

2008 Undergraduate Research Description

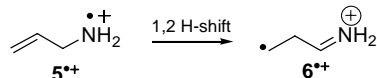
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Matrix ESR Studies of Radical Cations Related to Drug Chemistry

Radical cations are ionized molecules or “holes” formed as a result of electron transfer. These species are thought to be involved in a variety of organic reactions but their intermediacy is difficult to prove because they undergo reactions with incredibly short lifetimes under normal reaction conditions. However, matrix methods have recently been developed which allow us to generate these species and isolate them for periods long enough to observe them by ESR spectroscopy. In this technique, the organic molecule of interest is first dissolved in an inert freon matrix which is then frozen at liquid nitrogen temperature. This freon “solid solution” is then gamma irradiated, resulting in the one-electron oxidation of the organic solute. The interaction of the unpaired electron on the radical cation with its various protons (or other nuclei such as ^{13}C and ^{14}N with nuclear spin) results in a distinct hyperfine splitting pattern or fingerprint in the ESR spectrum. Chemical transformations of the initially generated radical cation (which take place by rearrangement or ion-molecule reaction) can thus be followed by corresponding changes in the ESR pattern. The student will learn how to interpret such spectra in order to identify these radical cation intermediates.

We are interested in the mechanism whereby substituted cyclopropylamines, allylamines, and propargylamines function as efficient inactivators of oxidation enzymes such as monoamine oxidase and cytochrome P-450. Essentially, it has been proposed that the key step leading to enzyme inactivation by these substrates is the conversion of the initially-formed aminium radical cation (a nitrogen-centered radical) to a carbon-centered radical which subsequently attacks the active site of the enzyme in a “suicide” action.. This rearrangement leads to the formation of a distonic species in which the spin (on carbon) and positive charge (on nitrogen) become separated. We have observed this radical cation rearrangement for the parent cyclopropylamine and allylamine molecules by ESR studies.² Kinetic studies in collaboration with a group at the University of Leipzig^{2,6} reveal that the allylamine radical cation $5^{+\bullet}$ rearranges to the distonic species $6^{+\bullet}$ (see below) with a half-life of 40 min at 77 K.



Interestingly, many of the drugs (tranylcypromine, selegiline, vigabatrin) that are used in the treatment of depression, Parkinson’s disease, and epilepsy do in fact contain a cyclopropyl, allyl, or other unsaturated group adjacent to the amine function that undergoes oxidation. Thus, these drug molecules are structured to undergo a very similar type of radical cation rearrangement in the brain to that described for the much simpler model amine-type molecules discussed in the previous paragraph. The pertinent literature will be surveyed for evidence of such rearrangements where the distonic radical cations are thought to be implicated as the key intermediates in the “suicide” inactivation of the enzyme (monoamine oxidases A & B).

Recent Journal Articles

1. M. Shiotani, A. Lund, S. Lunell, and F. Williams, “Structures of the Hexafluorocyclopropane, Octafluorocyclobutane, and Decafluorocyclopentane Radical Anions Probed by Experimental and Computational Studies of Anisotropic ESR Spectra,” *J. Phys. Chem. A* **2007**, *111*, 321-338. Published on Web 12/22/2006.
2. W. Knolle, I. Janovský, S. Naumov, and F. Williams, “EPR Studies of Amine Radical Cations, Part 2: “Thermal and Photoinduced Rearrangements of Propargyl and Allylamine Radical Cations in Low-Temperature Matrices,” *J. Phys. Chem. A* **2006**, *110*, 13816-13826. Published on Web 12/07/2006.
3. M. Shiotani, P. Persson, S. Lunell, A. Lund, and F. Williams, “Structures of Tetrafluorocyclopropene, Hexafluorocyclobutene, Octafluorocyclopentene, and Related Perfluoroalkene Radical Anions Revealed by Electron Spin Resonance Spectroscopic and Computational Studies,” *J. Phys. Chem. A* **2006**, *110*, 6307-6323. Published on Web 04/27/2006.
4. A. M. ElSohly, G. S. Tschumper, R. A. Crocombe, J. T. Wang and F. Williams, “Computational and ESR Studies of Electron Attachment to Decafluorocyclopentane, Octafluorocyclobutane, and Hexafluorocyclopropane: Electron Affinities of the Molecules and the Structures of their Stable Negative Ions as Determined from the ^{13}C and ^{19}F Hyperfine Coupling Constants,” *J. Am. Chem. Soc* **2005**, *127*, 10573-10583. Published on Web 07/08/2005.
5. F. Williams, “Re-evaluation of the Propagation Rate Constant in the Radiation-Induced Cationic Polymerization of Isobutylene in Solution,” *Macromolecules* **2005**, *38*, 206-209. Published on Web 12/08/2004.
6. I. Janovsky, W. Knolle, S. Naumov, and F. Williams, “EPR Studies of Amine Radical Cations, Part 1: Thermal and Photoinduced Rearrangements of n-Alkylamine Radical Cations to their Distonic Forms in Low-Temperature Freon Matrices,” *Chem. Eur. J.* **2004** *10*, 5524-5534. Published on Web 09/29/2004.