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Metal counterion modulated single proton transfer process in guanine base

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ABSTRACT

The influence of metal cations (M^{n+} = Na^+, K^+, Mg^{2+}, Ca^{2+}, Zn^{2+}) on the single proton transfer process in guanine base has been studied at the MP2/6-31G* and B3LYP/6-311++G** levels of theory. Two main basic binding sites, N_3 and N_7 of guanine, are considered for M^{n+} coordination. It is observed that the tautomerism behavior of guanine, induced by intramolecular single proton transfer, can be modulated by surrounding metal counterions. Calculated results show that the single proton transfer process in guanine is favored and even becomes thermodynamically spontaneous due to the presence of M^{n+} interacting at the N_3 position of guanine. On the contrary, if M^{n+} coordinated to N_7 of guanine, the single proton transfer process will become unfavorable than that in the neutral system. Moreover, the effects are more pronounced for the divalent cations than for the monovalent ones. All of them can be understood from the electrostatic and oxidative effects of metal cations on the guanine base obtained from further natural bond orbital (NBO) analyses.

1. Introduction

Chemical reactions that involve single- or multiple-proton transfers are of permanent interest to scientists because they play a significant role in the most vital chemical and biological processes [1,2]. As suggested by Watson and Crick in their famous hypothesis, the fidelity of DNA replication should be directly coupled with the proton transfer ability of the DNA bases [3–7]. In DNA synthesis process, forming the "rare" tautomeric forms, products of intra- and/or intermolecular proton transfer, will increase the probability of mispairing of purines and pyrimidines and hence may lead to an increase in the chance of point spontaneous mutations [7–11]. Moreover, Gervasio and his coworkers observed that double proton transfer in guanine–cytosine base pair was able to trigger the charge transfer in DNA [12]. That is why proton transfer phenomenon occupies a special place in the studies of structures and properties of DNA bases and many experimental and theoretical investigations have been devoted to understanding the mechanism of single- and double-proton-transfer reactions in DNA bases [13–19].

Leszczynski and his co-workers demonstrated that proton transfer in adenine–thymine or guanine–cytosine base pairs is governed by their structural characteristics, thermodynamic and kinetic factors [10]. It is also proved that the chemical environment of DNA (e.g., water molecules and various specific counterion configurations) could also induce a considerable influence on the proton transfer reaction [19–21]. Actually, the natural base pairs perturbed by surrounding factors such as metal ion coupling may represent a general case in which DNA exhibits versatility in their functional processes.

Metal counterions, playing an important role in neutralizing the negatively charged backbone phosphate groups, have a pronounced effect on mutation in DNA. As reported by Noguera and his coworkers, the intramolecular single proton transfer reaction in guanine–cytosine base pair turns from thermodynamically unfeasible to thermodynamically favorable when M^{n+} (M = Cu^+, Ca^{2+}, Cu^{2+}) interact with N_7 of guanine [20]. Important effects of metal cation ($Cu^{+/2+}$) coordination on the intermolecular proton transfer processes in adenine–thymine base pair has also been reported [21]. Moreover, metal cation effects are more pronounced for the divalent cations than for the monovalent ones.

Metal counterion binding effects on the stabilization of isolated DNA bases have also been studied theoretically by previous workers [22,23]. However, little is known about the metal counterions binding effect on the single proton transfer process in an isolate DNA base though such single intramolecular proton transfer plays an important role during the step of catalytic incorporation of new nucleotides into the growing DNA stand when a "rare" form of a nucleic acid base forms a pair with an incorrect base [10].

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It is known that guanine is the only nucleic acid base of biological significance for which high concentrations of the "rare" tautomer have been observed [24,25]. Among the possible tautomers of guanine, two of the lowest energy forms [11,26] were chosen for the present study. According to the scheme shown in Fig. 1, these two lowest energy forms related by the oxo-hydroxo equilibrium can be taumerized by the intramolecular single proton transfer process. The main goal of this paper is to theoretically analyze the influence of metal counterion coordination on such single intramolecular proton transfer reactions in guanine base.

A series of most stable natural or M^{n+}-bound guanine base (denoted by M^{n+}—G, where $M^{n+} = Na^+$, K^+, Mg^{2+}, Ca^{2+}, Zn^{2+}) were considered here. It is well known that the N_7 and N_3 positions of guanine are preferred binding sites for metal counterions [21,27]. Calculated results show that different binding sites will make different effect on the tautomerism behavior in guanine (G) base.

2. Computational details

All local minimum structures and the transition state structures discussed here were fully gradient optimized without symmetry restrictions (C_1 symmetry was assumed) employing the density functional theory with Becke's three-parameter (B3) exchange functional [28] along with the Lee–Yang–Parr (LYP) nonlocal correlation functional [29,30] (B3LYP) and the ab initio approach at the second-order Møller-Plesset level (MP2) [31–35] level. The 6-311++G** and 6-31G* basis sets were used at B3LYP and MP2 levels, respectively. Harmonic vibrational frequency analyses were made for all the stationary points using the same methods to ascertain the nature of the optimized structures. Moreover, the validity of these computational methods used here were confirmed by the calculated results for the single proton transfer process from the nitrogen to oxygen atom in formamide after comparison with more accurate results from the CCSD(T) method, see Supporting information.

The binding energy (E_b) between metal cation and guanine base of the M^{n+}—G system was determined as

$$E_b = E(M^{n+} - G) - [(E(G) + E(M^{n+}))$$

where $E(M^{n+}$—G), E(G) and $E(M^{n+})$ mean the minimum energies of the metal counterions coordinated guanine base system and corresponding isolated monomers for simplicity. All of the energies discussed above were corrected by the zero-point vibrational energy (ZPVE) and the basis set superposition error (BSSE) corrections using the supermolecule method, where the BSSEs were evaluated using the Boys–Bernardi counter-poise technique [36]. With this definition, more positive E_b values imply more stable configurations of the M^{n+}—G systems.

The natural bond orbital (NBO) analysis [37,38] used for monitoring the sp*n* hybrid character of the sigma bonding (σ) was also performed using the DFT method with the B3LYP functional and 6-311+G* basis set. Corresponding charges from a natural population analysis (NPA) were used to evaluate the charge distribution; in particular, we used the NPA charges to examine the degree of charge transfer between the guanine base and the metal counterions.

All calculations reported here were carried out using the Gaussian 09 software suite [39].

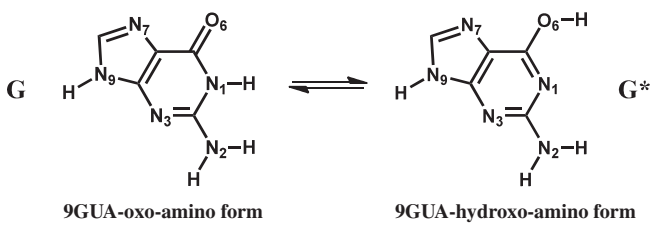

Fig. 1. Single intramolecular proton transfer in guanine base.

3. Results and discussions

As shown in Fig. 1, the intramolecular single proton transfer (SPT) process could lead to the tautomerism of guanine base from canonical 9GUA-oxo-amino form (G) to a "rare" 9GUA-hydroxo-amino form (G*). There is a general consensus that N_7 and N_3 of guanine base are preferred binding sites for metal counterion coordination. Additional stabilization is achieved in these positions via the interaction with O_6 or N_2 site, in such a way that calculations for metal counterions interacting with guanine show (N_7, O_6) or (N_3, N_2)-bidentate coordination mode. Isolate or metal ions coordinated G and *G bases as well as their corresponding transition states are displayed in Fig. 2.

3.1. Geometrical parameters

Geometrical parameters of guanine base may change substantially upon tautomerism or coordination with metal counterions (M^{n+}). So, an analysis of geometry changes with the SPT process in isolated or M^{n+} coordinated guanine base (viz. C=O_6, C—N_1 and N_1—H/O_6—H bonds) is crucial for understanding the influence come from metal counterions.

Optimized geometrical parameters related to the intramolecular proton transition process are collected in Tables 1 and 2. It is shown that the carbonyl C=O_6 is lengthened for about 0.121 and 0.126 Å, the C—N_1 bond is shortened for about 0.103 and 0.113 Å by SPT at MP2/6-31G* and B3LYP/6-311G* levels. Our results are in good agreement with previous theoretical results for guanine tautomerism process reported by Gorb and Leszczynski [11], which are also collected in Tables 1 and 2 for comparison. The variations of the bond distance can be reflected by the sp*n* hybridization [40], that is, the bond is weakened and elongated along with the increase of the *p*-character of the σ orbital. As shown in Tables 4 and 5, the sp^n hybridization of the orbital localized at C is 1.90 in G and 2.79 in G*. The sp^n hybridization of the orbital localized at O6 increases from 1.46 to 1.88 upon tautomerism. As a result, *p*-character is increased and *s*-character is decreased in the (C—O_6) σ orbital. Differently, the s-character of (C—N_1) σ orbital increases upon tautomerism because the sp^n character of σ orbital localized at C decreases. As a result, the C—N_1 bond in G is longer than that in G* base. Same changes for the C=O_6 and C—N_1 bonds of metal counterion coordinated G bases upon intramolecular SPT process are observed.

The C—O_6 and C—N_1 bonds of G and G* bases also change substantially upon coordination with metal counterions. Both optimization results obtained at the MP2/6-31G* and B3LYP/6-311G** levels indicate that the carbonyl C=O_6 bond is shortened and the C—N_1 bond is lengthened by Na^+ coordination at (O_6, N_7) site of guanine. A different situation is found for the geometry changes in Na^+ coordinated guanine at (N_2, N_3) site. The carbonyl C=O_6 bond is lengthened and the C—N_1 bond is shortened by Na^+ binding at (N_2, N_3) site of G. The influence of Na^+ coordination on the geometrical parameters of G* is similar. Namely, the C—O_6 bond is strengthened and C=N_1 bond is weakened by Na^+ counterion coordination at (O_6, N_7) site of G* and opposite changes is observed if Na^+ is coordinated at (N_2, N_3) site of G* base.

The N_1—H bond in G and the O_6—H bond in G* are weakened and elongated by metal counterion coordination. All of these changes owing to the complexion with metal counterions can be confirmed by the sp^n hybridization results obtained from NBO