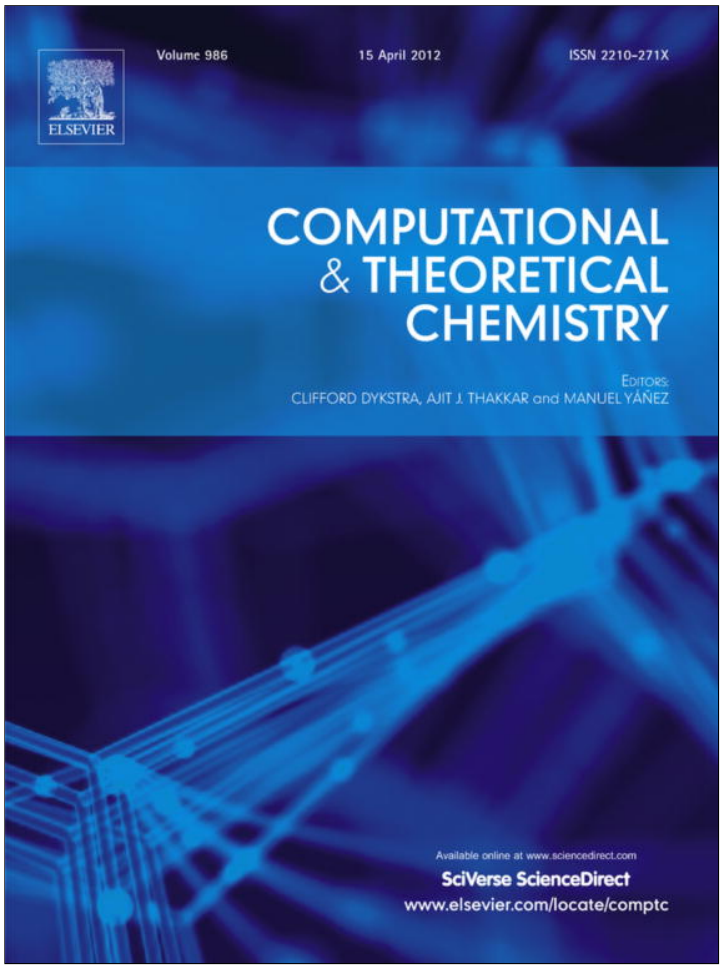

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Structural variation facilitate alkylation: A conceptual DFT study

Babul Neog [a], Nabajit Sarmah [a], Rahul Kar [b,*], Pradip Kr. Bhattacharyya [a,*]

[a] Department of Chemistry, Arya Vidyapeeth College, Guwahati, Assam, India
[b] Department of Chemistry, Dibrugarh University, Dibrugarh, Assam, India

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ABSTRACT

In this paper, the variation of the DFT-based reactivity descriptors, such as chemical potential, chemical hardness, electrophilicity, Fukui function and local electrophilicity, for a family of anticancer drug intermediate have been analyzed. Based on our findings, we suggest that structural variation in the drug intermediate assist alkylation of DNA. In addition, the interaction energy of the prototype drug intermediates with the GC base pair in gas phase is found to be higher than that in aqueous phase. A linear dependence of interaction energy on the global parameter of the drug intermediate is also observed.

1. Introduction

Nitrogen mustards are bis-alkylating drugs that have been used in cancer chemotherapy since several decades [1,2]. These drug molecules are best known for their ability to alkylate DNA. Bendamustine, chlorambucil, melphalan, phosphoramide mustard, spiromustine and uracil mustard belong to this family. During alkylation, these drug molecules form a very reactive aziridinium ion intermediate which alkylate different nucleophilic centres in the biomolecules [3,4]. During the alkylation process, overall stability/reactivity of the aziridinium ion intermediate plays an important role and hence study of variation of reactivity of the drug intermediate becomes very much important. Very recently, it was shown in case of mustine (the oldest member of this family) that the drug intermediate must undergo some structural changes before alkylating DNA [5]. Bhattacharyya and Kar [5] analyzed how the position of the LUMO (lowest unoccupied molecular orbital) of the drug intermediate shifted with a variation in the bond angle of the tricyclic ring of aziridinium ion of mustine in gas phase as well as in aqueous medium. For more details and references one may refer to our article [5].

Conceptual DFT concentrates on the definition and application of the reactivity descriptors, defined within the framework of density functional theory (DFT). In general, the reactivity descriptors are classified as global reactivity descriptor (GRD) and local reactivity descriptor (LRD) [6–8]. Chemical potential, hardness, softness, electrophilicity index, etc. fall under GRD and they describe about the overall stability of the system. On the other hand, the LRDs such as Fukui function, local softness, local philicity, relative electrophilicity, and dual descriptors describe the site reactivity. These descriptors have been well tested and studied in the literature by several research groups and are found to be very useful in rationalizing the reactivity patterns of the molecular and biomolecular systems [7–9].

In order to follow the overall reactivity/stability of the drug intermediates we have chosen the global reactivity descriptors. Moreover, in the process of alkylation of DNA, the aziridinium ion intermediate accepts the electron density from the N7 centre of guanine base (in DNA) [1,3,4]. The stability of the LUMO and local reactivity of the aziridinium ion becomes very important. Thus, apart from global reactivity descriptors, it is important to observe the local reactivity (on the C-centres) of the tricyclic ring of the drug intermediate. Therefore, our objective in this article is to examine how the reactivity descriptors (local and global) of the set of drug intermediates of bendamustine, chlorambucil, melphalan, phosphoramide, spiromustine and uracil (Fig. 1) changes with a variation in ∠NCC bond angle. As our body fluid contains mostly water, therefore, in addition to gas phase, we have analyzed the variation in aqueous medium. In addition, we have analyzed the interaction energy between each of the prototype drug intermediate and the GC (guanine–cytosine) base pair. This would in turn throw some light on the extent of alkylation of guanine base in DNA.

2. Theoretical and computational details

In DFT, Hohenberg–Kohn theorem defines the ground state energy of a system as $E[\rho] = F_{HK} + \int \rho(r)\upsilon(r)\,dr$. The first derivative

* Corresponding authors.
E-mail addresses: rahul.kar.dib@gmail.com (R. Kar), prdpbhatta@yahoo.com (P.Kr. Bhattacharyya).

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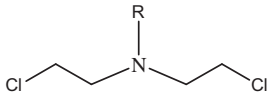


Nitrogen mustard

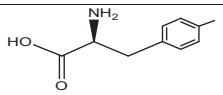
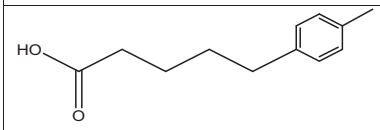
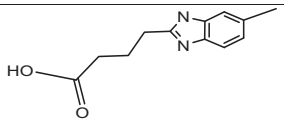
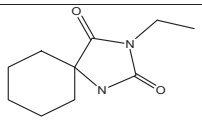
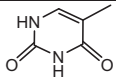
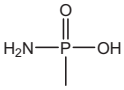
R=	DRUG
	Melphalan
	Chlorambucil
	Bendamustine
	Spiromustine
	Uracil mustard
	Phosphoramide mustard

Fig. 1. Structure of the drug molecules.

of energy with respect to the number of electrons defines the chemical potential [10] as $\mu = \left(\frac{\partial E}{\partial N}\right)_{v(\vec{r})}$ and chemical hardness [11] as $\eta = \frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right)_{v(\vec{r})}$, where, E is the energy and N is the number of electrons of an electronic system at constant external potential, $v(\vec{r})$. Operational definition, using the finite difference approximation, of the above quantities in terms of ionization potential (IP) and electron affinity (EA) of the system can be written as $\eta = \frac{IP-EA}{2}$ and $\mu = -\left(\frac{IP+EA}{2}\right)$. It should be noted that the IP and EA values are calculated from the three point finite difference approximation using the energies of neutral and ionic systems. As the drug intermediate accepts the electron density from guanine base during the process of alkylation (i.e., addition of an electron to the drug intermediate), we have calculated the hardness and chemical potential of the drug intermediate using Koopmans' theorem. Recently, Parr and his co-workers proposed electrophilicity index [12] as a measure of electrophilicity of a ligand (ω) as, $\omega = \frac{\mu^2}{2\eta}$ and its local counterpart is defined as $\omega(r) = f(r) \cdot \omega$ [13], where, $f(r)$ is another local reactivity descriptor called Fukui function. The operational definition of condensed Fukui function and local electrophilicity for an atom k undergoing nucleophilic attack, respectively, are $f_k^+ = q_k^{N+1} - q_k^N$, $f_k^- = q_k^N - q_k^{N-1}$ [14] and $w_k^+ = w \cdot f_k^+$ [13].

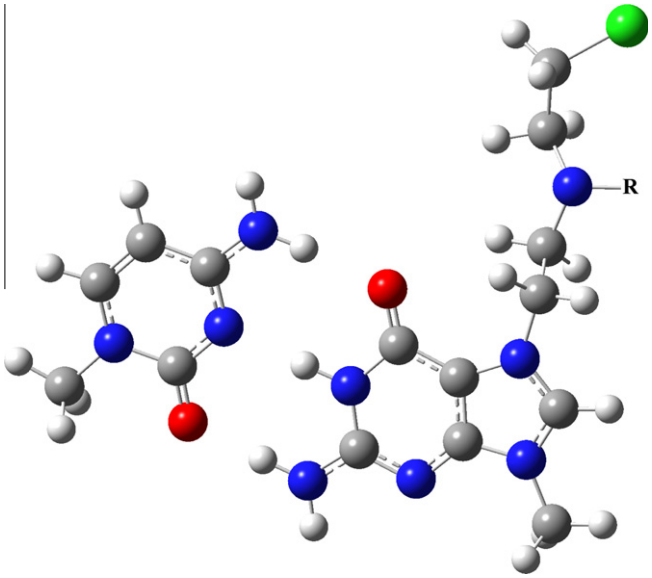


Fig. 3. Structure of the supermolecule GC base pair and the drug intermediate.

All calculations were performed using Gaussian09 software [15]. The structure of the drug intermediates (bendamustine, chlorambucil, melphalan, phosphoramide, spiromustine and uracil) were optimized (Fig. 2) using B3LYP/6-311++G (d, p) level of theory and the minima were confirmed by frequency calculations.

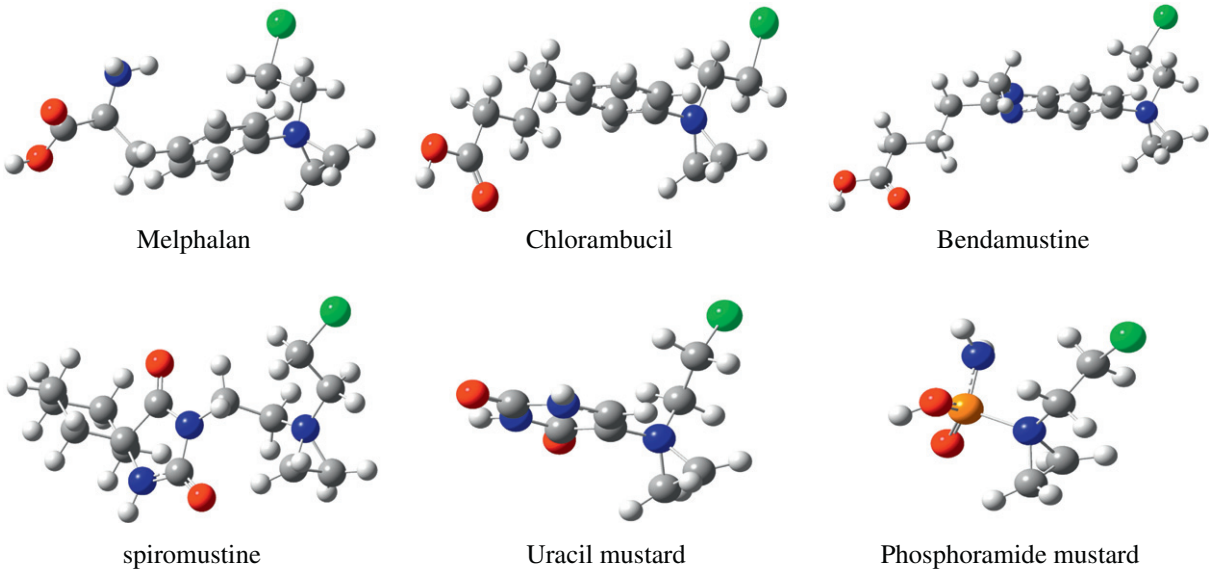


Fig. 2. Optimized structure of the corresponding aziridinium ions.

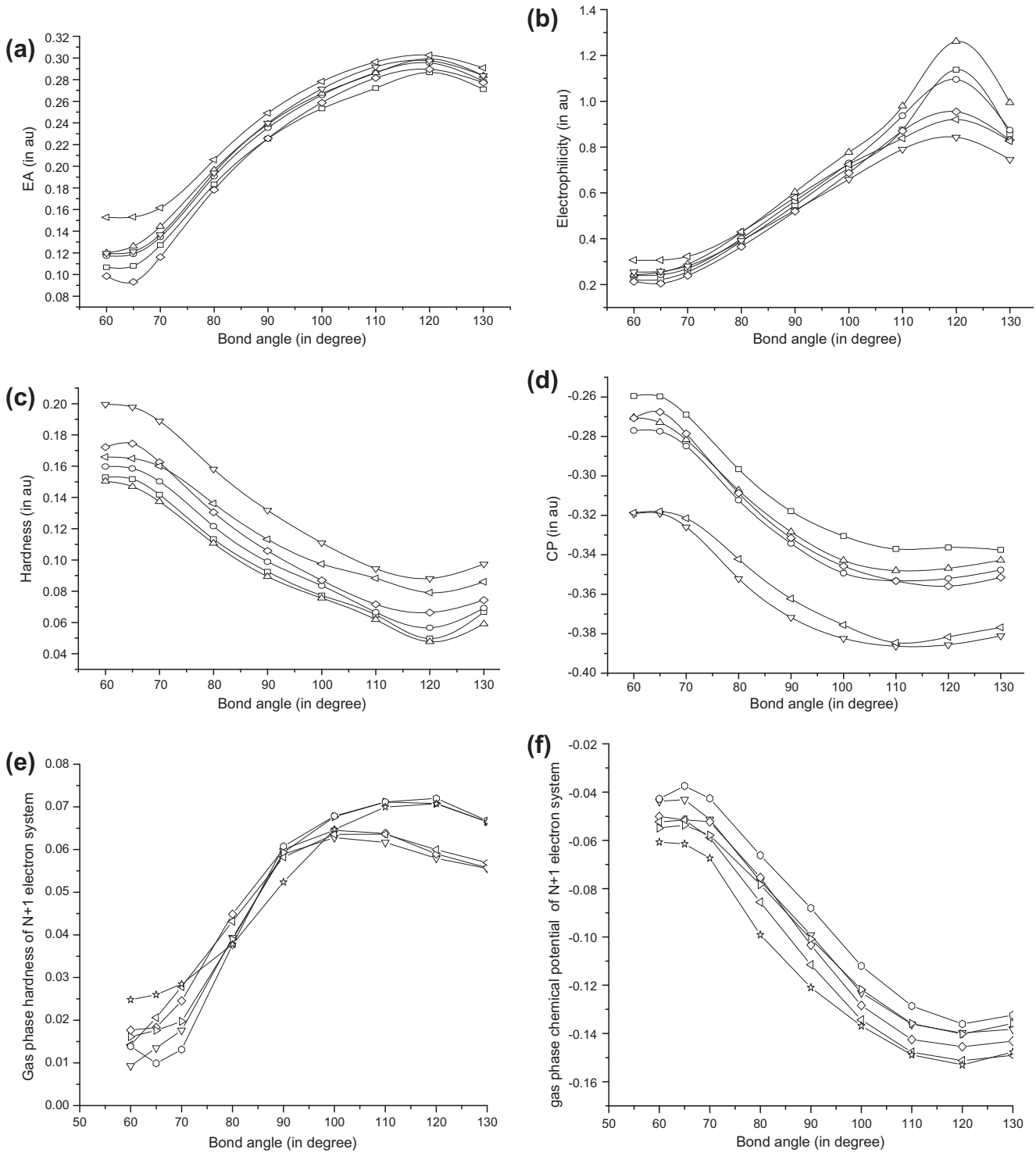


Fig. 4. Variation of EA, CP, hardness and electrophilicity with ∠NCC bond angle (in degrees) in gas phase. Square = bendamustine; circle = chlorambucil; triangle = melphalan; inverted triangle = phosphoramide mustard; rhombus = spiromustine; arrow = uracil mustard.

Thereafter, at the same level of theory, single point energy calculations were performed by varying the ∠NCC bond angle of the tricyclic ring from 60° to 130°. IP and EA along with chemical potential, hardness and electrophilicity were calculated using the above relations. Similar calculations were performed in solvent phase using PCM (Polarizable Continuum Model) [16] and water as a solvent. The Hirshfeld population partitioning scheme [17] was employed in order to calculate the values of local electrophilicity.

For calculating the interaction energy between the drug intermediate and GC base pair, we have optimized the structure of each of the component molecules and their supermolecule (GC base pair and prototype drug intermediate) as shown in Fig. 3. The free energy of solvation was computed using the SMD keyword, as implemented in Gaussian09, which does an IEFPCM calculation with radii and non-electrostatic terms for Truhlar and coworkers' SMD solvation model [20].

3. Results and discussion

3.1. Global reactivity descriptors

The variation of gas phase EA, chemical potential, hardness and electrophilicity index with different ∠NCC bond angles of the tricyclic ring are presented in Fig. 4a–f (the values are presented in Tables 1a–6a, Supporting material). The drug intermediate is a positively charged species and it is expected that its electron affinity might play an important role during the alkylation of DNA. It is interesting to see that the gas phase EA values for each drug intermediate increase on increasing the ∠NCC bond angle and it passes through a maximum (Fig. 4a). This suggest that as the tricyclic ring open up tendency to accept electron density becomes more, with a maximum at ∠NCC ≈ 115°. Thus, at this bond angle, all the drug intermediates have much more affinity to accept electron density from the guanine base during alkylation of DNA. Similar trend is observed in case of gas phase electrophilicity; exhibiting maxima at ∠NCC ≈ 120° (Fig. 4b). This signifies that the drug molecules have maximum electrophilic character and hence, accept the electron density from guanine base. Hence, as the equilibrium geometry (at a ∠NCC = 60°) of these drug intermediates has minimum value of electrophilicity, the minimum electrophilicity principle (MEP) [18] is also obeyed. On comparing the electrophilicity of the above series of drug intermediates, melphalan exhibit the highest value.

It is interesting to note that the drug intermediates are most stable (higher value of hardness) at ∠NCC ≈ 60° and least at ∠NCC ≈ 115° (Fig. 4c). However, maximum stability of the drug intermediate at ∠NCC ≈ 60° does not explain the formation of drug–GC mono-adduct. Therefore, we have observed the trend in gas phase hardness of the drug intermediate on addition of an electron (i.e., $N+1$ electron drug intermediate), shown in Fig. 4e. Interestingly, it can be observed that the maxima in hardness shifted from ∠NCC ≈ 60° (in N electron drug intermediate) to ∠NCC ≈ 110°—115° (in $N+1$ electron drug intermediate). This indicates that the driving force for the ring opening may be due to shifting of stability (maximum hardness) from ∠NCC ≈ 60° to 110° as the electron density shifted to the drug intermediate from guanine (N7 position). Moreover, chemical potential of all drug intermediates exhibit a minimum at a ∠NCC ≈ 110° for both N electron (using three point finite difference approximation theorem) and $N+1$ electron systems (using Koopmans' theorem). Figs. 4d and 4f, indicate more stable adduct formation at that bond angle. In addition, it should be noted that the maximum hardness principle (MHP) is applicable for the set of drug intermediates [19]. Thus, there is a minimum hardness corresponding to least stability in the drug intermediates for all the drug molecules.

It was shown, in an earlier report, that with the variation in the bond angle of the tricyclic ring (∠NCC ≈ 60° bond angle) the hardness and electrophilicity of the drug intermediate of mustine passes through a maximum and minimum, respectively [5]. In the present context, we have similar findings and confirm that this class of drug molecules must undergo some structural changes before binding with DNA base and this structural change is facilitated by shifting of electron density to the aziridinium ion from DNA base. Similar conclusions on their behaviour can be drawn for the chosen set of molecules in aqueous medium (Supporting material, Tables 1b–6b).

3.2. Local reactivity descriptors

Aziridinium ion intermediate is an electron deficient species and one of the symmetrical C-atom (C2; Fig. 6) in the tricyclic ring act as an electrophilic centre during the alkylation at N7 centre of guanine. We have checked, using reactivity indices, if the sites that couple (C2 of the aziridinium ion intermediate and N7 centre of guanine), to compute the interaction energies, really represent the most favourable interaction sites and the values of condensed FF are presented in Supporting information (Table 7). As we validate above that the tricyclic ring must open up during the alkylation process, we therefore, would like to understand through the local electrophilicity (ω_C^+) about the reactivity of the C2 centre (that binds with N7 centre of guanine) in the tricyclic ring of the drug intermediates. The variation of local electrophilicity of the C2 atom for all the drug intermediates in aqueous phase is shown in Fig. 5. It is also observed that the value of local electrophilicity of C2 atom of the tricyclic ring in all the drug intermediates is a maximum at ∠NCC ≈ 120° (Fig. 5). This maximum value of ω_C^+ clearly indicate that electronic charge transfer from N7 of guanine to C2 centre of aziridinium ion is feasible at ∠NCC ≈ 60°. We also observed similar trend in gas phase local electrophilicity (Supporting material, Tables 1a–6a).

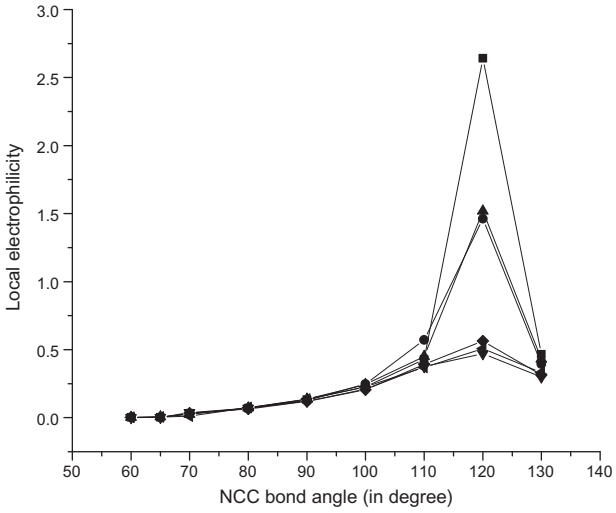


Fig. 5. Variation of local electrophilicity with variation in bond angle (in degrees) in aqueous phase. Square = bendamustine; circle = chlorambucil; triangle = melphalan; inverted triangle = phosphoramide mustard; rhombus = spiromustine; arrow = uracil mustard.

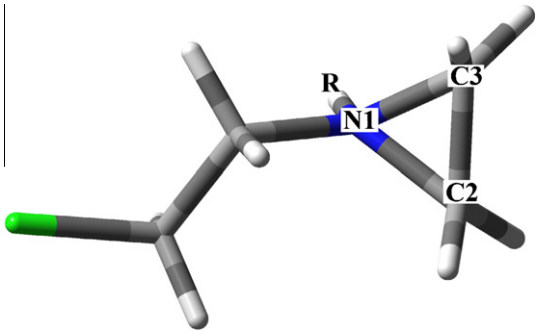


Fig. 6. Structure of the drug intermediate.

3.3. Interaction energy

The measure of the extent of alkylation is provided by the concept of interaction energy. We, therefore, have made an attempt to model and calculate the interaction energy between the GC base pair and the prototype drug intermediates using supermolecular approach, $(\Delta E_{int} = E_{aziridinium+GC} - E_{aziridinium} - E_{GC})$. We have presented in Table 1, the values of the interaction energy

Table 1
Values of BSSE corrected interaction energy (ΔE_{int}) (in kcal/mol) between the drug intermediate and the GC base pair and free energy of solvation (ΔG_{sol}) (in kcal/mol) of the drug–GC adduct.

Drug	ΔE_{int} (gas phase)	ΔE_{int} (aq. phase)	ΔG_{sol}
Uracil mustard	−55.7	−25.2	−67.0
Chlorambucil	−49.0	−25.0	−64.9
Phosphoramide mustard	−58.2	−47.1	−70.8
Bendamustine	−43.6	−24.3	−69.8
Spiromustine	−51.3	−20.9	−59.1
Melphalan	−45.0	−35.0	−70.4

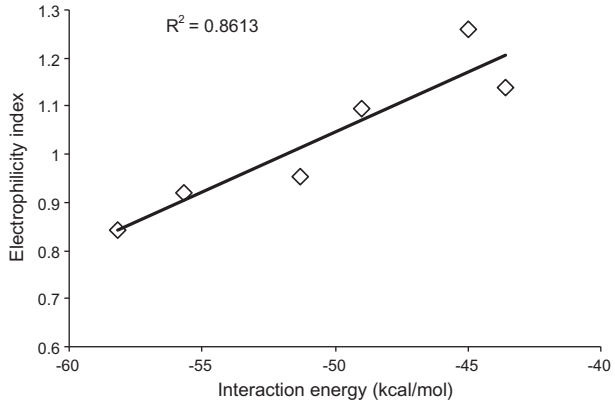


Fig. 7a. Variation of interaction energy with global electrophilicity.

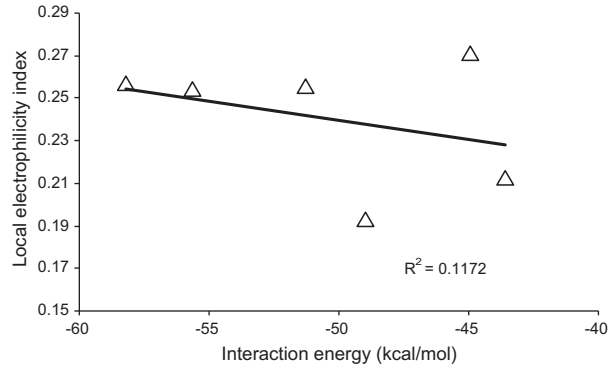


Fig. 7b. Variation of interaction energy with local electrophilicity.

(in kcal/mol) in gas and aqueous phase which includes the basis set super position error (BSSE) corrections. The structure of the supermolecule (GC base pair and the drug intermediate) is shown in Fig. 3, where R-group varies for different drugs.

The interaction energy in gas phase is in the following order: phosphoramide mustard > uracil mustard > spiromustine > chlorambucil > melphalan > bendamustine (Table 1). On the other hand, the trend is quite different in aqueous phase: phosphoramide > melphalan > uracil mustard > chlorambucil > bendamustine > spiromustine (Table 1). Interestingly, the values of interaction energy in gas phase are higher than those in aqueous phase. For instance, the gas phase interaction energy is almost twice of that in aqueous phase except for the phosphoramide mustard. The lower value of interaction energy in aqueous phase may be attributed to the fact that the extent of solvation is different in drug intermediates as well as in the drug–GC adduct, although both possess positive charge.

On analyzing the free energy of solvation for the supermolecule, it is observed that they obey the order: phosphoramide mustard > melphalan > bendamustine > uracil mustard > chlorambucil > spiromustine (Table 1). The value indicates that the drug–GC adduct with melphalan and phosphoramide mustard are more stable in aqueous medium as compared to others.

In addition, we have also tried to find a correlation between the density-based reactivity indices and the calculated interaction energy. A plot of electrophilicity and its local counterpart versus the interaction energy (Figs. 7a and 7b, respectively) reveals that there is a linear dependence on the global parameter of the drug intermediate. However, there is no such concrete relationship with the local electrophilicity. This may be explained due to cooperative effect of all the atoms i.e., the reactivity of all the atoms present in the drug intermediate contribute in some way and hence, there is a correlation between electrophilicity and the complexation energy.

4. Conclusion

In this article, we have studied the variation of the density-based reactivity descriptors on changing the ∠NCC bond angle of the drug intermediate. It can be concluded that the drug intermediate must undergo some structural changes to possess higher reactivity which is essential for the alkylation of DNA. A shifting in maximum hardness is observed on addition of an extra electron to the drug intermediate, thus advocate the opening of tricyclic ring during alkylation of DNA. In addition, gas phase interaction energy of the prototype drug intermediates is found to be higher than that in aqueous phase. A linear dependence of interaction energy on the global parameter of the drug intermediate is also observed.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.comptc.2012.02.015.

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