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DFT Study on the Carcinogenicity of some Common Polycyclic Aromatic Hydrocarbons (PAH)

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Quantum mechanical study on the interaction between carcinogens and DNA nucleobase is an exciting and significant aspect of cancer research. Common aromatic carcinogens like; β-napthylamine, α-benzopyrone, phthalazine, quinoline, α-naphthol and β-naphthol; comfortably interact with DNA nucleobases (*i.e.*, A, T, G, C, AT and GC) and it happens due to the effective π-π stacking interactions. In general, such type of interaction occurs through intercalation mechanism which takes place via π-stacking and results in very strong interaction with DNA nucleobases. In our case, all the carcinogen-DNA base pair stacked models have been investigated using density functional theory (DFT) method; as it theoretically helps to predict the proper molecular interaction and selectivity of carcinogens with DNA base pairs. Herein, computational calculations have been carried out to analyse the carcinogenicity of some common polycyclic aromatic hydrocarbons (PAH); and the study reveals that β-naphthylamine (BNA) is highly GC-specific than that of other aromatic carcinogens. Hence, BNA shows higher carcinogenic or toxic effect on the DNA nucleobase than other selected carcinogens. On the other hand, carcinogens like quinoline (QUN) and phthalazine (PHZ) results in the least carcinogenic effect on AT and GC base pairs of DNA nucleobases.

Keywords: Carcinogens, Nucleobase, DFT, PAH, AT, GC, *etc.*

INTRODUCTION

Most chemical carcinogens usually do not participate in any biochemical processes; but, they still continue to follow some competitive metabolic activation and detoxication activities. Such processes lead to a variation among individuals' chances of developing cancer, which could reflect gene-environment interactions; this concept of inherited traits alters the effects of exposure to chemical carcinogens and it takes place in several stages that result in different complex chemical reactions in the environment or in our everyday lifestyle and diet [1-2]. In multistage carcinogenesis, the primary genetic change caused by the carcinogenic-nucleoside DNA interaction is known as tumor initiation [3-4]. The main tool used in the experimental long-term chemical carcinogenesis bioassay for early detection of carcinogens; however, the negative side of the standard bioassay is that it is lengthy and expensive which also requires the sacrifice of many animals [5-8]. For this reason, chemical carcinogenicity has undergone several attempts to develop alternative predictive models, which is ranging from short-term bioassays (*e.g.*, mutagenic assays) to theoretical and computational models [9-12].

Therefore, investigating the mechanism of chemical carcinogenesis is an important aspect for the development of efficient preventive strategies and measures [13-14]. From the mechanical point of view, there are mainly two types of carcinogens, *i.e.*, genotoxic and non-genotoxic or epigenetic. Genotoxic carcinogens are DNA-reactive carcinogens,

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chemicals that directly interact with DNA base pairs either act as their parent substances or as reactive metabolites. In contrast, non-genotoxic carcinogens don't result in immediate DNA damage; instead, they work through a secondary process [15]. A complete carcinogenic process may be carried out by powerful genotoxic carcinogens and their epigenetic actions; which may interact synergistically. On the other hand, non-genotoxic carcinogens may indirectly induce DNA damage that promotes mutagenesis by fixing pro-mutagenic DNA damage that is present but not yet repaired or increasing error-prone DNA repair; some may even be reactive to DNA by a minor mechanism [16-17]. However, primarily genotoxic carcinogens such as DNA-reactive carcinogens, have the most unique property of being electrophiles or activating into electrophile-reactive intermediates; but, non-genotoxic carcinogens act through a variety of different specific mechanisms without a clear unified concept [18-19]. The mechanism of genotoxicity and carcinogenicity has been the subject of much research. In contrast, non-genotoxic carcinogenicity is elusive and less studied, and also sometimes poorly assessed for human risk [20-22]. Generally, normal cells turn into cancer cells in at least two steps; the first step involves changing normal cells into cancerous cells by using carcinogenic irreversible stem cells. The second step of the process is generally reversible and less effective as well; since everyone does not become ill when exposed to carcinogens. Despite being carcinogens, they are not capable of initiating tumors themselves [23].

In 1895, *Frankfurter and L. Rehn* noticed an increase in bladder cancer among aniline plant workers and they concluded that the origin of these rumors was aniline. Later research revealed that the main cancer-causing chemicals include aniline and other aromatic amines such as benzidine, diphenylamine, β-napthylamine *etc*. as most of the time, chemical carcinogens often need to be activated in order to work [24]. In recent years, there have been tremendous advancements in understanding how poly aromatic hydrocarbons (PAHs) affect biological processes. Researchers have identified some poly aromatic diol epoxides as the primary metabolites that cause cancer [25-26]. The importance of these poly aromatic diol epoxides has inspired researchers to investigate the synthesis as well as the chemical and biological characteristics of these compounds. The aza-polynuclear aromatic compounds, such as quinoline, benzo[f]quinoline and dibenzo[a,h], exhibit significant carcinogenic activity. Acridine is an aza-aromatic substance with important mutagenesis potential [27]. The study reveals that the major carcinogenic metabolites of the aromatic hydrocarbons are the *'bay region'* diol epoxides [28]. Additionally, considering the biological functions of nitrogen, it has been claimed that the position of the nitrogen atom is very much crucial. The biological activity of the major polycyclic aromatic hydrocarbons can be increased or decreased by substituting the aza group [29-30]. The electronic effect of nitrogen on the mutagenicity or carcinogenicity of diol epoxides may be studied and understood using phthalazine as a key model compound. Theoretical studies also suggest that aza-aromatic compound diol epoxides are predicted to be the most electrophilic and mutagenic metabolites in the bay region [31]. Therefore, the two electron-withdrawing groups on the phthalazine skeleton should increase the biological activity of these molecules [32].

In this current work, we have taken a few common aromatic intercalating carcinogens, *e.g*., β-napthylamine, α-benzopyrone, phthalazine, quinoline, α-naphthol and β-naphthol *etc*., based on their reactivity towards the single nucleobases, *viz*., adenine (A), thymine (T), guanine (G) and cytosine (C) as well as with AT and GC base pairs to investigate and understand the reactivity of these carcinogens within DNA nucleobases. Our main objective of such computational analysis is to study the comparative π-stacking interaction of carcinogen-DNA base-pair complexes, which may be helpful in predicting the proper molecular interaction, toxic effect and selectivity of carcinogens within DNA bases pairs.

Methodology

Herein, all the selected carcinogen molecules and DNA nucleobases, *i.e*., A, T, G, C, AT and GC; were constructed and then the geometries were optimized. Furthermore, these optimized geometries were used to build the various stacked models for carcinogen-DNA nucleobase complexes using the joinMolecule software package [33]. However, Arguslab was also used to visualize the molecular geometries of different carcinogen-DNA nucleobase stacked models. For studying the long-range non-covalent interaction, such as van der Waals, π-π interaction *etc*., in the carcinogen-DNA

nucleobase systems, quantum mechanical density functional theory (DFT) method is the most useful one. Therefore, all the stacked models have been computed using M062X method where GaussView5.0 and Gaussian09 software packages were used [34]. The basis set 6-311++G(d,p) was used for optimization as well as the single point energy calculation of the stacked models; the whole analysis was carried out in the gas phase at 298 K and 1 atm. The interaction energies for the carcinogen-DNA nucleobase complexes were computed by the following equation:

$$\text{Interaction energy} = E_{Car\text{-}Nuc} - E_{Car} - E_{Nuc}$$

Here, the $E_{Car\text{-}Nuc}$ pair is the single point energy of the stacked carcinogen-DNA nucleobase complex, E_{Car} is the single point energy of the carcinogen and E_{Nuc} is the single point energy of the DNA nucleobase.

RESULTS AND DISCUSSION

a) Construction of Carcinogen-DNA Nucleobase Stacked Models

In cancer research, the study of the intercalation of aromatic carcinogens into DNA nucleobase (A, T, G, C, AT and GC) is an essential aspect; herein, we are trying to investigate the non-covalent, π-π stacking interactions of some intercalating organic carcinogens within DNA nucleobase stacked complexes. Although carcinogens might have many paths of intercalation with DNA nucleobases, our study has focused exclusively on the favored intercalating sites for carcinogens. It is well established that the standard intermolecular distance for any long-range non-covalent interaction of DNA nucleobase lies within a range of 2.8-3.8 Å; therefore, while constructing the stacked models of carcinogen-DNA nucleobase (AT and GC) complexes, the intermolecular separation was kept constant at 3.6 Å, which results in the effective interaction. The stacked models of carcinogen-DNA nucleobase complexes have been studied by horizontal shifting of carcinogens above the DNA nucleobase, keeping the nucleobase at a constant position. The horizontal movement of carcinogens above the DNA nucleobase was done either along -X, -Y, or Z-axis; both in the right (positive) and left (negative) directions. Herein, for each carcinogen-DNA nucleobase stacked model, the horizontal shifting of carcinogens along the X-axis from -2.0 to +2.0 Å direction.

b) Analysis of Carcinogen-DNA Nucleobase Stacked Models

The stacking interaction energy of carcinogen-DNA nucleobase stacked complexes is greatly influenced by the mode of interaction of carcinogen with single A, T, G and C nucleobases or AT and GC base pairs. Hence, carcinogens may also show DNA sequence-specific binding during carcinogen-DNA nucleobase stacking interactions. In our investigation, we have taken several poly aromatic intercalating carcinogens, as shown in Table 1 and Fig. 1; and tried to analyze the π-π stacking interaction energy with DNA nucleobase. Usually, carcinogen-DNA nucleobase stacked system follows a very complicated mechanism and is difficult to understand; so, we have investigated the carcinogen-DNA nucleobase interactions in various ways.

Primarily, we have studied the stacking interaction of carcinogens with single nucleobases of DNA *i.e*., Adenine (A), Thymine (T), Guanine (G) and Cytosine (C); such investigation plays a key role in observing how effectively carcinogens bind with a single nucleobase of DNA. The computed interaction energy calculation for the carcinogens and single nucleobase of DNA reveals that most of the poly aromatic carcinogens efficiently bind with a single DNA nucleobase, as they show negative interaction energy values, which is reflected in Table 2.

In computational methods, it is well established that more is the negative stacking interaction energy value for any stacked model; more is the stability of such stacked complexes. Therefore, the carcinogen-DNA nucleobase stacked models which show more negative interaction energy value results in the most stable and favored geometry. All those interaction energies for carcinogens and single nucleobase (A, T, G and C) and AT and GC pairs can easily be reflected by the minima of interaction energy plots *i.e*., interaction energy *vs*. horizontal shifting as shown in the Figs. 2-7. Our study also reveals that the stacking interaction energy values for carcinogens-DNA nucleobase pair are found to be greater than that of the carcinogens-DNA single nucleobase stacked complexes; *i.e*., carcinogens usually bind with AT and GC nucleobase pairs; hence, the computed stacking interaction energy value is found to be more

Table 1. IUPAC Name and Structures of Sudied Carcinogens

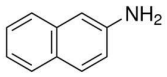
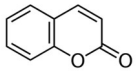
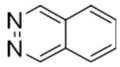
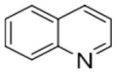
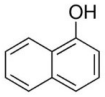
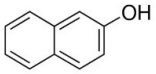
Sl. No.	Carcinogens	IUPAC Names	Structures
1	β-Naphthylamine (BNA)	Naphthalen-2-amine	
2	α-Benzopyrone (ABP)	2-Hydroxy-1,2-di-2-pyridylethanone	
3	Phthalazine (PHZ)	2,3-Diazanaphthalene Benzo[d]pyridazine	
4	Quinoline (QUN)	1-Azanaphthalene 1-Benzazine	
5	α-Naphthol (ANP)	Naphthalen-1-ol	
5	β-Naphthol (BNP)	Naphthalen-2-ol	

Table 2. Computed Stacking Interaction Energies (kcal mol^{-1}) of Different Carcinogens with A, T, G, C, AT, and GC Nucleobase Pairs (M062X/6-311++G(d,p))

Sl. No.	Carcinogens	Interaction energies (kcal mol^{-1})					
		A	T	G	C	AT	GC
1	β-Napthylamine	-8.59	-8.98	-10.67	-10.19	-9.95	-11.25
2	α-Benzopyrone	-7.26	-6.67	-10.04	-9.65	-9.16	-10.98
3	Phthalazine	-7.00	-7.60	-12.19	-10.09	-7.79	-9.57
4	Quinoline	-7.08	-4.85	-10.70	-7.86	-7.82	-8.36
5	α-Naphthol	-7.57	-8.40	-9.39	-8.22	-9.02	-9.77
6	β-Naphthol	-8.61	-9.16	-9.57	-7.47	-9.16	-8.94

negative for carcinogen-DNA stacked complexes in comparison to a single DNA nucleobase *i.e*., A, T, G and C (Table 2).

The sequence of stability in terms of interaction energy values for the stacked poly aromatic carcinogen-DNA nucleobase (*i.e*., A, T, G and C) complexes have been found as follows:

For A nucleobase, PHZ ~ QUN < ABP< ANP < BNA ~ BNP

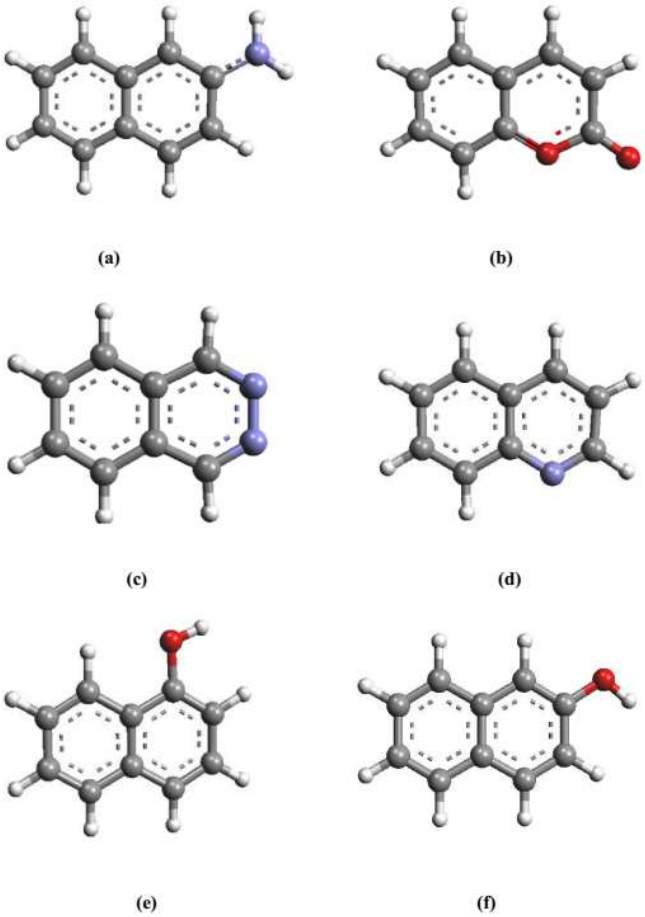


Fig. 1. Optimized models of carcinogens (a) β-napthylamine, (b) α-benzopyrone, (c) phthalazine, (d) quinoline, (e) α-naphthol and (f) α-naphthol.

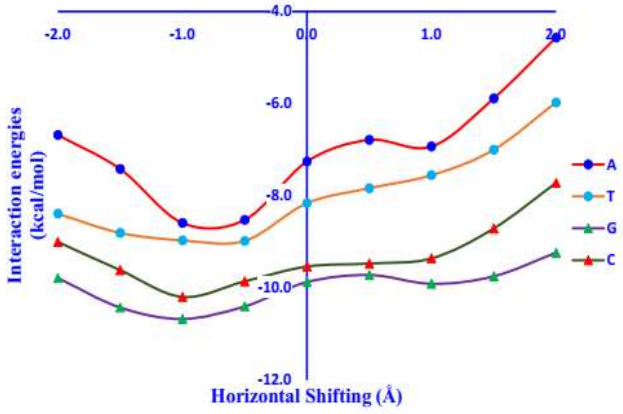


Fig. 2a. Plots of Interaction energies (kcal mol^{-1}) *vs.* Horizontal shifting (Å) for different stacked models of β-napthylamine and A, T, G and C nucleobases.

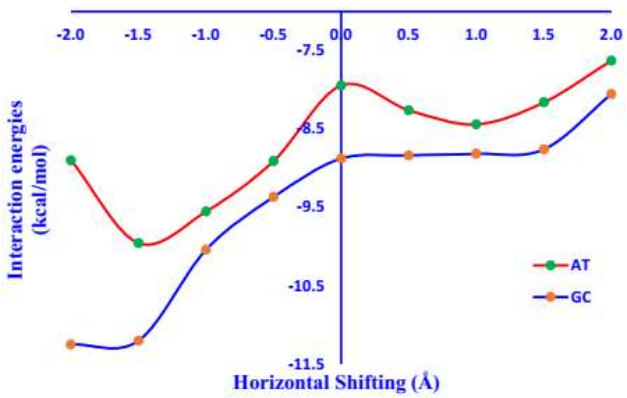


Fig. 2b. Plots of Interaction energies (kcal mol^{-1}) *vs.* Horizontal shifting (Å) for different stacked models of β-napthylamine and AT & GC base pair.

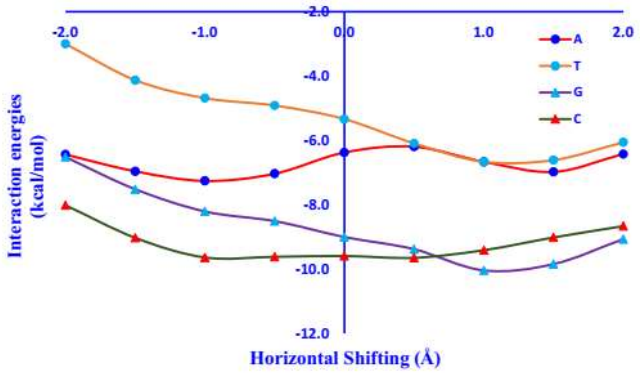


Fig. 3a. Plots of Interaction energies (kcal mol^{-1}) *vs.* Horizontal shifting (Å) for different stacked models of α-benzopyrone and A, T, G and C nucleobases.

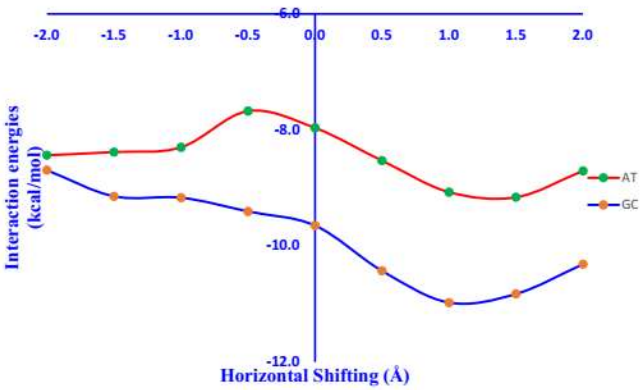


Fig. 3b. Plots of Interaction energies (kcal mol^{-1}) *vs.* Horizontal shifting (Å) for different stacked models of α-benzopyrone and AT & GC base pair.

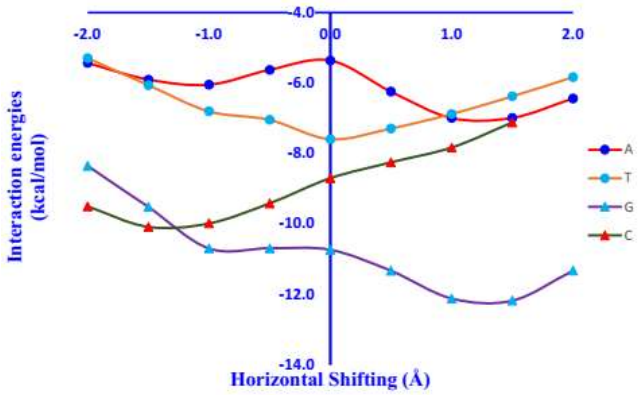


Fig. 4a. Plots of Interaction energies (kcal mol^{-1}) *vs*. Horizontal shifting (Å) for different stacked models of phthalazine and A, T, G & C nucleobases.

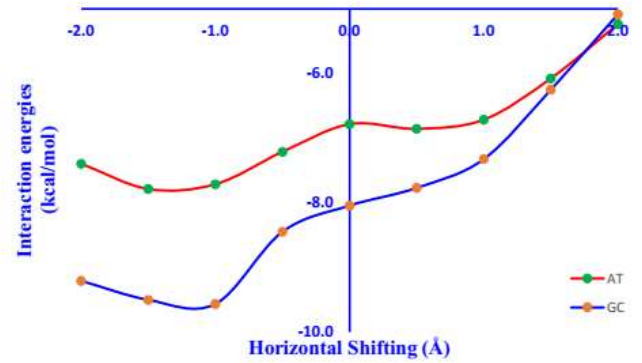


Fig. 4b. Plots of Interaction energies (kcal mol^{-1}) *vs*. Horizontal shifting (Å) for different stacked models of phthalazine and AT & GC base pair.

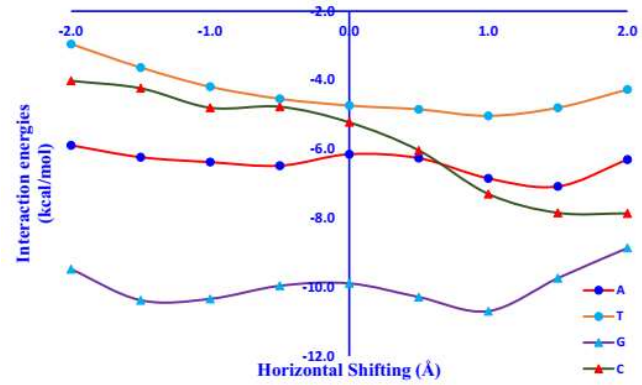


Fig. 5a. Plots of Interaction energies (kcal mol^{-1}) *vs*. Horizontal shifting (Å) for different stacked models of quinoline A, T, G & C nucleobases.

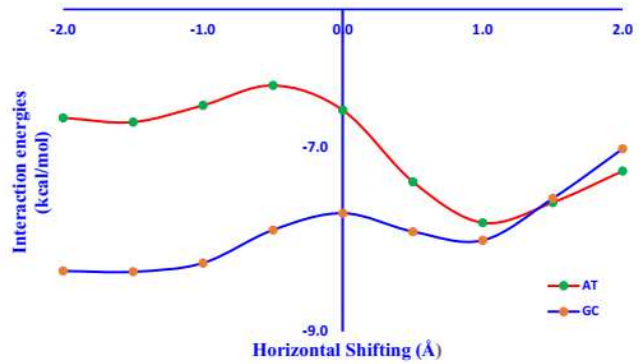


Fig. 5b. Plots of Interaction energies (kcal mol^{-1}) *vs*. Horizontal shifting (Å) for different stacked models of quinoline and AT & GC base pair.

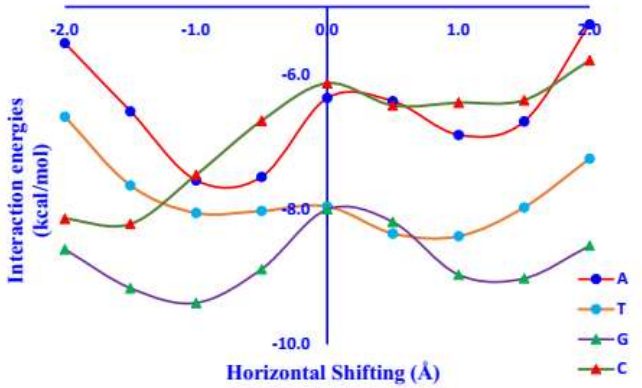


Fig. 6a. Plots of Interaction energies (kcal mol^{-1}) *vs*. Horizontal shifting (Å) for different stacked models of α-naphthol and A, T, G & C nucleobases.

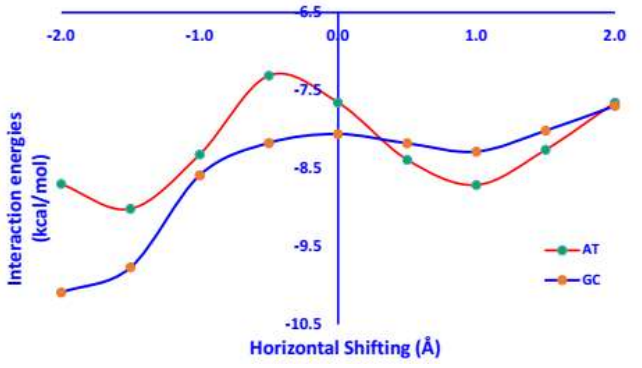


Fig. 6b. Plots of Interaction energies (kcal mol^{-1}) *vs*. Horizontal shifting (Å) for different stacked models of α-naphthol and AT & GC base pair.

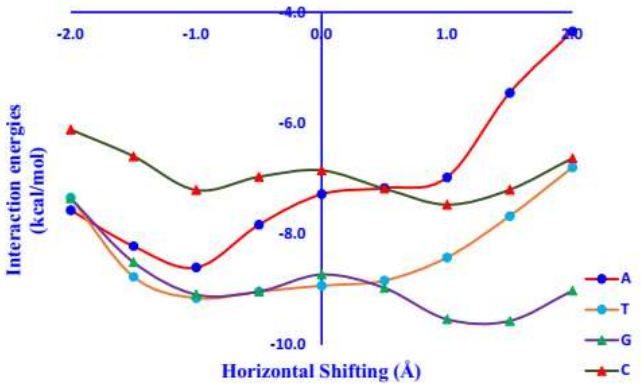


Fig. 7a. Plots of Interaction energies (kcal mol^{-1}) *vs.* Horizontal shifting (Å) for different stacked models of β-naphthol and A, T, G & C nucleobases.

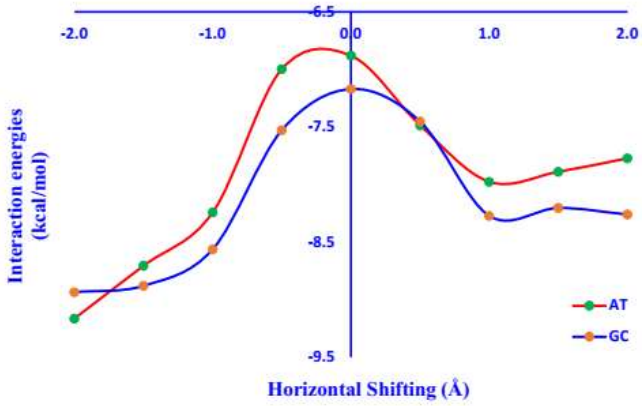


Fig. 7b. Plots of Interaction energies (kcal mol^{-1}) *vs.* Horizontal shifting (Å) for different stacked models of β-naphthol and AT & GC base pair.

The above study clearly reveals that the stacked models of A and T nucleobases with β-naphthol (BNP) results in more negative interaction energy values, *i.e.*, -8.61 and -9.16 kcal mol^{-1} respectively; interestingly, the stacking interaction energy values for β-naphthylamine (BNA) is also closer to β-naphthol (BNP) (*i.e.*, -8.59 and -8.98 kcal mol^{-1}); hence, both of them give stable stacked conformation and show effective binding with A and T nucleobases. Moreover, for G nucleobase, phthalazine (PHZ) gives a favored stacked complex with an interaction energy value of -12.19 kcal mol^{-1}. Again, the C nucleobase gives favored stacked model with β-naphthylamine (BNA) with an interaction energy value -10.19 kcal mol^{-1} (Table 2). Therefore, the overall analysis clearly explains that β-naphthol (BNP), β-naphthylamine (BNA) and phthalazine (PHZ) result in more negative interaction energy value and they show quite strong interaction with single nucleobases than that of other carcinogens. All those interaction energies for poly aromatic carcinogens and DNA nucleobases (A, T, G, C, AT, and GC) can easily be reflected by the minima of interaction energy plots, *i.e.*, interaction energy vs. horizontal shifting as shown in the Figs. 2-7. Stacking interaction energy values for all the selected carcinogen-AT base stacked pair interactions lie in a range of -7.79 to -9.95 kcal mol^{-1}; whereas for carcinogens-GC base pair, it is found to be -8.36 to -11.25 kcal mol^{-1}, which reveals that the binding between carcinogen and GC base pair is quite stronger than that of AT base pair of DNA nucleobase (Table 2). Thus, most of the poly aromatic carcinogens predominantly intercalate within the GC base pair of DNA nucleobase rather than that of AT base pair, *i.e.*, we may reveal that all the above studied

Table 2. Computed Stacking Interaction Energies (kcal mol^{-1}) of Different Carcinogens with A, T, G, C, AT, and GC Nucleobase Pairs (M062X/6-311++G(d,p))

Sl. No.	Carcinogens	Interaction Energies (kcal mol^{-1})					
		A	T	G	C	AT	GC
1	β-Napthylamine	-8.59	-8.98	-10.67	-10.19	-9.95	-11.25
2	α-Benzopyrone	-7.26	-6.67	-10.04	-9.65	-9.16	-10.98
3	Phthalazine	-7.00	-7.60	-12.19	-10.09	-7.79	-9.57
4	Quinoline	-7.08	-4.85	-10.70	-7.86	-7.82	-8.36
5	α-Naphthol	-7.57	-8.40	-9.39	-8.22	-9.02	-9.77
6	β-Naphthol	-8.61	-9.16	-9.57	-7.47	-9.16	-8.94

carcinogens are usually GC-specific. From the above sequence-specific analysis of stacked carcinogen-DNA nucleobase pair complexes, it has been found that the GC binding carcinogen is highly G specific within the GC base pair as the computed interaction energy gives a more negative value, *i.e.*, -9.39 to -12.19 kcal mol^{-1}; whereas for C nucleobase, the interaction energy value gives a less negative value, *i.e.*, -7.47 to -10.19 kcal mol^{-1}, which is clearly reflected in Table 2. Therefore, the sequence of stability for the stacked carcinogen-DNA nucleobase pair *i.e.*, AT and GC, complexes has been found as follows:

For AT base pair, PHZ ~ QUN < ANP < ABP ~ BNP < BNA

For GC base pair, QUN < PHZ < ANP < BNP < ABP < BNA

From the above sequence of stability of carcinogen-DNA nucleobase pair stacked complexes, it has been observed that among all studied carcinogens, β-naphthylamine (BNA) could directly enter through AT and GC base pairs and it is highly GC specific with a more negative interaction energy value *i.e.*, -11.25 kcal mol^{-1}, than that of other carcinogens. It happens because of the presence of an active -NH_2 group at β-position in the fused aromatic hydrocarbon, which could easily intercalate within DNA nucleobase. Therefore, due to the more negative computed interaction energy value of β-naphthylamine (BNA), it causes a highly carcinogenic effect on DNA nucleobase, which results in rapid distortion of DNA. Similarly, according to the interaction energy calculation for α-benzopyrone (ABP) and β-naphthol (BNP) stacked systems, they are also toxic next to the BNA system. However, the other poly aromatic carcinogens like quinoline (QUN) and phthalazine (PHZ) result in less carcinogenic effects on AT and GC base pairs of DNA nucleobase as they show less negative interaction energy values ranging from -7.82 to -9.57 kcal mol^{-1}, than those of other carcinogens.

c) Analysis of HOMO-LUMO Energy

The calculation of interaction energy for carcinogen-DNA nucleobase stacked models may also be justified by computing the HOMO-LUMO energy gap of the complexes. The highest occupied energy of HOMO represents the electron-donating ability of a molecule, while the lowest unoccupied LUMO determines the ability to accept an electron. The computed energy of these orbitals determines how a molecule interacts with other species and it gives information about the stability or reactivity of specific molecule regions. The HOMO-LUMO energies for minimized stacked models were obtained at the level of M062X theories and the values of carcinogen-DNA nucleobase complexes, which are incorporated in Table 3.

The higher values of HOMO and LUMO energy (ev) indicate that the molecule is chemically stable, while the small HOMO-LUMO energy gap represents the less stable states. Therefore, we can directly tally the computed interaction energies of the above studied carcinogen-DNA nucleobase complexes with HOMO-LUMO energy to justify their calculated interaction energies; it has been found that all those stacked systems have more negative interaction energy values resulting in higher values (positive) HOMO-LUMO

Table 3. Computed HOMO-LUMO Energy (eV) Gap for Carcinogens with A, T, G, C, AT and GC Nucleobase Pairs

Sl. No.	Carcinogens	HOMO-LUMO energy (eV)					
		A	T	G	C	AT	GC
1	β-Napthylamine	2.74	2.94	2.44	3.09	2.50	2.81
2	α-Benzopyrone	2.73	2.83	2.43	2.98	2.39	2.72
3	Phthalazine	2.55	2.90	2.54	2.99	2.20	2.69
4	Quinoline	2.60	2.76	2.44	2.85	2.27	2.53
5	α-Naphthol	2.73	2.94	2.24	2.97	2.37	2.71
6	β-Naphthol	2.84	3.02	2.32	2.80	2.40	2.58

energy gap. Although we could not compute the accurate HOMO-LUMO energy for all such stacked molecular complexes, still in most cases, higher HOMO-LUMO energy results in stable carcinogen-DNA nucleobase complexes (*i.e.*, more negative interaction energy and more positive HOMO-LUMO energy). For example, among all conformations, the most stable AT and GC stacked conformation of BNA results in the interaction energy value of -9.95 and -11.25 kcal mol^{-1} with HOMO-LUMO energy 2.50 and 2.81 eV, respectively; whereas, for unfavoured AT and GC stacked conformation of QUN results in the interaction energy value of -7.82 and -8.36 kcal mol^{-1} which gives the lower HOMO-LUMO energy *i.e.*, 2.27 and 2.53 eV than that of the other stacked systems. The frontier molecular energy, HOMO-LUMO orbital diagram for the minimized carcinogens-GC stacked systems are shown in Fig. 8. Thus, the computed HOMO-LUMO energy of poly aromatic carcinogen-DNA nucleobase minimized stacked complexes is the following sequence, which follows an almost similar trend as we have previously obtained for interaction energy values.

For A nucleobase, PHZ < QUN < ABP ~ ANP ~ BNA < BNP

For T nucleobase, QUN < ABP < PHZ < ANP ~ BNA < BNP

For G nucleobase, ANP < BNP < ABP ~ BNA ~ QUN < PHZ

For C nucleobase, BNP < QUN < ANP ~ ABP ~ PHZ < BNA

For AT base pair, PHZ < QUN < ANP < ABP ~ BNP < BNA

For GC base pair, QUN < ANP < PHZ < BNP ~ ABP < BNA

d) Analysis of Mulliken Charge Density

To analyze the relative changes within the carcinogens-DNA nucleobase stacked complexes, we also compute the Mulliken Charge (MC) density of the heavy atom (*i.e.*, N or O) of carcinogens and then compare it with unstacked and stacked models. The MC density values usually show a significant change for minimized stacked carcinogen-DNA base pair models and optimized geometry of the single carcinogen molecule. More is the variation in MC density values (positive or negative) in stacked and unstacked models; more is the stability and effectiveness of intercalation of such models, which is reflected in the bar graph as shown in Fig. 9.

In our study, when we compare the MC densities of heteroatoms, either O or N (MC of O for ABP, ANP & BNP and MC of N for BNA, PHZ & QUN) of the unstacked and stacked carcinogens, there is a significant variation on the MC density in GC than that of AT stacked system which is displayed in Fig. 9. For example, in an unstacked BNP molecule, the computed MC density of heteroatom (N) is found to be -0.226; but, for the AT stacked conformation, the MC on N becomes -0.127; again for the most GC stacked conformation, it becomes -0.105; which results that more is the change in MC value of the heteroatom, more is the stability of such stacked systems. Therefore, the GC base pair favors the formation of most stable stacked complexes with the above studied carcinogens than that of AT system.

CONCLUSIONS

In this work, we studied the stacking interaction of poly aromatic carcinogen-DNA nucleobase pair complexes using quantum mechanical calculations. It has been found that some of the carcinogens interact nicely and show effective stacking interactions with DNA nucleobases, *i.e.*, A, T, G, C, AT and GC. The most negative stacking interaction energy is computed for the most stable minimized stacked models for each carcinogen-DNA nucleobase pair complex. Herein, it has been found that β-naphthylamine (BNA) is highly GC-specific with more negative interaction energy value of -11.25 kcal mol^{-1} than that of other carcinogen-DNA nucleobase pair complexes. However, it also reveals that β-naphthylamine (BNA) is highly G-specific within the GC nucleobase pair as the interaction energy for BNA-G and BNA-C complexes are found to be -10.67 and -10.19 kcal mol^{-1} respectively than that of other carcinogen-DNA nucleobase stacked complexes. Therefore, BNA is highly toxic and shows a stronger carcinogenic effect on DNA nucleobase than that of other carcinogens. Moreover,

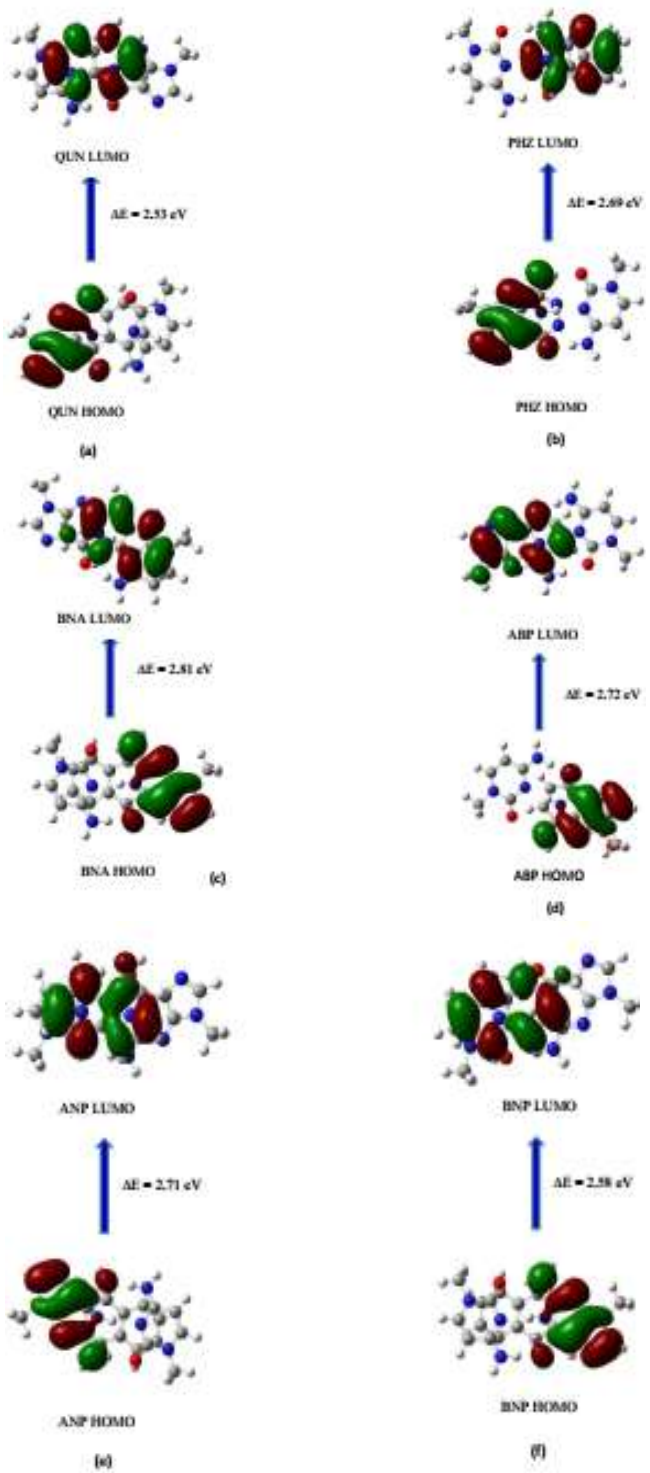


Fig. 8. Frontier molecular energy, HOMO-LUMO orbital diagram for the minimized carcinogens-GC stacked systems for (a) QUN, (b) PHZ, (c) BNA, (d) ABP, (e) ANP, and (f) BNP models.

next to the BNA system, both ABP and BNP results in a strong affinity for binding towards DNA nucleobases, which may also cause a high carcinogenic effect. On the other hand, carcinogens like quinoline (QUN) and phthalazine (PHZ) with less negative interaction energy values result in the least carcinogenic effect on AT and GC base pairs of DNA nucleobases.

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