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A quantum chemical insight to intermolecular hydrogen bonding interaction between cytosine and nitrosamine: Structural and energetic investigations

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ABSTRACT

Hydrogen bond interactions which are formed during complex formation between cytosine and nitrosamine have been fully investigated using B3LYP, B3PW91 and MP2 methods in conjunction with various basis sets including 6−311++G (d,p), 6−311++G (2d,2p), 6−311++G (df,pd) and AUG-cc-pVDZ. Three regions around the most stable conformer of cytosine in the gas phase with six possible double H-bonded interactions were considered.

Two intermolecular hydrogen bonds of type N_C−N-H_{NA} and O−H(N−H)$_C$−O_{NA} were found on the potential energy surface in a cyclic system with 8-member in CN1, CN3, CN5 and 7-member in CN2, CN4, CN6 systems.

Results of binding energy calculation at all applied methods reveal that the CN1 structure is the most stable one which is formed by interaction of nitrosamine with cytosine in S1 region. The BSSE-corrected binding energy for six complex system is ranging from −23.8 to −43.6 kJ/mol at MP2/6−311++G (df,pd) level and the stability order is as CN1 > CN2 > CN3 > CN4 > CN5 > CN6 in all studied levels of theories. The NBO results reveal that the charge transfer occurred from cytosine to nitrosamine in CN1, CN3, CN5 and CN6 whereas this matter in the case of CN2 and CN4 was reversed.

The relationship between BEs with red shift of H-bond involved bonds vibrational frequencies, charge transfer energies during complex formation and electron densities at H-bond BCPs were discussed. In addition activation energetic properties related to the proton transfer process between cytosine and nitrosamine have been calculated at MP2/6−311++G (df,pd) level.

AIM results imply that H-bond interactions are electrostatic with partially covalent characteristic in nature.

1. Introduction

Between long−range interactions, hydrogen bonding is so interesting. It's responsible for many important roles in chemical and biochemical systems [1]. In addition many of important inter and intra molecular interactions such as those lead to formation of DNA molecule which is the origin of life in double and triple helices are hydrogen bonds [2,3].

The Hydrogen bonding type in many of DNA molecules is as N−H···O and N−H···N. Because of theirs importance, they have been widely investigated. The results of investigations indicated that the nature of hydrogen bonding interactions is mainly electrostatic with some contribution of charge transfer and polarization [4–10].

Hydrogen bonding also stabilizes the structures of biological molecules such as proteins and nucleic acids. In addition activity of many of enzymes depends on the hydrogen bonding type interactions of substrates and enzymes active sites.

Hydrogen bond type interactions between bioactive molecules are very common. Therefor investigations including the effects of hydrogen bonds on the properties and activity of biologically active molecules such as cytosine are of great interest.

Cytosine is a pyrimidine type base and a constituent of nucleotides. It is also one of the important components of DNA and could be made complex with peptides or proteins [11].

One of the reasons for alteration of normal base pairing of nucleic acid bases is the formation of rare tautomer's of bases due

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to tatomerization which is generally the result of proton transfer reactions [12,13]. During tautomerization reactions one tautomer converts to the other which is slightly different in chemical and physical properties. Then the structure and functioning of nucleic acid bases maybe undergo some changes and lead to spontaneous mutations in the genetic code [14,15]. A lot of experimental and theoretical research works has been focused on hydrogen bond interactions [16–35].

Some noncanonical tautomeric isomers for cytosine due to proton transfer reactions are known which may cause some changes on neucleobase structures and then gene mutation [11]. Because of its great importance lots of research works including cytosine have been reported in the chemistry and biology domain [36–39]. N-Nitrosamines are categorized as potent carcinogens and mutagen compounds which could be induced tumors in human's body as well as animals [40–42]. They could be formed readily from nitrites and theirs derivatives [40,43]. They also occur in various foods, beverages, vegetable oil, cheese, drinking water and etc. as contaminants [44–48].

Carcinogenic effects of nitrosamines are well known and to be proven that they need to activate metabolically to exert their carcinogenic effect and react with DNA to cause mutation and cancer [49]. Therefore the potent role of N-nitrosamines interactions with RNA, DNA and proteins in carcinogenesis is clear.

NH_2NO (NA) contains N═O group as well as NH_2 therefor it can acts as proton acceptor and proton donor at the same time to make binary H-bonded stable complex with different compound. Due to the abundance of nitrosamines in human dietary the interaction of theirs with cytosine as a part of DNA is of great interest. In addition studied binary complex molecules during this work may be used as a model system to better understanding of such similar interactions in biomolecules.

In the current work the main characteristics of the cyclic double hydrogen bonded complex structures which are formed on different H-bond-sites of the both nitrosamine and cytosine were investigated.

In continue natural bond orbital (NBO) [50] and Bader's quantum theory of atoms in molecules (QTAIM) [51–53] were used for analyzing of some geometrical and energetic features of above mentioned systems.

2. Computational details

The geometric optimization of the free nitrosamine and cytosine and the nitrosamine–cytosine complexes have been performed with the help of density functional theory methods (B3LYP and B3PW91) and second-order Moller–Plesset perturbation theory (MP2) at various basis sets (6–311++G (d,p), 6–311++G (2d,2p), 6–311++G (df,pd) and AUG-cc- pVDZ).

It is well understood that the considering of polarization and diffuse functions of basis sets are necessary for getting reliable data about hydrogen bound involved systems. Therefore various combinations of basis sets including both polarized and diffused functions were taking into account.

The harmonic frequencies have been calculated at the same levels of theory to characterize stationary points and calculation of zero-point vibrational energy (ZPVE).

The binding energy of various interacted systems such as our studied hydrogen bonded nitrosamine–cytosine complexes could be calculated as the energy difference of the complex with free monomers. Calculation of interaction energies are accompanied by the basis set superposition error (BSSE) correction according to the counterpoise procedure of Boys and Bernardi [54].

All calculations were performed using the GAMESS quantum chemistry package [55]. Topological properties were calculated at MP2/6–311++G (df,pd) level of theory by the AIM2000 program package [56]. The natural bond orbital analysis was carried out on the MP2/6–311++G (df,pd) wave function using version 3.1 of NBO package [57].

"The three lowest-energy tautomers of cytosine, two of which may exist in rotamer pairs, are shown in Fig. 1. There is general agreement that in solid state as well as in aqueous solutions only the canonical oxo form (1) is present. In the vapor state, however, all spectroscopic and quantum chemistry studies prove that the hydroxy tautomer dominates. For the latter, very often only one rotamer (2b) was taken into consideration, although its pair 2a is only 0.7–0.8 kcal mol^{-1} higher in energy. Isomer 3b is at ΔE° ~3.0 kcal mol^{-1} relative to 2b and will be omitted [58]."

The aim of the present study work is twofold: first, to find possible complex structures formed due to the interaction between nitrosamine and cytosine and second, the investigation of the characteristics of H-bond interactions between nitrosamine and cytosine.

All of the upcoming calculations and discussions will be carried out in gas phase there for in continue only tautomer 2b of cytosine is taking into account and all of the reported data during this paper relates to the structures including the tautomer 2b as the only candidate of cytosine.

3. Results and discussion

3.1. Geometries

There are three suitable regions around Cytosine (S1–S3) where NA can be placed in these sites to interact with it. With considering that cytosine can act as both proton acceptor and proton donor simultaneously the six cyclic double H-bonded complexes could be obtained on the potential energy surface which were named as CN1– CN6.

In complex structures of CN1, CN3 and CN5 the oxygen atom of NA involved in the interaction between cytosine and NA. Whereas in CN2, CN4 and CN6 the nitrogen atom acts as proton acceptor instead of oxygen atom. In all structures NH_2 of NA acts as proton donor. The CN1, CN3 and CN5 structures are 8-membered (8-mem) while the CN2, CN4 and CN6 are 7-membered (7-mem).

The fully optimized geometries of the equilibrium and transition state structures for all of the six nitrosamine–cytosine complexes and free monomers are shown in Fig. 2. The geometry parameters

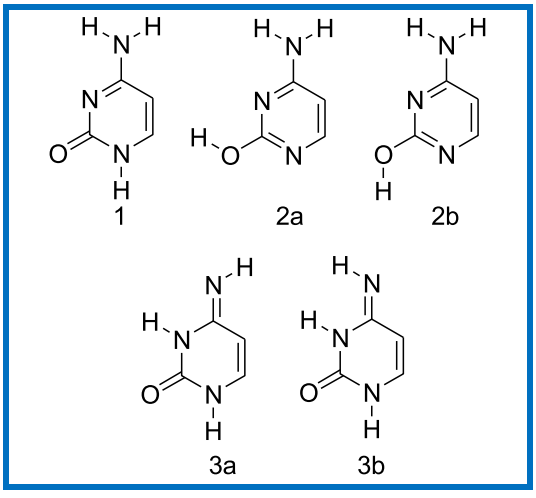

Fig. 1. The three most stable tautomers of cytosine: oxo (-amino) (1), hydroxy (-amino) (2) and (oxo-)imino (3). Both rotamers of 2 and 3 are shown.