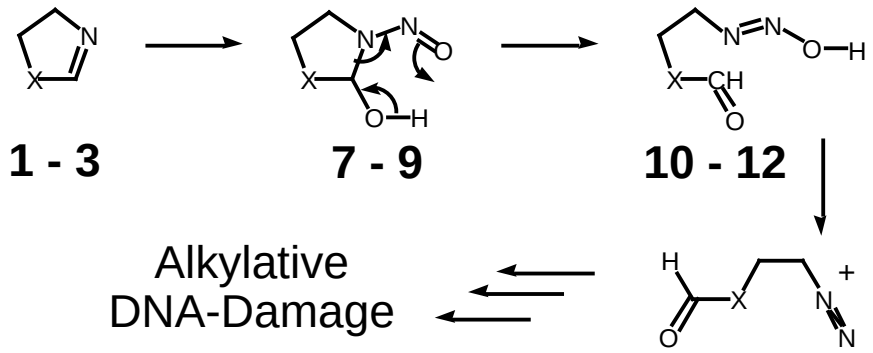
Nitrosamines and related *N*-nitroso compounds are one important class of compounds which are responsible for DNA damage and carcinogenesis.[1] While some of these compounds are contained in the human diet, more recently it has also been realized that endogenous nitrosation can generate such compounds *in vivo*. Our present efforts focus on the elucidation of the possible role of nitrosation of compounds with C=N double bonds in the generation of cell damaging electrophiles. In this context, we are discussing aspects of the nitrosation chemistry of three cyclic imines: Δ^1-pyrroline (3,4-dihydro-2*H*-pyrrolenine), **1** (X = CH_2), 2-imidazoline, **2** (X = NH), and 2-oxazoline, **3** (X = O). The skeletons of **1** – **3** occur in a number of drugs.



The imines **1** – **3** are converted to the α-hydroxynitrosamines **7** – **9** which formally result by electrophilic addition of HO-NO to imines **1** – **3** via the *N*-nitrosoiminium ions **4** – **6**.[2] One path for the decomposition of the α-hydroxynitrosamines **7** – **9** involves the retro-ene reaction leading to the δ-oxoalkyl diazotic acids **10** – **12**. The formation of **10** – **12** is expected to be the rate-limiting step since diazotic acids are known to decompose fast to aliphatic diazonium ions. The outlined reaction path was explored at the B3LYP/6-31G** level and in this presentation emphasis will be given to the conformations of the alcohols **7** – **9** and their retro-ene reactions to **10** – **12**.

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1 *DNA Damage and Cytotoxicity Caused by Nitric Oxide.* Tannenbaum, S. R.; Tamir, S.; Rojas-Walker, T. D.; Wishnok, J. S.; Chapter 10, in *Nitrosamines and Related N-Nitroso Compounds - Chemistry and Biochemistry.* Loeppky, R. N.; Michejda, C. L.; Eds., ACS Symposium Series 553, Washington, D. C.; **1994**, p. 120-135.

2 *An ab Initio Quantum-Mechanical Study of the Stability of Cyclic α-Acetoxy-N-nitrosamines.* Glaser, R. *J. Am. Chem. Soc.* **1999**, *121*, 5170-5175.