

The Fragmentation of Purine-PAH Adducts, a Theoretical Study

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INTRODUCTION

The first critical event in the carcinogenesis of polycyclic-aromatic hydrocarbons (PAH) is the metabolic activation of these compounds which subsequently react with the bases of DNA. Such adducts have been isolated from *in vitro* and *in vivo* studies of DNA damage. These compounds have been studied by tandem mass spectrometry, and the outline of their fragmentation has been characterized. But, studies of the fundamentals that underpin these fragmentation reactions are few and cover most thoroughly the free bases.

METHODS

For structural and mechanistic determination, we have performed theoretical calculations on selected adducts to characterize their associated potential energy surfaces and connections to products. Due to the large size of the adducts, calculations were performed by using the PM3 semi-empirical method despite known deficiencies. To characterize more fully the initial precursor, fragment and key intermediate ion, we are using density functional theory calculations at the level of B3LYP/6-31G(d,p) for geometric optimization and energies.

RESULTS AND DISCUSSION

We are interested in the fragmentation pathways of adduct ions, $[M + H]^+$, generated from the reaction of the one-electron oxidation products of benzo[a]pyrene (BP) and dibenzo[a,l]pyrene (DBP) and the purine bases. To facilitate the calculations, we have chosen anthracene as a surrogate for both BP and DBP because it possesses the same geometry about the reactive site and also has an ionization potential below that of guanine or adenine. We have concentrated in the following fragmentations: (1) the generation of $Ar-H^{++}$ and $Ar-CN^{++}$ from the C8 and N7 substituted guanine adducts, (2) the loss of NH_3 from positional isomers of N-substituted adenine adducts, and (3) the formation of $Ar-NH_2^{++}$ from the N^6 -substituted adenine adduct.

The fragmentations are highly endothermic, requiring 60-100 kcal/mol. That energetic requirement is greater than that required to promote H migration about the ring systems. Furthermore, various sites of H attachment serve as entry points for rearrangement pathways that lead to products.

The generation of $Ar-CN^{++}$ or $Ar-NC^{++}$ from the C8- and N7-guanine adducts involve two-step processes rather than concerted cycloreversion reactions. Proposed mechanisms of formation $Ar-CN^{++}$ (or $Ar-NC^{++}$) and $Ar-H^{++}$ from these isomers are presented in the **Figure**. By these mechanisms, we can account for the predominance of $Ar-CN^{++}$ formation over $Ar-H^{++}$ by collision activation (CA) of the precursor ion of the C8 adduct, whereas CA of the N7-adduct precursor ion produces similar fragments with relative abundances reversed. In both cases, the predominant fragment has a more energetically favorable trajectory through connecting transition states to products.

The general loss of NH_3 from the isomeric adenine-adduct precursor ions and the exclusive formation of $Ar-NH_2^{++}$ from the N^6 -Ade-adduct precursor both proceed by proposed pathways analogous to those proposed for loss of NH_3 from protonated adenine. The $Ar-NH_2^{++}$ is an aryl-substituted NH_3 which carries the charge because of its lower ionization potential.

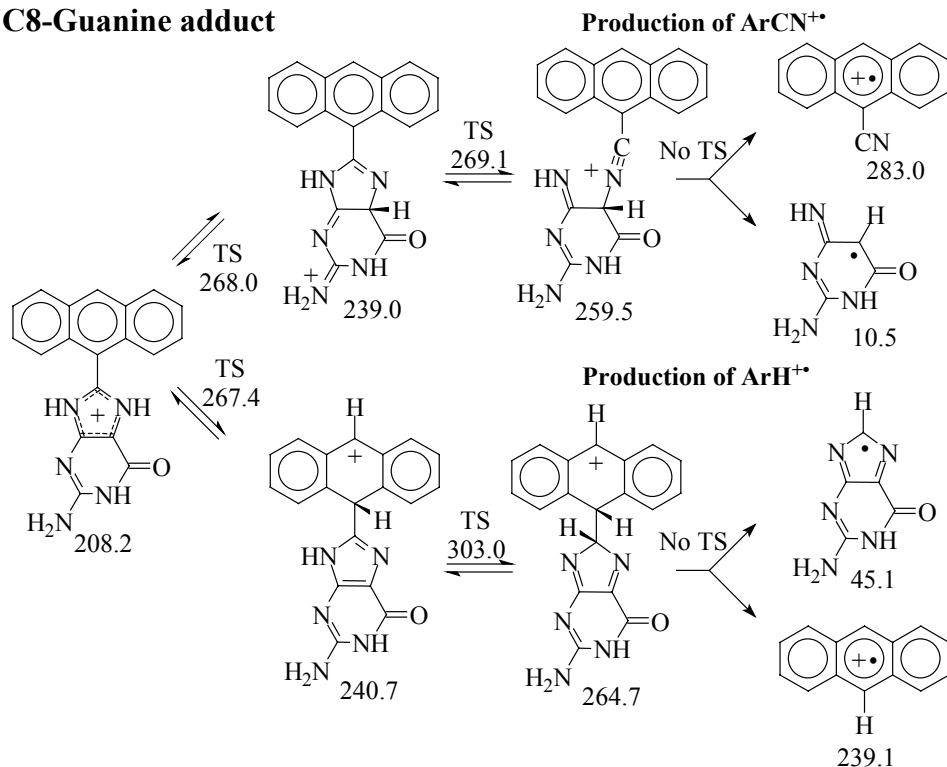
The enhanced loss of NH_3 from the precursor ion of the N7-Ade adduct is rationalized by a proposed second decomposition pathway for this isomer only. The specific geometry of this adduct allows cyclization between the C6 of the adenine and the C1 of the anthracene followed by elimination of NH_3 , a route more energetically favorable than the general mechanism for loss of NH_3 .

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Figure: Proposed fragmentation mechanisms for adduct $[M + H]^{+}$ ions from C9-anthracyl-C8- and C9-anthracyl-N7-guanine adducts. (Heats of Formation for stationary states and transition states (TS) are given in kcal/mol.)

C8-Guanine adduct



N7-Guanine adduct

