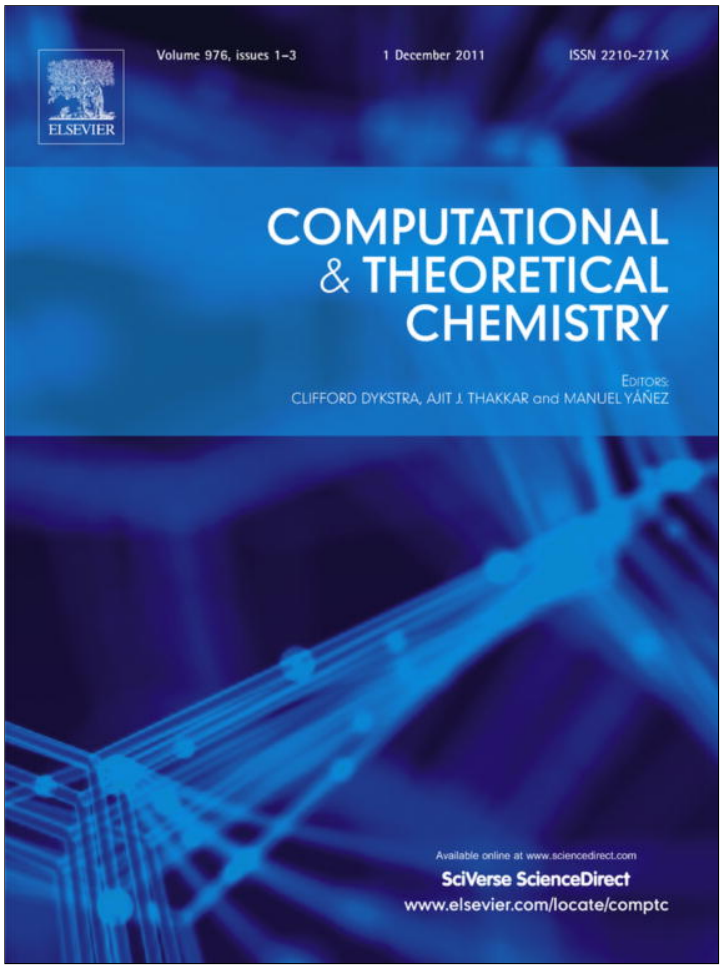

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Affinity of aziridinium ion towards different nucleophiles: A density functional study

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ABSTRACT

We have analyzed the affinity of aziridinium ion intermediate towards different nucleophilic centers using conceptual density functional theory based reactivity descriptors. The aziridinium ion is an unstable species, generated during the alkylation of DNA by nitrogen mustard, a class of bis-alkylating anticancer drug. The intermediate reacts with different nucleophilic (predominately on N7 of guanine in DNA) centers present in the biomolecules. It is expected that the interaction energy of the species with different nucleophiles depends on reactivity descriptors. To observe the interactions in gas phase as well as in aqueous phase we have used density functional theory (DFT) at B3LYP level of theory employing three different basis sets. Same method of calculation was carried out to obtain the DFT based reactivity descriptors.

1. Introduction

Nitrogen mustards are DNA inter-strand cross-linking agents which are being used in cancer chemotherapy for few decades [1,2]. Mustine, a member of nitrogen mustard family, is one of the most heavily employed clinical anti-cancer agents in use these days [3]. Although these bis-alkylating agents have been studied for over a period of five decades, they still provide an area of extremely intense and progressive investigation which perhaps opens a new door to design new drug molecules. Vasilescu and co-workers suggested that the alkylation of the DNA bases is the favoured mechanism of these drugs [4]. During alkylation, each of the chloroethyl side chains of the nitrogen mustard cyclizes spontaneously to form aziridinium ion that binds to DNA covalently resulting a mono-adduct. The mono-adduct can further react with a second DNA strand to afford cross-linked product [5]. The aziridinium ion is an unstable positively charged species that can react easily with nucleophilic centers of cellular molecules, e.g., DNA, RNA, proteins etc. [6]. It was also reported that the alkylation occur preferentially at the endocyclic nitrogen and exocyclic oxygen atoms of the DNA bases [7,8]. In an important work Shukla et al. have used quantum mechanical calculations to observe the interaction of mustine molecule with different DNA bases [9]. The cytotoxic and antitumor activities of nitrogen mustards are mainly associated with their ability to form inter-strand crosslinks in DNA. These were known to block DNA replication and transcription that can lead to cell death and inhibition of tumor growth [10,11]. Quantum chemical calculations validated that out of different nucleophilic sites in DNA bases, N7 position of guanine is the most nucleophilic and was shown to be a highly preferred site over others for alkylation [12]. In addition, the formation of mono- as well as cross-linked product during alkylation, by intra- and inter-strand cross-linking, was well established and the mono-adduct was found to be the major product [13]. Thus the affinity of the aziridinium ion intermediate towards different nucleophilic centers become very much interesting for its cytotoxicity.

The reactivity descriptors, defined within the density functional theory, are chemical potential, global hardness, softness, electrophilicity etc. These descriptors have been 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 systems [14–16]. Geerlings et al. along with Roy and co-workers have reviewed and tested the theoretical basis for these descriptors and their applications [17]. Chattaraj et al. also have recently reviewed the theoretical basis for these descriptors and their applications in various molecular systems [18]. In general, the descriptors are classified as global and local reactivity descriptors. Since most of these descriptors are the derivatives of energy and electron density variables, it is expected that they will provide the modified reactivity information of the molecular systems [19].

In the present work we have studied the affinity of the aziridinium ion intermediate of mustine with different nucleophilic centers (in terms of interaction energy) and observed its dependence on DFT based reactivity descriptors. For the check of simplicity, we have considered small molecules having different nucleophilic centers such as N, O, S and Cl instead of large biomolecules.

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2. Theoretical details of reactivity descriptors

Conceptual density functional theory defines the chemical potential μ as the first derivative of energy with respect to the number of electrons [20]

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{v(\vec{r})} \tag{1}$$

and global hardness (η) [21]

$$\eta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{v(\vec{r})} = \frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right)_{v(\vec{r})} \tag{2}$$

where E is the energy and N is the number of electrons of an electronic system at constant external potential, $v(\vec{r})$. In most numerical applications, chemical potential (μ) and chemical hardness (η) are calculated using finite difference approximation in terms of IP and EA and therefore, μ and η, given below, can be used as working formulae

$$\mu = \frac{-(\mathrm{IP} + \mathrm{EA})}{2} \tag{3}$$

$$\eta = \frac{\mathrm{IP} - \mathrm{EA}}{2} \tag{4}$$

The ΔSCF method defines the above quantities in terms of ionization potential (IP) and electron affinity (EA) of the system [22]

$$\mathrm{IP} = E_{N-1} - E_N \tag{5}$$

$$\mathrm{EA} = E_N - E_{N+1} \tag{6}$$

where E_N, E_{N-1} and E_{N+1} are energies of N, $N-1$ and $N+1$ systems respectively.

Approximations, involving the use of Koopmans' theorem [23] defines the IP and EA in terms of the energies of highest occupied molecular orbital ($\varepsilon_{\mathrm{HOMO}}$) and lowest unoccupied molecular orbital ($\varepsilon_{\mathrm{LUMO}}$) as

$$\mathrm{IP} = -\varepsilon_{\mathrm{HOMO}} \tag{7}$$

$$\mathrm{EA} = -\varepsilon_{\mathrm{LUMO}} \tag{8}$$

and therefore, μ and η can be expressed as

$$\eta = \frac{\varepsilon_{\mathrm{LUMO}} - \varepsilon_{\mathrm{HOMO}}}{2} \tag{9}$$

and

$$\mu = \frac{\varepsilon_{\mathrm{LUMO}} + \varepsilon_{\mathrm{HOMO}}}{2} \tag{10}$$

Parr and his coworkers proposed global electrophilicity (ω) as a measure of electrophilicity of a ligand as [24]

$$\omega = \frac{\mu^2}{2\eta} \tag{11}$$

It is the measure of capacity of a species to accept an arbitrary number of electrons. Recently Chattaraj et al. proposed a more broad and very general local reactivity descriptor, named as philicity, which encompass electrophilic, nucleophilic and radical reactions [25]. Later Roy et al. discussed the limitations of applicability of this index [26]. Earlier Roy et al. proposed two new reactivity descriptors for nucleophilic and electrophilic attacks [27]. Here we have used global electrophilicity index for the purpose.

3. Computational details

The geometrical minima of the species were optimized with 6-31++g(d,p) basis set with Becke three parameter exchange and Lee, Yang and Parr correlation functional, B3LYP [28] and was confirmed by frequency calculations. Additionally, to check the consistency of our results we have performed single point calculations with augmented correlation consistent double zeta valence with polarization function basis set (Aug-cc-pVDZ) [29] and 6-311++g(d,p) basis set using B3LYP functional. The interaction energies (ΔE_{int}) were calculated using supermolecular approach, $[\Delta E_{\mathrm{int}} = (E_{\mathrm{azi\text{-}nu}}) - (E_{\mathrm{azi}} + E_{\mathrm{nu}})]$, where, $E_{\mathrm{azi\text{-}nu}}$ is the energy of the aziridinium ion-nucleophile adduct, E_{azi} is the energy of the aziridinium ion and E_{nu} is the energy of the nucleophile. Recently Bagria et al. proposed an alternative method for calculation of interaction energy which was further applied to Diels–Alder pairs by Pal and co-workers [30].

The global reactivity descriptors (chemical potential, hardness and electrophilicity index) were calculated using Eqs. (3) and (4) (finite difference approximation) and Eqs. (7)–(10) (Koopmans' approximation). Similarly, we have performed calculations in aqueous phase using Polarizable Continuum Model [31]. All calculations have been performed using Gaussian09 [32].

4. Results and discussion

4.1. Interaction energy of the aziridinium ion with different nucleophiles

The aziridinium ion has a tendency to form covalent bond with different nucleophilic centers and it is expected that interaction energy plays an important role in determining the stability of the drug-nucleophile adduct. The structures of the nucleophiles as well as the mono-adducts were optimized without any constraint at B3LYP/6-31++g(d,p) level. Fig. 1 shows the optimized structure of few aziridinium ion-nucleophile mono-adducts. Fig. 1a–d show adducts with four group I nucleophiles and Fig. 1e–h with four group II nucleophiles. In all cases we have observed formation of strong covalent bond between carbon center of the aziridinium ion and nucleophilic center of the nucleophiles (bond lengths between the two centers (r) are shown in the Fig. 1). This bond lengths were found to be shorter in case of group I nucleophile-aziridinium ion adducts compared to group II nucleophile. To check the consistency in results we have carried out single point calculations on the optimized structures at B3LYP/Aug-cc-pVDZ and B3LYP/6-311++g(d,p) level of theories. During its life time, a drug intermediate has to pass through different environments; in one extreme it experiences polar environment (e.g., in blood) and at the other extreme it experiences a non-polar environment (e.g., in cell membrane). Therefore we have performed our calculations in gas phase as well as in aqueous phase. In all cases we have taken care of basis set superposition error (BSSE) using counterpoise correction method. The interaction energies of aziridinium ion with different nucleophiles at different level of theories are summarized in Table 1, (the atom of the nucleophile at which aziridinium ion interact is shown in italics in the table).

Table 1 reveals that in all three level of theories, the interaction energies for group I nucleophiles exceptionally higher in gas phase compared to aqueous phase. Presence of charges on the nucleophiles as well as on the aziridinium ion make them stable in aqueous phase. Thus it becomes easier for these species to remain in unreacted form as a result of which interaction energies fall in aqueous phase. In aqueous phase the interaction energies with group I nucleophiles are in the range −4.51 kcal/mol to −87.48 kcal/mol in B3LYP/6-31++g(d,p) level. Consistency in results are observed with two other level of theories (from −4.75 kcal/mol to −85.68 kcal/mol at B3LYP/Aug-cc-pVDZ and −7.0 kcal/mol to −85.05 kcal/mol at B3LYP/6-311++g(d,p) level). All these three level of theories showed that in aqueous phase,

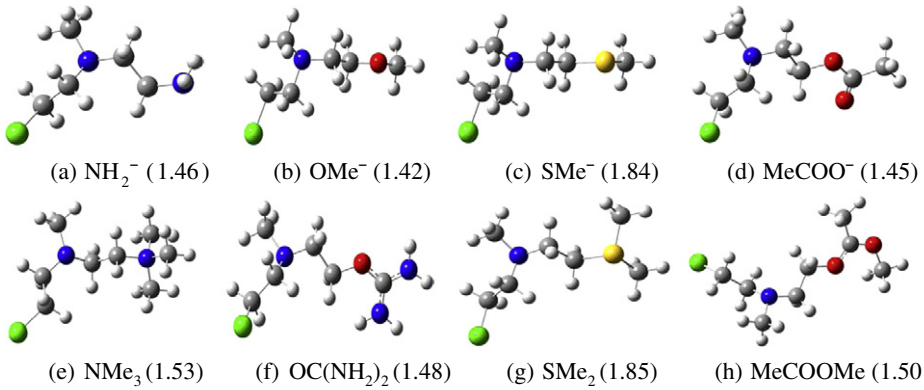

Fig. 1. Optimized structures of few aziridinium ion-nucleophile adduct obtained at B3LYP/6-31++g(d,p) level of theory. The bond lengths '*r*' (in Å) are shown in bracket.

Table 1
Interaction energy (in kcal/mol) of different nucleophiles with aziridinium ion at three different level of theories in gas and aqueous phase.

Nucleophile	Interaction energy (in kcal/mol)					
	In gas phase			In aqueous phase		
	B3LYP/6-31++g(d,p)	B3LYP/Aug-cc-pVDZ	B3LYP/6-311++g(d,p)	B3LYP/6-31++g(d,p)	B3LYP/Aug-cc-pVDZ	B3LYP/6-311++g(d,p)
Group I nucleophiles						
Cl^-	−125.89	−126.20	−126.65	−4.51	−4.75	−7.00
NH_2^-	−198.42	−197.84	−198.87	−78.42	−77.38	−73.08
$NHMe^-$	−200.60	−200.09	−200.83	−85.27	−82.85	−80.91
NMe_2^-	−197.18	−195.67	−197.11	−87.48	−85.68	−85.05
OH^-	−180.75	−180.65	−181.17	−52.61	−51.98	−49.81
OMe^-	−177.16	−176.98	−177.29	−58.30	−57.11	−56.82
SH^-	−146.63	−146.33	−147.40	−32.57	−31.96	−24.56
SMe^-	−155.65	−154.75	−156.13	−39.16	−38.44	−20.24
$MeCOO^-$	−141.20	−141.52	−141.33	−26.34	−26.40	−40.59
$HCOO^-$	−137.15	−137.43	−137.45	−34.30	−34.30	−30.81
Group II nucleophiles						
MeCOOMe	−0.45	−0.84	0.02	9.02	8.04	8.38
NH_3	−12.27	−12.37	−12.58	−23.09	−23.94	−19.39
$NHMe_2$	−24.56	−24.67	−24.80	−24.02	−24.10	−22.85
NMe_3	−26.28	−26.18	−26.43	−20.87	−20.60	−22.68
$OC(NH_2)_2$	−41.58	−44.56	−40.93	−36.31	−37.05	−27.03
$OCHNH_2$	−22.35	−21.98	−21.77	−22.75	−23.37	−15.34
$OCMe_2$	−2.02	−1.60	−1.57	6.80	6.78	1.57
$OCMeNH_2$	−26.34	−25.70	−24.69	−21.39	−21.37	−15.69
SHMe	−0.96	−0.49	−0.49	−1.71	−1.31	−1.70
SMe_2	−13.04	−12.35	−12.57	−7.24	−6.83	−8.39

nucleophiles with N center exhibit highest interaction energies and the least is shown by Cl^-. The order of interaction energies is found to be N center > O center > S center > Cl^- center with an exception in case of oxygen center in carboxylic group which shows low interaction energy due to delocalization of the charge over the $-COO^-$ group. In aqueous phase, nucleophiles with N center exhibit the order NMe_2^- > $NHMe^-$ > NH_2^-. The higher affinity of the nucleophiles with N center suggested that the aziridinium ion might attack different nitrogen center (preferentially tertiary N centers) present in DNA, RNA and in different protein molecules. The chloride nucleophile shows exceptionally low affinity towards the aziridinium ion and it clarify why the mustine molecule form aziridinium ion in solvent by release of Cl^- ion. It is important to note that none of the negatively charged nucleophiles show positive interaction energies (repulsive interaction) in gas phase or in aqueous phase.

Within body cells, except in few cases (Cl^-, OH^- etc.) we do not find nucleophiles with negative charges. Therefore we have modeled few nucleophiles, bearing no negative charge (group II, Table 1) and observed the interaction energies in both gas phase and aqueous phase using same level of theories. The interaction energies of the aziridinium ion with group II nucleophiles (bearing no negative charge) are shown in Table 1. It is observed that most of the nucleophiles show significant amount of interaction with the aziridinium ion in gas phase as well as in solvent phase and few of them show repulsive interaction (positive interaction energy). In solvent phase, the oxygen center of the >CO group in MeCOOMe and $OCMe_2$ show repulsive interaction. On the other hand, nucleophiles with nitrogen center show strong interactions in both phases. All three nucleophiles with N center show comparable interaction energies in both phases. In case of nucleophiles with oxygen center in $OC(NH_2)_2$ shows strongest interaction with aziridinium ion in both gas as well as in solvent phase. Replacement of NH_2 group by Methyl group (in $OCNH_2Me$ and $OCMe_2$) lowers the interaction energy in both phases. Nucleophile with sulfur center shows weak interaction with the aziridinium ion in both phases. In the case of group II nucleophiles, we have not observed abrupt variation in interaction energy as we move from gas to aqueous phase.

In aqueous phase different nucleophiles as well as the aziridinium ion might undergo extensive solvation and thus it is expected that interaction energy depends on solvent and the presence of hydrophobic or hydrophilic groups in the nucleophiles.

Table 2
HOMO energy, hardness, chemical potential and philicity of different nucleophiles (in kcal/mol) at B3LYP/6-31++g(d,p) level of theory in gas phase and aqueous phase.

Nucleophile	In gas phase				In aqueous phase			
	HOMO	Hardness	Chemical potential	Philicity	HOMO	Hardness	Chemical potential	Philicity
Group I								
Cl^-	−17.73	76.82	59.09	22.73	−161.31	89.29	−72.02	29.04
NH_2^-	42.66	26.20	68.87	90.50	−98.65	48.91	−49.74	25.30
*N*HMe−	44.51	16.66	61.17	112.29	−83.05	41.70	−41.35	20.50
NMe_2^-	36.09	18.57	54.66	80.44	−71.77	35.44	−36.33	18.62
OH^-	29.30	37.98	67.28	59.60	−129.27	65.87	−63.41	30.52
OMe^-	21.44	29.31	50.75	43.94	−109.14	54.98	−54.15	26.66
SH^-	3.621	43.68	47.30	25.61	−123.89	62.85	−61.04	29.64
SMe^-	11.28	31.74	43.03	29.16	−116.39	58.07	−58.32	29.29
$MeCOO^-$	−21.73	47.12	25.39	6.84	−148.41	74.22	−74.18	37.07
$HCOO^-$	−23.42	55.77	32.34	9.38	−151.37	80.47	−70.90	31.23
Group II								
MeCOOMe	−179.43	86.85	−92.58	49.34	−187.74	90.34	−97.40	52.50
NH_3	−168.32	78.83	−89.49	50.79	−168.08	81.51	−86.56	45.96
$NHMe_2$	−141.09	67.66	−73.43	39.84	−142.36	69.44	−72.92	38.28
NMe_3	−136.12	65.02	−71.10	38.88	−138.22	66.66	−71.56	38.41
$OC(NH_2)_2$	−167.12	70.30	−96.82	66.67	−163.55	70.65	−92.89	61.07
$OCHNH_2$	−176.13	70.61	−105.52	78.84	−173.61	71.38	−102.24	73.22
$OCMe_2$	−161.82	71.66	−90.16	56.72	−168.93	73.28	−95.65	62.42
$OCMeNH_2$	−165.76	71.57	−94.19	61.99	−166.75	72.15	−94.60	62.02
SHMe	−151.94	69.93	−82.00	48.08	−153.72	73.18	−80.54	44.32
SMe_2	−138.79	66.24	−72.55	39.74	−145.16	70.81	−74.36	39.04

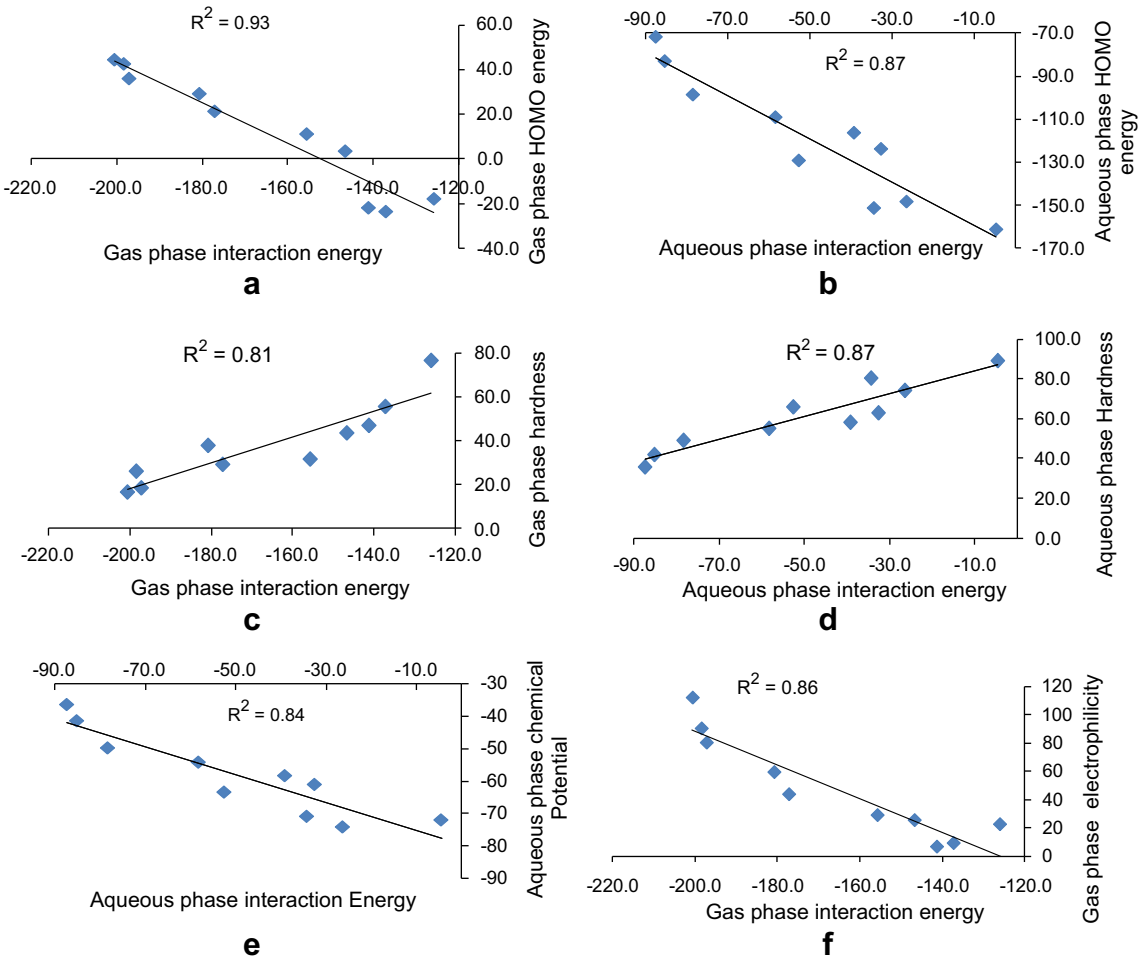

Fig. 2. Variation of interaction energy with HOMO energy, global hardness, chemical potential and global electrophilicity of group I nucleophiles at B3LYP/6-31++g(d,p) level of theory in gas and aqueous phase (all parameters are in kcal/mol).

4.2. Reactivity descriptors of the nucleophiles

The reactivity of a nucleophile is expected to play an important role during its interaction with the aziridinium ion and hence we have calculated the reactivity in terms of global hardness, chemical potential and global electrophilicity. The values of HOMO energy and the reactivity descriptors calculated using Koopmans' approximation in gas and aqueous phases are presented in Table 2.

It is observed that most of the group I nucleophiles show positive values of HOMO (hence unstable) which facilitated electron donation to the aziridinium ion resulting exceptionally high interaction energy in gas phase. Presence of aqueous phase leads to stabilization of the HOMO (more negative values) and as a result interaction energy decreases. Group II nucleophiles show negative HOMO energies in gas as well as in aqueous phase and hence lead to low interaction energies in both phases.

Hardness of group I and II nucleophiles in both phases are found to be comparable but little higher values are observed in aqueous phase compared to gas phase. The gas phase and aqueous phase hardness values show almost same order. The aqueous phase hardness of the nucleophiles is in order $Cl^- > HCOO^- > MeCOO^- > OH^- > SH^- > SMe^- > OMe^- > NH_2^- > NHMe^- > NMe_2^-$ and $MeCOOMe > NH_3 > OCMe_2 > SHMe > OCMeNH_2 > OCHNH_2 > SMe_2 > OC(NH_2) > NHMe_2 > NMe_3$. These values indicate the stability of the nucleophiles in aqueous phase compared to gas phase.

Chemical potential values revealed instability of the group I nucleophiles in gas phase (positive values). On the other hand in aqueous phase all nucleophiles are found to be stable; group II nucleophiles are found to be more stable compared to the group I nucleophiles. These values supported low interaction energies exhibit by group II nucleophiles. electrophilicity values indicate that the group I nucleophiles behave as good nucleophiles (less electrophilic) in aqueous phase, but reverse is the case in gas phase. In case of group I nucleophiles, abrupt variation on moving from gas to solvent phase is observed. On the other hand, in case of group II nucleophiles such a variation is not observed.

4.3. Plots of interaction energy vs. reactivity descriptors

We have observed how the interaction energy varies with reactivity descriptors (derived using Koopmans' approximation) of the nucleophiles. It is seen that group I nucleophiles exhibit some linear relationship between the reactivity descriptors and interaction energies, but group II nucleophiles do not exhibit such relationships. Fig. 2 shows the variation of interaction energy of group I nucleophiles with different reactivity descriptors at B3LYP/6-31++g(d,p) level of theory in gas and aqueous phase.

Fig. 2a and b shows a good linear relationship between the two parameters (with $R^2 = 0.93$ in gas phase and $R^2 = 0.87$ in aqueous phase). It is observed that as HOMO energy decreases (more negative), interaction energy decreases. This is obvious, as the HOMO drops, the electron donating capacity of the nucleophiles decreases and as a result interaction energy decreases. Fig. 2c and d shows the variation of interaction energy with hardness of the nucleophiles in gas phase as well as in aqueous phase. Here also we have observed a linear relationship (with $R^2 = 0.81$ in gas phase and $R^2 = 0.87$ in aqueous phase) between the two parameters. It is observed that as hardness decreases, interaction energy increases. In case of chemical potential, (Fig. 2e) we have observed good linear relationship in aqueous phase and in case of electrophilicity, (Fig. 2f) same linear relationship is observed in gas phase. We have also calculated the same reactivity descriptors using ΔSCF method (Eqs. (5) and (6)). The results obtained by this method showed poor correlations (low R^2 values) compared to the method using Koopmans' approximation.

5. Conclusion

We have made an effort to examine the interaction energy of different nucleophilic centers with aziridinium ion in gas phase as well as in aqueous phase using supermolecular approach and DFT based reactivity descriptors at three different levels of theory. It is observed that the negatively charged nucleophiles show higher interaction energies over the neutral nucleophiles. The aqueous phase interaction energies are lower than the gas phase one and in almost all cases interaction energies are found to be negative. Both gas phase as well as aqueous phase calculations indicate that the drug intermediate might interact with different nucleophilic centers (preferentially at N centers) in biomolecules. Apart from this, we have studied the reactivity of the nucleophiles in terms of the density based reactivity descriptors which supported the observed trend in interaction energy.

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