

Isomer-Specific Fragmentation of PAH-C8-Guanine and PAH-N7-Guanine Adducts: a Study of Mechanism by Theoretical Modeling

Daryl Giblin and Michael L. Gross

Department of Chemistry, Washington University, St. Louis, MO 63130

Introduction. Carcinogenesis by polycyclic-aromatic hydrocarbons (PAH) begins with metabolic activation followed by subsequent reaction with the bases of DNA. Our interest involves adducts formed by PAHs activated by one-electron oxidation. Such adducts have been isolated from *in vitro* and *in vivo* in studies of DNA damage. Fragmentations of the adduct precursor ions have been determined by tandem mass spectrometry¹. The relative abundances of the Ar-CN⁺ (or Ar-NC⁺) and Ar-H⁺ products serve to distinguish the C8- and N7-PAH-guanine isomers; the former is more abundant for the C8 isomer whereas the latter is for the N7 isomer. To provide an understanding of the mechanisms of the isomer-specific fragmentations is the goal of this ongoing investigation².

Methods. To elucidate mechanisms, we have employed theoretical calculations to find the minima and transition states on the associated potential energy (PE) surfaces of the C8- and N7-PAH-guanine adducts. Owing to the large size of the adducts, anthracene was chosen as surrogate PAH for modeling studies; it has a low ionization potential, similar to that of benzo[a]pyrene and dibenzo[a,l]pyrene, that allows formation of radical cation products from even-electron precursor cations, and has similar attachment site geometries and reactivities. The PE surfaces were extensively scanned by using the PM3 semi-empirical method. The results of the initial surveys of the PE surfaces were reported last year. For structural and energetic accuracy, we refined the calculations by using density-functional theory, ultimately reaching the level B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d,p). All minima and transition-states were characterized by vibrational frequency analyses, and thermal-energy corrections and relative reaction enthalpies were calculated.

Results and Discussion. The formation of Ar-H⁺ and Ar-CN⁺ from the C8-PAH-guanine [M + H]⁺ is endothermic by 64 and 79 (or 77) kcal/mol, respectively. The equivalent products (here presumably Ar-NC⁺) from the N7-PAH-guanine precursor ion are endothermic by 53 and 87 kcal/mol, respectively. The endothermicities are ~12 kcal/mol lower than those obtained earlier by PM3 and reported last year². Fragmentation entails additional energetic requirements to surmount transition state barriers, but internal energies >50 kcal/mol are sufficient to promote H⁺ migration about the precursor ions. The formation of Ar-CN⁺ (or Ar-NC⁺) from the adduct precursor ions is initiated by H⁺ migration to the C5 of guanine (and also to guanine C4 of the C8 isomer) followed by sequential bond cleavages rather than a single-step cycloreversion. (There is no reasonable transition state for the concerted cycloreversion reaction.) The formation of Ar-H⁺ from the precursor ions is initiated by H⁺ migration to C9 of the PAH. On the fragmentation trajectory of the N7 isomer some key, previously reported intermediates² that were located by PM3 are artifacts as determined by DFT calculations, offering a warning about PM3 use for gas-phase ion chemistry. One intermediate becomes a shoulder on the reaction trajectory as determined by DFT methods.

The proposed mechanisms for the production of ArCN⁺ or ArNC⁺ and ArH⁺ from the [M + H]⁺ of the C8 and N7 Anth-Gua isomers can rationalize the relative abundance distributions of these products. The rate-limiting steps in the formation of ArCN⁺ from Anth-C8-Gua requires ~10 kcal/mol less energy than the rate-limiting step for the formation of ArH⁺. Whereas for the Anth-N7-Gua isomer, the rate-limiting steps to ArNC⁺ and ArH⁺ favor the latter by >10 kcal/mol. Proposed mechanisms and relative heats of formation are given on the **Figure**.

Acknowledgments. This research project was supported by the NIH-supported Mass Spectrometry Research Resource at Washington University (Grant No. P41RR00954-25).

1. (a) Byun, J.; Gooden, J.; Ramanathan, R.; Li, K.-M.; Cavalieri, E. L.; Gross, M. L. *J. Am. Soc. Mass Spectrom.* **1997**, *8*, 977-986; (b) RamaKrishna, N. V. S.; Gao, F.; Padmavathi, N. S.; Cavalieri, E. L.; Rogan, E. G.; Cerny, R. L.; Gross, M. L. *Chem. Res. Toxicol.* **1992**, *5*, 293-302.
2. Giblin, D.; Gross, M. L. *Proceedings of the 48th ASMS Conference on Mass Spectrometry and Allied Topics*, **2000**, 732.

