First-principles study of interaction of serine with nucleobases of DNA and RNA

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Abstract The nature of interaction between serine—a vital molecule for cancer cell proliferation and nucleic acid bases—adenine (A), guanine (G), cytosine (C), thymine (T), and uracil (U) is investigated within the framework of Møller–Plesset perturbation theory (MP2) and density functional theory (DFT). To quantify the interaction strength between serine and nucleobases, the corresponding binding energies were computed, showing energetic ordering such that $G > C > T > A > U$. This shows that the interaction energy of serine with guanine is the highest, while with uracil it is the lowest. The amount of charge transferred is the lowest in case of the serine-guanine complex and highest in case of the serine-uracil complex. The results show the serine-guanine complex to be more stable and to have a salt bridge structure involving the $-COOH$ group. Theoretical analysis based on MP2 and DFT shows that the interaction between the serine and nucleobases is mainly determined by hydrogen bonding.

Keywords Serine · Cancer cell proliferation · Nucleobase · Serine-nucleobase complex

1 Introduction

Cancer is one of the major causes of mortality in the world. It is known to progress using several complex survival mechanisms after development via a multistep carcinogenesis processes in the body. The cell metabolic alternation is accompanied by genetic changes that are responsible for abnormal proliferation, growth, invasion, and survival [1–5]. The study of the metabolic processes associated with cancer has emerged as an important area of research.

It has been known that cancer cells selectively consume exogenous serine and convert it into intracellular glycine and one carbon unit for building nucleotides [6]. Serine and glycine, which are biosynthetically linked, provide precursors for protein synthesis and contribute to anabolic pathways required for the production of glutathione, phospholipids, nucleotides, and

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other metabolites [7–9]. Serine, a polar amino acid, is not essential to the human diet, since it is synthesized in the body from other metabolites, including glycine. This amino acid is essential for the proper functioning of the brain and the central nervous system.

Protein–protein interaction network analysis has been widely used in the investigation of the mechanism of diseases, especially cancer. It also plays an important role in signal transduction, molecule transportation, and DNA replication. Recently, Vousden et al. have shown that in nucleotide synthesis and cancer cell proliferation, exogenous glycine cannot be substituted for serine[6]. Note that adenine (A), cytosine (C), guanine (G), thymine (T), and uracil (U) nucleobases are the building blocks of the genetic macromolecules (DNA/RNA). A prerequisite step to understand cancer pathogenesis and targeted antimetabolic therapy will therefore involve a detailed study of atomic-level interaction of serine with nucleobases of DNA and RNA. This information is crucial to the biological function of cancer proteins in cellular systems. To this end, here we report the results of calculations based on density functional theory and Møller–Plesset perturbation theory.

2 Computational methods

Many-body perturbation theory is an appropriate choice for calculating the interaction energies of weakly bonded system because it satisfactorily treats the long-range forces. In this paper, we employ the second-order Møller–Plesset perturbation theory (MP2) and density functional theory (DFT) for electronic structure calculations. The 6-31G (d,p) basis set was chosen for the atoms considered. In DFT calculations, we used Becke’s three-parameter hybrid method combined with the Lee, Yang, and Parr correction (B3LYP) functional. All calculations were performed with the GAMESS [10] package. No constraints were applied during the geometry optimization and the calculations were considered to be converged when the density change between two consecutive SCF (*self-consistent field*) cycles was less than 10^{-5} . The graphical package Gchemical was used to draw the molecules and Macmolplt was used to visualize the results.

3 Results

To check the validity of the modeling methods in our computational approach, the ground-state configurations of isolated serine and nucleobase molecules were determined. The calculated bond lengths and bond angles are in good agreement with previous results [11–14], justifying our choice of the modeling methods.

The binding energy can be considered as a measure of interaction strength between serine and nucleobase molecules. It is defined as the difference in total energy of the equilibrium geometry of the complex and the isolated constituent molecules. Table 1 lists the calculated binding energies for each molecular complex consisting of serine and nucleobase. The calculated binding energies from B3LYP/6-31G(d,p) are 0.84, 0.69, 0.63, 0.52, and 0.23 eV for serine–G, serine–C, serine–T, serine–A, and serine–U complexes, respectively. These values are 0.86, 0.76, 0.74, 0.58, and 0.27 eV for serine–G, serine–C, serine–T, serine–A, and serine–U complexes, respectively, with the MP2/6-31G(d,p) theory. It therefore appears that strength of the serine interaction with the nucleobase molecule follows the order $G > C > T > A > U$ in both the MP2 and DFT calculations. Interestingly, a metallic carbon nanotube interacting with

Table 1 Parameters obtained for the serine-nucleobases complexes

Molecule/ complex	B3LYP with 6-31G(d,p) basis set			MP2 with 6-31G(d,p) basis set		
	Binding energy (eV)	Dipole moment (D)	HOMO–LUMO gap (Hartree)	Binding energy (eV)	Dipole moment (D)	HOMO–LUMO gap (Hartree)
Serine		2.00			2.04	
Serine-guanine	0.8436	5.45	0.193	0.8672	6.16	0.432
Serine-cytosine	0.6999	5.02	0.198	0.7652	6.15	0.447
Serine-thymine	0.6319	3.34	0.193	0.7436	4.04	0.444
Serine-adenine	0.5250	1.00	0.198	0.5855	2.71	0.427
Serine-uracil	0.2371	5.63	0.161	0.2770	4.145	0.460

nucleobase molecules has the following order $G > A > T > C > U$ [13], and silicon nanowires follow $G > A \sim C \sim T \sim U$ [14]. Overall, guanine shows a higher interaction strength compared to the other nucleobase molecules.

We now perform Mulliken population analysis of the equilibrium configuration of the serine-guanine complex and show the results in Fig. 1. We find that C(3), C(18), and C(19) atoms acquire a positive charge due to their bonding with highly electronegative atoms. The N(20) and N(25) atoms get a negative charge. Following their electronegativity, all the oxygen atoms are the second most negative charge holders while nitrogen atoms remain most negative. It is clear that all the hydrogen atoms follow the electronegativity of the adjacent atoms and donate their charge.

To calculate the intermolecular charge transfer, we compare the charge on a molecule before and after the formation of the complex. In the serine-guanine complex, DFT calculations show that a negligible charge of 0.005 e is transferred from serine to guanine while in the case of the serine-uracil complex, serine acquires a charge of 0.048 e from uracil. In MP2 calculations, these values are equal to 0.0149 and 0.0184 e, respectively. The amount of charge transferred is the lowest in the case of the serine-guanine complex and highest in the case of the serine-uracil complex. These results indicate that charge transfer is not the sole cause behind the interaction strength in the serine-nucleobase complexes. Furthermore, the calculated dipole moment of G, C, T, and A is found to decrease while the dipole moment of uracil is found to increase upon forming the complex with serine.

In Fig. 1, hydrogen bonding is represented by dotted lines. In the serine-guanine molecular complex, we find two hydrogen bonds at 1.67 and 1.86 Å formed between O(24)–H(14) and O(4)–H(28) atoms, respectively. A larger binding energy of the serine-guanine complex, therefore, appears to be due to these hydrogen bonds. This is not the case of the serine-uracil complex where the minimum distance between the molecules is 2.14 Å. The results therefore suggest that the interaction between the nucleobases and the serine is mainly due to the presence of hydrogen bonds. No proton transfer occurred in the molecular complexes. The structural modification induced by the interaction is localized within the entire complex. The MP2 calculations did not show any hydrogen bonding between serine and guanine.

Fig. 1 Ground-state configurations of nucleobases and the serine complex calculated using B3LYP/6-31G (d,p). Atoms in *grey* are carbon, in *white* are hydrogen, in *red* are oxygen, and in *blue* are nitrogen

Tables 2 and 3 list the bond lengths of the equilibrated complex and isolated molecules. First, we notice that structural modifications in the complex depend on the strength of the interaction between serine and nucleobase molecules. In the case of the serine–guanine complex, C1–C2 and C2–C3 bonds of serine and bonds in the ring of guanine change considerably. On the other hand, the respective changes in the bond lengths of the serine–uracil complex are negligible. Following the nomenclature based on protein chemistry, the interaction of serine and guanine can be classified as a salt bridge structure due to involvement of the -COOH group of serine.

Figure 2 shows HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) of the molecular complexes. In chemical reactivity, kinetic stability, and optical polarizability of any molecule, these molecular orbitals play a significant role. HOMO, which can be thought of outermost orbital containing electrons, tends to act as an electron donor. On the other hand, LUMO can be thought of as the innermost orbital containing a free orbital which could accept an electron. In the serine–guanine and serine–adenine complexes, HOMO and LUMO are located on the guanine and adenine molecules, respectively, while in the case of the serine–uracil complex, HOMO is localized on serine and LUMO is on uracil. For the serine–thymine complex, location of HOMO is mainly on thymine while LUMO is localized over the entire molecular complex. In case of the serine–cytosine complex, HOMO is partially located on serine and LUMO is completely on cytosine. Note that neither decreasing nor increasing trend is seen in the HOMO–LUMO gaps of the serine–nucleobases complexes.

Table 2 Calculated bond distances (Å) for the serine-guanine complex using B3LYP/6-31G(d,p)

Pair	Bond distance (actual)	Bond distance (in complex)	Pair	Bond distance (actual)	Bond distance (in complex)
H11-N7	1.018	1.018	N22-H27	1.009	1.009
H12-N7	1.017	1.016	N22-C15	1.385	1.387
N7-C2	1.459	1.460	C15-N23	1.308	1.307
C2-H13	1.098	1.099	N23-C16	1.382	1.382
C1-C2	1.550	1.544	C16-C17	1.396	1.401
C1-H9	1.095	1.095	C17-N22	1.370	1.370
C1-H10	1.103	1.101	C17-N21	1.359	1.353
C1-O6	1.416	1.427	N21-C19	1.313	1.318
O6-H8	0.967	0.972	C19-N25	1.377	1.367
C2-C3	1.521	1.533	C19-N20	1.371	1.373
C3-O4	1.212	1.238	N20-H28	1.013	1.023
C3-O5	1.349	1.311	N20-C18	1.440	1.413
O5-H14	0.973	1.012	C18-O24	1.218	1.241
C15-H26	1.082	1.082	C18-C16	1.441	1.430

Finally, the functional groups -COOH and -NH₂ are identified as the main reactive sites for serine (Fig. 2). In the equilibrium configuration, these two functional groups are separated by 108°. The calculated HOMO–LUMO gap and dipole moment are 6.63 eV and 2 Debye (D), respectively. Following Table 1, the salt bridge structure involving the -COOH group is energetically preferred to other interacting sites of the molecule. The calculated distance between serine and the nucleobases in the equilibrated configuration of the complexes reflects the predicted order of the interaction strengths.

Table 3 Calculated bond distances (Å) for the serine-uracil complex using B3LYP/6-31G(d,p)

Pair	Bond distance (actual)	Bond distance (in complex)	Pair	Bond distance (actual)	Bond distance (in complex)
C1-C2	1.461	1.456	N19-H23	1.017	1.018
C2-C3	1.350	1.351	N19-C14	1.459	1.460
C3-N6	1.376	1.374	C14-H22	1.098	1.098
N6-C4	1.395	1.395	C14-C13	1.550	1.550
C4-N5	1.385	1.388	C14-C15	1.521	1.520
N5-H11	1.013	1.013	C15-O16	1.212	1.212
C4-O7	1.217	1.215	C15-O19	1.349	1.352
C1-O8	1.220	1.226	O19-H25	0.973	0.973
C2-H9	1.081	1.081	C13-H21	1.103	1.100
C3-H10	1.085	1.085	C13-H20	1.095	1.095
N6-H12	1.010	1.010	C13-O18	1.416	1.421
N19-H24	1.018	1.020	O18-H26	0.967	0.967

Fig. 2 HOMO and LUMO representations of the nucleobases-serine complex calculated using B3LYP/6-31G(d,p). Red and blue lobes represent the positive and negative phases of the orbital, respectively

4 Conclusions

The calculated binding energies of the nucleobases with serine have the following energetic order: $G > C > T > A > U$. This shows that the interaction of serine with guanine is the highest, while with uracil it is the lowest. The results show that the interaction between the serine and nucleobases depends strongly on the formation of hydrogen bonds.

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