A Theoretical Study of Intramolecular Reaction Paths of α-hydroxynitrosamine in Gas Phase

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INTRODUCTION

Nitrosamines are generally considered potent carcinogens. The carcinogenic potential of nitrosamines such as N-nitrosodimethylamine (NDMA) is activated after their reaction with the OH group which is bound to the iron porphyrin cytochrome P450.[1] This reaction yields α-hydroxynitrosamine, which is then dissociated through release of carbonyl and OH^- to form the diazonium ion[2], as shown in Figure 1:

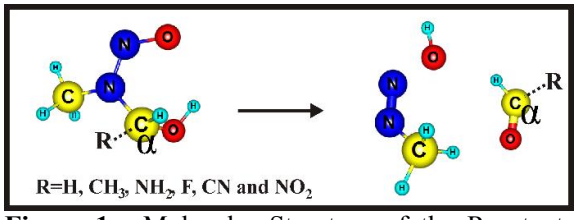

Figure 1. Molecular Structure of the Reactant Complex (RC) -Left- and Products Complex (PC) -Right- involved in the intramolecular hydrogen transfer reaction of the α-hydroxynitrosamine.

The aim of this work is to study the effect of the Cα substituents on the possible reaction pathways for the formation of the diazonium species of α-hydroxynitrosamine. Both kinetic and Thermodynamic aspects of four reaction pathways were investigated.

METHODS

The reaction pathways studied in this work involve R= H, CH_3, NH_2, F, CN and NO_2 (see Fig.1). The stationary points along each reaction pathway have been optimized at the B2PLYP/aug-cc-pVDZ level, followed by single-point calculations with the aug-cc-pVTZ basis set. IRC calculations were performed to ensure the correct connection between transition states and minima. Frequency calculations were performed to ensure the correct nature of each stationary point and provide the vibrational zero-point energies (ZPE). All calculations were performed with Gaussian 09 using its default criteria.

RESULTS AND DISCUSSION

According to potential energy profiles the barrier heights for the four reaction mechanisms are significantly dependent on the substituents. Among the four reaction pathways studied for R=H three of them yield products observed experimentally[3], while the remaining one yields products in agreement with the work of Silva.[4]

CONCLUSIONS

The calculations performed in this work comprise four distinct reaction mechanisms which yield diazonium ions from intramolecular hydrogen transfer reaction of the α-hydroxynitrosamine. These reaction mechanisms are significantly dependent on the type of substituent connected to the Cα atom. For R = H three of them are consistent with experiments.[3]

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