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Mechanism of the CH_3NH_2–HNO_2 reaction: *Ab initio* DFT/TST study

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ABSTRACT

The methyl amine-nitrous acid reaction in gas phase has been studied by *ab initio* MO and DFT methods at the B3LYP and MP2 levels using 6-31++G(d,p) basis set. Minima on the potential energy surface (PES) were characterized by absence of any imaginary frequency and the transition states by single imaginary frequencies. Intrinsic reaction coordinate method was used to find the minimum energy paths along which reactants and products are connected to the transition states. The reaction involves a number of steps: bimolecular decomposition of nitrous acid to form the ion-pair $O{=}N^{+}\ldots{}^{-}ONO$ (as revealed by NPA), is the first step and is theoretically found to be the rate determining step in compliance with the experimental findings. Subsequently, a proton shuttle mechanism operates resulting finally in the formation of methanol and diazomethane as substitution and elimination product, respectively; the former is identified as the major product on the basis of computed rate constants using the transition state theory. Cleavage of old bonds and formation of new bonds during the different steps have been monitored by the study of the electronic population arrangement and the calculated IR spectra of the species occurring at the minima of the PES. A stepwise mechanism of the title reaction is thus theoretically established.

1. Introduction

Elucidation of electronic structures and related chemical and spectroscopic properties of molecules, designing routes for synthesis and theoretical characterization of novel molecules of medicinal and biochemical importance and following reaction paths by *ab initio* quantum mechanical methods and density functional theory (DFT) [1–5] are topics of recent interest [6–15]. For such purposes newer functionals and methodologies are currently being developed [16–18]. Reaction mechanisms established by kinetic evidences can be verified through electronic structure calculations by such methods [19–21]. Such quantum mechanical calculations can be decisive when more than one mechanism seems to be possible from kinetic evidences. Interest in theoretical study of the mechanism of the title reaction stems from the fact that many nucleobases undergo deamination, i.e., spontaneous loss of their exocyclic amino groups [22] in the presence of HNO_2 to form a different base. Thus, nitrosative deamination converts cytosine, adenine, guanine and 5-methylcytosine to uracil, hypoxanthine, xanthine and thymine, respectively [23–26]. Very recently, a theoretical study of two different mechanisms for the spontaneous deamination of cytosine from the perspective of reaction force analysis has been carried out by Labet et al. [27]. Nitrous acid formed from organic precursors such as nitrosamines and from nitrite and nitrate salts is a potent reagent for deamination of the bases, which may lead to abnormal cell growth. On the basis of the diazo-chemistry of primary amines [28], it is generally assumed that the deamination of nucleobases and cross-link formation proceed through the diazonium ions [29,30] followed by S_N1 or S_N2 attack by water to form the NH_2/OH replacement product or by an amino group of a neighbouring nucleobase to form a cross-link. Experimental studies of the reaction between the amines and HNO_2 have been carried out extensively [31,32] and several possible mechanisms have been proposed. One belief is that the actual attacking species is N_2O_3 which acts as carrier of NO^+. Experimental evidence is that the reaction is of second order in HNO_2, and at sufficient acidities, the amine does not appear in the rate equation [33]. Experiments have also revealed that the HNO_2-primary amine reaction yields both primary alcohol (substitution product) and an alkene (elimination product) [34]. While numerous such simple reactions are known to mimic actual biochemical reactions occurring *in vivo* [35] many of them are yet to be studied theoretically. The objective of the present work is to carry out theoretical *ab initio* DFT studies on model reactions of nitrous acid with aliphatic amines which mimic the DNA/RNA bases of real biochemical system. The first step of such reactions is the bimolecular decomposition of HNO_2, which has been studied both experimentally [36] and theoretically by *ab initio* DFT method

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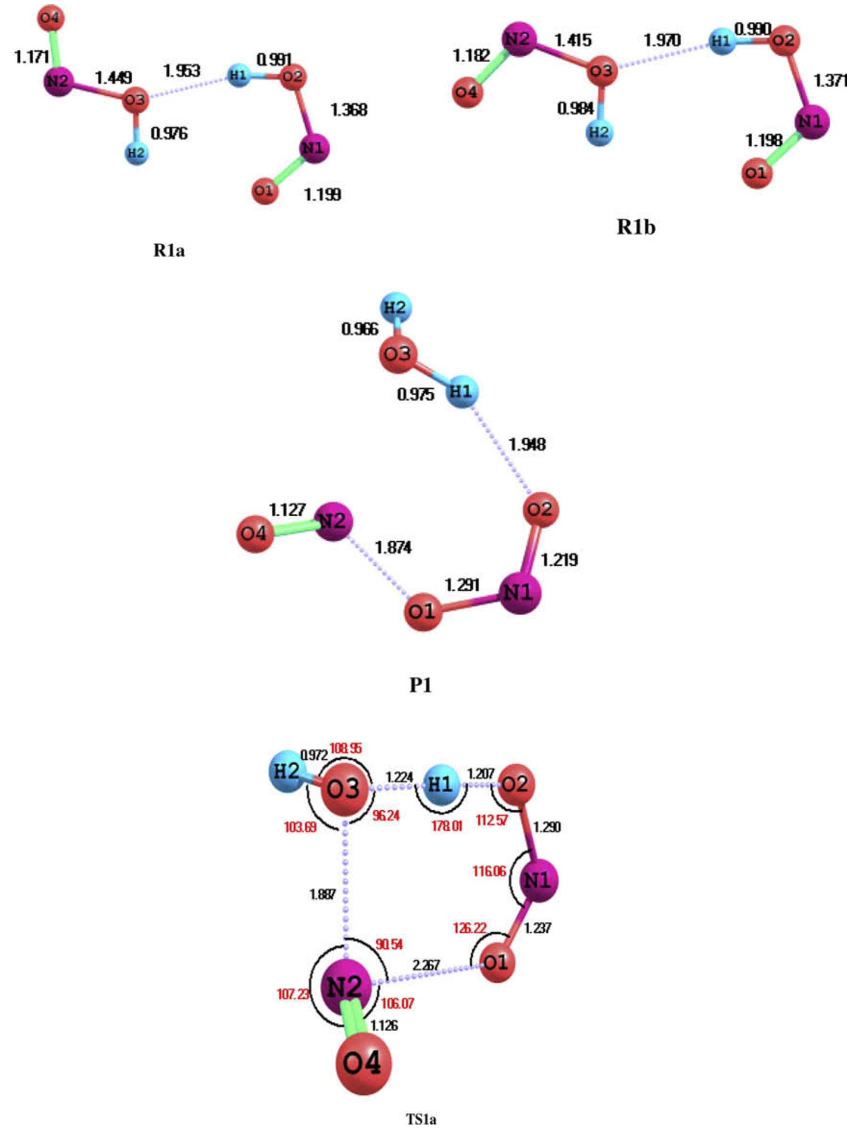

Fig. 1. Optimized geometries of the reactant and product complexes and transition states on the PES of the different steps involved in the nitrous acid-methyl amine reaction.

employing the transition state theory (TST) [37]. Reaction of the HNO_2 decomposition product N_2O_3 with NH_3 has also been studied both experimentally [38] and theoretically [39,40]. However, the formation of substitution product (alcohol) or other elimination product(s) as permissible by the structure of the amine via the formation of diazonium ion have not been considered in these works. In the present work we show that the methyl amine-HNO_2 reaction gives both diazomethane as the elimination product and methanol as substitution product through the formation of $CH_3N_2^+$ ion.

2. Computational methods

All computations were carried out using the Gaussian 03 Rev-D.01 suite of programmes [41] implemented on a Pentium computer. DFT calculations were performed by using a combination of the Becke's three parameter hybrid [42] exchange potential with the correlation functional of Lee et al. (B3LYP) [43]. The basis sets used were uniformly 6-31++G(d,p). The geometries of the reactants, products, intermediates and transition states (TS) were optimized and the harmonic vibrational frequencies, zero point energies (ZPE) and thermochemical quantities were calculated for finding the minimum energy path (MEP) by the intrinsic reaction coordinate (IRC) theory [19,20,44] at the DFT/B3LYP/6-31++G(d,p) level. The calculated transition states were confirmed to have one imaginary frequency. For more accurate estimation of energy of the stationary points along the potential energy surface, single point calculations were also performed at the MP2/6-31++G(d,p) level. All the energies quoted and discussed in the present paper include the ZPE correction. Cleavage of old bonds and formation of new bonds during the different steps have been monitored by studying the charges on relevant atoms calculated by natural population analysis (NPA) and also by analyzing the theoretically constructed IR spectra of the species occurring at the minima of the PES.

3. Results and discussion

The title reaction is believed [34] to involve a number of steps 1a–5, as listed below.

Step 1a: *cis*-HNO_2 + *trans*-$HNO_2 \rightarrow N_2O_3 + H_2O$
Step 1b: *cis*-HNO_2 + *cis*-$HNO_2 \rightarrow N_2O_3 + H_2O$
Step 2: $N_2O_3 + H_2O + CH_3NH_2 \rightarrow CH_3\text{–}NH\text{–}N{=}O + HNO_2 + H_2O$