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Alkylation of DNA by nitrogen mustards: A DFT study

Babul Neog, Sourab Sinha, Pradip Kr. Bhattacharyya *

Department of Chemistry, Arya Vidyapeeth College, Gopinath Nagar, Guwahati, Assam 781 016, India

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ABSTRACT

Reactivity of aziridinium ion and mono- as well as cross-linked adducts formed during alkylation of DNA (GC base pair) by nitrogen mustards were analysed, using density functional theory (DFT). DFT based global- and local reactivity descriptors were used to compare reactivity of the aziridinium ion intermediates and mono-adducts. Our results witnessed the inability of global reactivity parameters to explain higher reactivity of mustine. Out of the chosen set of seven drug molecules, propensity of cross-linked adduct formation by uracil mustard was observed to be highest compared to other family members. Electrophilic Fukui function was found to be useful in explaining the local reactivity pattern. Gibbs free energy of solvation for the second aziridinium ions were observed to be higher compared to that of the first aziridinium ions.

1. Introduction

Bis-alkylating nitrogen mustards are a versatile class of chemotherapeutic agents used for treatment of different types of cancers like chronic leukemia, breast, lung and ovarian cancer [1,2]. Mustine, the smallest member of the family, was the first effective clinically employed drug, still in use [3,4]. Other members of the family are melphalan [5,6], chlorambucil [7,8], bendamustine [9], phosphoramide mustard [10], uracil mustard [11], spiromustine [12], etc., Fig. 1. During alkylation, one of the chloroethyl side chains of the nitrogen mustard (A) cyclises to form the aziridinium ion (B, Az_1^+) that binds to DNA covalently, resulting in a mono-adduct (C). The mono-adduct further cyclises to form the second aziridinium ion (D, Az_2^{2+}) that reacts with a second DNA strand and afford to form a cross-linked adduct (E), Fig. 2 [13–15]. Formation of mono- and cross-linked adducts by inter- and intra-strand cross-linking leads to cell death. Preferential alkylation at the endocyclic nitrogen and exocyclic oxygen atoms of the DNA bases has already been established; out of different nucleophilic centres, N7 of guanine is the most nucleophilic site and hence is more prone to alkylation [16,17].

Mustine is highly reactive and prone to hydrolysis; it also reacts immediately with the nucleophilic centres in biomolecules. Because of its high affinity towards water, it is marketed as a dry solid and when required, its aqueous solution is prepared just prior to injection. Therefore, more stable analogues were sought. Substitution of the methyl group on the N-atom (of mustine) by aryl conjugate groups make it less nucleophilic, and slows down the rate of Az^+ ion formation [18] and in turn decreases the reactivity of the nitrogen mustard. Because of such stabilization, some of the drugs can be administered orally. A number of such drugs have been synthesised and their cytotoxicity has been tested in the last few decades [19–21].

Understanding the reactivity of Az^+ ions/drug-guanine adducts thus became crucial for designing new potent anticancer drugs. Previous works mostly laid emphasis on the activation energy and related thermodynamic aspects of the reaction [13,22,23]. Study of the reaction in terms of kinetic aspects also bear importance, and may prove to be fruitful in understanding the mechanistic intricacies of the pathway. Polavarapu et al. showed that Az^+ ion of mustine is more stable ($\Delta G = -2.52$ kcal/mol) compared to the corresponding drug molecule, whereas reverse was the case in melphalan and chlorambucil [22]; thus, studying the reactivity of the Az^+ ions bear commensurate importance. Moreover, interaction energy (between Az^+ ion and guanine) as well as global and local reactivity of the species are important to get insight into their chemical reactivity. In our present investigation, we endeavour to explain the DFT based local and global reactivity of the Az^+ ion and mono-/cross-linked adducts formed by a few nitrogen mustards.

Earlier, Shukla et al. performed a quantum mechanical study on the reaction between different DNA bases and mustine [13]. They calculated energy barrier for the reactions at different sites of DNA bases and was observed to lie in the range −15 to −24 kcal/mol. However, compared to mustine, a higher energy barrier during mono-adduct formation has been observed in case of melphalan and chlorambucil [22]. Mann from his explicit study on the formation of Az^+ ion of nitrogen mustards using ab initio

* Corrsponding author. Tel.: +91 9864087494.
E-mail addresses: Sourabsinha39@gmail.com (S. Sinha), prdpbhatta@yahoo.com (P.Kr. Bhattacharyya).
URL: http://pkb-chem.co.in (P.Kr. Bhattacharyya).

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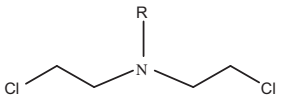


Nitrogen mustard

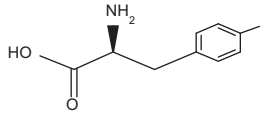
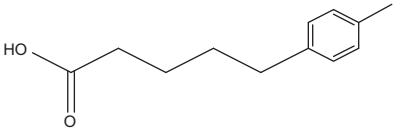
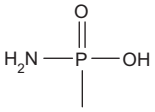
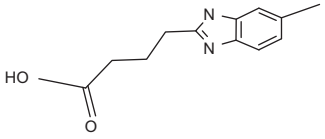
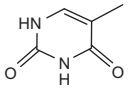
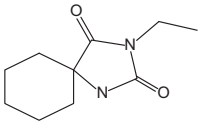
Entry no.	R=	DRUG (dipole moment)
1	-CH_3	Mustine (1.95)
2		Melphalan (2.01)
3		Chlorambucil (2.33)
4		Phosphoramide mustard (2.63)
5		Bendamustine (3.94)
6		Uracil mustard (4.42)
7		Spiromustine (4.97)

Fig. 1. Structure of few clinically used bis-alkylating drug molecules (arranged according to increasing dipole moment (in Debye)).

dynamics confirmed a concerted nucleophilic displacement reaction involving simultaneous dissociation of the C–Cl bond and internal cyclisation of the Az^+ ring [23]. Several independent research groups performed studies on drug–DNA adducts and confirmed that alkylation of DNA bases is the favoured mechanism for this class of drugs [24–27].

Density functional theory (DFT) based reactivity descriptors play a fundamental role in explaining and understanding the basic characteristics of a vast range of problems of chemical interest, and in rationalising the reactivity patterns of diverse molecular systems [28,29]. In general, these descriptors are classified as global reactivity descriptors (GRDs) and local reactivity descriptors (LRDs). Fukui function, local softness, local philicity, etc. are examples of local reactivity descriptors. Similarly, global reactivity descriptors such as chemical hardness, and global electrophilicity are utilized to study the reactivity trends in molecules [30,31].

2. Theoretical details of reactivity descriptors

In DFT, chemical potential (μ) is defined as the first derivative of energy with respect to the number of electrons [32]:

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

and global hardness (η) [33,34] as:

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

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 of the applications, chemical potential (μ) and global hardness (η) are calculated using finite difference approximation [35] in terms of IP and EA, which leads to the working formulae-

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

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

global softness (S) is defined as:

$$S = \frac{1}{2\eta} \tag{5}$$

Use of Koopmans' theorem [36] defines the IP and EA in terms of energies of the highest occupied molecular orbital (ε_{HOMO}) and of the lowest unoccupied molecular orbital (ε_{LUMO}) as:

$$\mathrm{IP} = -\varepsilon_{HOMO} \tag{6}$$

$$\mathrm{EA} = -\varepsilon_{LUMO} \tag{7}$$

Therefore, μ and η can be expressed as:

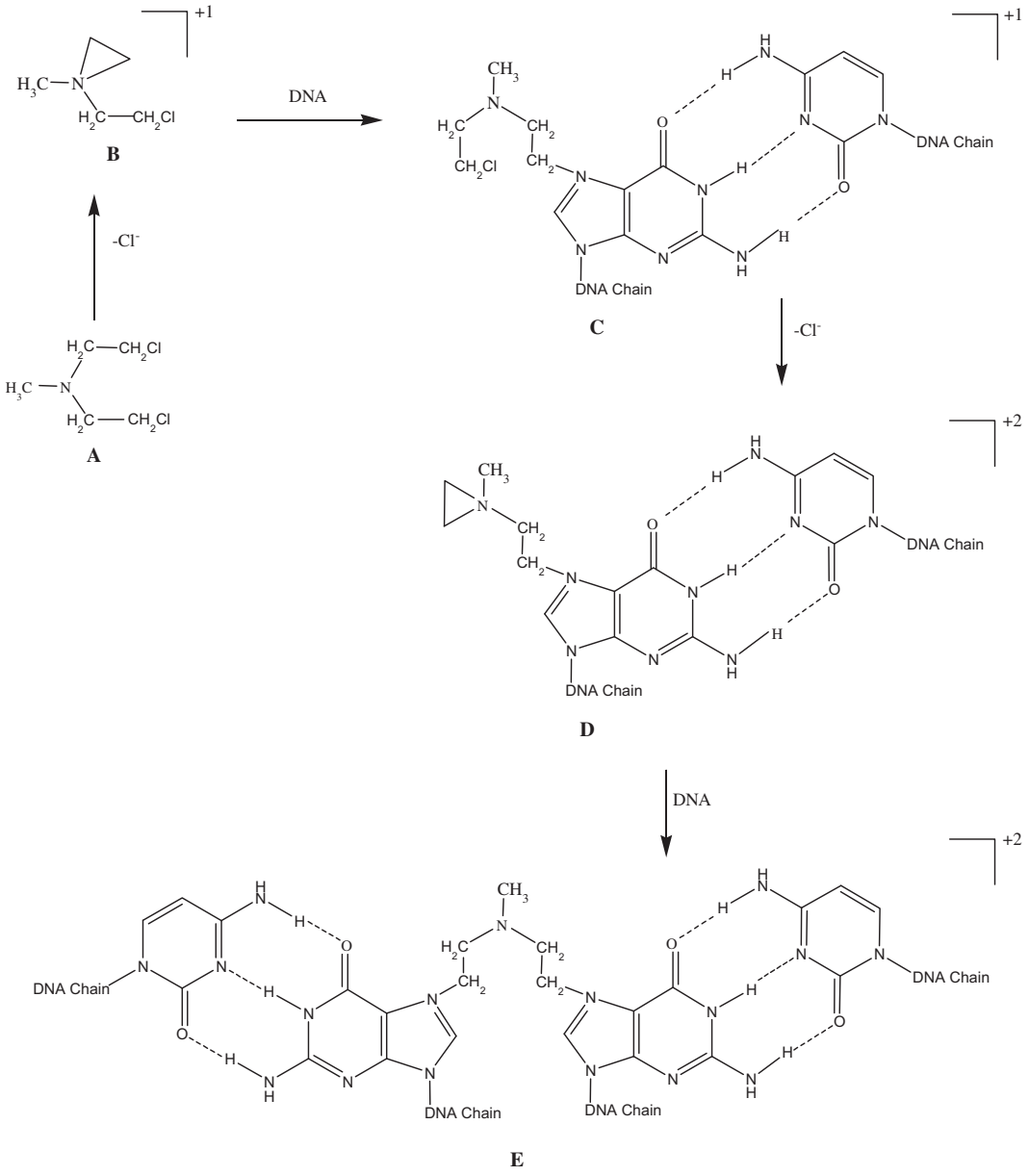


Fig. 2. Mechanism of alkylation of DNA by bisalkylating nitrogen mustard.

$$\eta = \frac{\varepsilon_{LUMO} - \varepsilon_{HOMO}}{2} \tag{8}$$

and

$$\mu = \frac{\varepsilon_{LUMO} + \varepsilon_{HOMO}}{2} \tag{9}$$

Parr and co-workers proposed global electrophilicity (ω) as a measure of electrophilicity of a molecule [37] as:

$$\omega = \frac{\mu^2}{2\eta} \tag{10}$$

It is the measure of the capacity of a species to accept an arbitrary number of electrons. Chattaraj et al. [38] also proposed a generalised concept of philicity containing electrophilic, nucleophilic and radical reactions. The condensed-to-atom variant for the atomic site k in a molecule is written as:

$$\omega_k^{\alpha} = f_k^{\alpha}\omega; \quad \alpha = +, -, 0 \tag{11}$$

where α = +, − and 0 refer to nucleophilic, electrophilic and radical attacks respectively and f_k^{α} is the Fukui function of atom k. Here we have considered, $\omega_k^{+} = f_k^{+}\omega$, f_k^{+} is the electrophilic Fukui function.

Condensed Fukui function (CFF) for an atomic site 'k' in a molecule with N electrons in a constant external potential, $v(\vec{r})$ can be obtained from finite difference approximation as:

$$f_k^{+} = [\rho_k(N_0 + 1) - \rho_k(N_0)], \quad \text{for nucleophilic attack} \tag{12}$$

where $\rho_k(N_0)$ and $\rho_k(N_0 + 1)$ are electronic population on atom k of the molecule, with N_0 and N_0 + 1 electron-systems respectively.

Another important local descriptor is the local softness (s), defined as:

$$s = Sf_k^{+} \tag{13}$$

where S is the global softness.

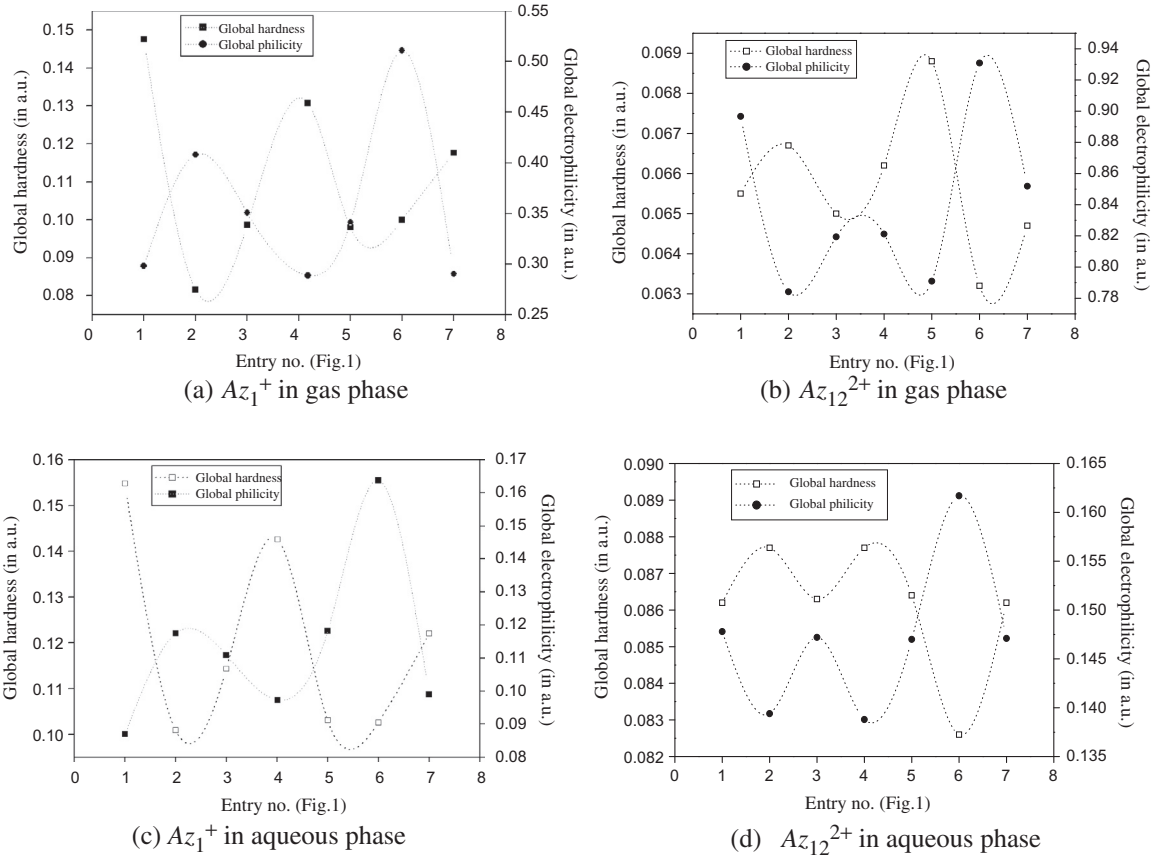


Fig. 3. Global hardness (η) and global electrophilicity (ω) of Az_1^+ and Az_2^{2+} ions in gas and aqueous phases at 6-31+G(d) level of theory (lines connecting the points do not represent any average).

Table 1
CFF, local softness and local electrophilicity of first and second aziridinium ions at B3LYP/6-31+G(d) level of theory in gas and aqueous phase (given in bracket).

Drug molecule	f_1^+	f_2^+	s_1	s_2	ω_1^+	ω_2^+
Mustine	0.2162(0.1413)	0.0358 (0.0133)	0.0159(0.0756)	0.0011(0.0057)	0.0643(0.0387)	0.0321(0.0196)
Melphalan	0.0991 (0.0502)	0.0356 (0.0081)	0.0040(0.0025)	0.0011(0.0003)	0.0404(0.0058)	0.0278(0.0010)
Chlorambucil	0.1102 (0.0423)	0.0293 (0.0122)	0.0054(0.0024)	0.0010(0.0005)	0.0385(0.0046)	0.0240(0.0017)
Bendamustine	0.0621 (0.0362)	0.0286 (0.0123)	0.0030(0.0018)	0.0009(0.0005)	0.0210(0.0043)	0.0226(0.0018)
Phosphoramide mustard	0.0802 (0.0613)	0.0375 (0.0083)	0.0052(0.0043)	0.0012(0.0003)	0.0277(0.0065)	0.0308(0.0011)
Uracil mustard	0.0653 (0.0472)	0.0415 (0.0402)	0.0032(0.0024)	0.0013(0.0016)	0.0334(0.0077)	0.0385(0.0064)
Spiromustine	0.1422 (0.0251)	0.0319 (0.0121)	0.0083(0.0015)	0.0010(0.0005)	0.0413(0.0024)	0.0272(0.0018)

3. Computational details

The geometrical minima of the species were obtained using 6-31+G(d) basis set, with Becke three-parameter exchange and Lee, Yang and Parr correlation functional, B3LYP, and was confirmed by frequency calculations. Additionally, to check the consistency of our results, we performed single point calculations with a triple zeta basis set 6-311++G(d,p), using the same functional. Interaction energies (ΔE_{int}) were calculated using super molecular approach [for A + B → AB, $\Delta E_{int} = (E_{AB}) - (E_A + E_B)$, where E is the total energy of the corresponding species]. For the sake of simplicity, only the guanine–cytosine base pair has been considered (of the whole DNA fragment), and we replaced the glycosidic linkage by a methyl group. Global reactivity descriptors (global hardness, chemical potential and global electrophilicity) were calculated using Eqs. (8)–(10). Local philicity, CFF (using Hirshfeld charges) and local softness were evaluated using Eqs. (11)–(13). Similarly, we also performed our calculations in aqueous phase using Polarizable Continuum Model [39]. The free energy of solvation (ΔG_{sol}) of the species was computed using SMD solvation model proposed by Truhlar and coworkers [40]. All calculations were performed using Gaussian09 [41].

4. Results and discussion

4.1. Reactivity of aziridinium ions: global perspective

Efficiency of global hardness (η) and global electrophilicity (ω) to explain the overall stability of a system has been well acknowledged by several research groups [28,29,42]. Consequently, we have calculated the two descriptors (η and ω) for Az_1^+ and Az_2^{2+} ions in gas and aqueous phase at B3LYP/6-31+G(d) level of theory, Fig. 3. Gas phase global hardness of Az_1^+ ion follows the order: mustine > phosphoramide mustard > spiromustine > uracil mustard > bendamustine > chlorambucil > melphalan. However, in aqueous phase this trend changes to: mustine > phosphoramide mustard > spiromustine > chlorambucil > uracil mustard > melphalan > bendamustine. Above trend indicates that the effect

exerted by aqueous phase on different species is not uniform. Interestingly, hardness order in case of Az_2^{2+} ions is different from that of Az_1^+ ions. Mustine forms the most stable Az_1^+ ion in both phases (of maximum hardness, according to maximum hardness principle [43,44]), where as in case of Az_2^{2+} ion, highest hardness values are displayed by bendamustine and phosphoramide in gas and in aqueous phases respectively. It is noteworthy to mention that, in all cases, the reactivity pattern follows the maximum hardness principle (MHP) and the minimum electrophilicity principle (MEP). Corresponding Az_2^{2+} ions of the drug molecules are observed to be less stable, compared to Az_1^+ ions, Fig 3. Thus, an obvious expectation is that the Az_2^{2+} ions would react with DNA at an ease compared to Az_1^+ ions. We observed similar trends at B3LYP/6-311++G(d,p) level of theory (Supplement Table 1). Maximum hardness (and hence the maximum stability) of Az_1^+ ion of mustine is in striking contrast to its high reactivity. So, global parameters are not sufficient to explain the reactivity pattern of the drug molecules. Reactivity of a species depends on its reactive centre, and it is anticipated that some local parameters might be helpful in understanding the alkylation reaction. To investigate the local reactivity pattern, some local parameters of the electrophilic carbon (C) centres, in Az_1^+ and Az_2^{2+} ions of the corresponding drug molecules have been calculated.

4.2. Reactivity of aziridinium ions: the local perspective

Condensed Fukui function (CFF) is one of the most widely used local reactivity descriptor; f_k^+ (for 'k' site) is the best choice for a nucleophilic attack [45,46]. Calculated values of CFF (f_1^+ for Az_1^+ and f_2^+ for Az_2^{2+}) at the C-centre(s) for different drug molecules at B3LYP/6-31+G(d) level of theory in gas as well as in aqueous phase are presented in Table 1. Interestingly, f_1^+ gas phase trend at B3LYP/6-31+G(d) level is observed to be: mustine > spiromustine > chlorambucil > melphalan > phosphoramide mustard > uracil mustard > bendamustine; the aqueous phase trend is somewhat different and follows the order: mustine > phosphoramide mustard > melphalan > uracil mustard > chlorambucil > bendamustine > spiromustine; it may be due to different extents of solvation for different Az^+ ions. Usually, it is expected that the extent of solvation shall depend on the dipole moment. However, in this case, we observed no linear relationship between solvation energy and dipole moment of the corresponding species, (Supplement Fig. 1). Similar trends are observed at B3LYP/6-311++G(d,p) level of theory, (Supplement Table 2). It is important to mention that among the drug molecules, the C-centres in Az_1^+ ring of mustine exhibit highest reactivity, confirming reduction of reactivity by conjugation of aromatic groups at the N-centre in mustine, as proposed earlier [24]. However, the reactivity trend among the Az_2^{2+} ions is different from that of Az_1^+ ions, and is observed to be: uracil mustard > phosphoramide mustard > mustine > melphalan > spiromustine > chlorambucil > bendamustine in gas phase and uracil mustard > mustine > chlorambucil ≈ bendamustine ≈ spiromustine > phosphoramide mustard > melphalan, in aqueous phase. Results obtained reflect the higher tendency of uracil mustard to form cross-linked adducts and is consistent with the experimental findings by Mattes et al. who observed that, compared to other mustards, uracil mustard greatly enhances the reactivity with guanine in 5′-TGCC-3′ sequence [47]. Cross-linked adduct formation is of utmost importance for these drug molecules to exert their cytotoxicity, and hence reactivity of Az_2^{2+} ions is crucial for these drug molecules.

Another remarkable observation is that, reactivity of Az_2^{2+} ions is lower compared to that of Az_1^+ ions. The ratio f_1^+/f_2^+ lies in the range 1.5–6.0 in gas phase, and 1.2–10.6 in aqueous phase, indicating high reactivity of Az_1^+ ions. Thus, we expect that formation of mono-adduct would be much easier compared to cross-linked adduct. Local softness of C-centres (s_1 for Az_1^+ ions and s_2 for Az_2^{2+} ions) of the Az^+ ions also shows the similar trends, in both phases as CFF (Table 1). Similarly, local philicities, ω_1^+ and ω_2^+ agrees well with CFF trends (Table 1). All the three local parameters suggest that the Az_1^+ ion of mustine exhibit maximum reactivity towards nucleophilic attack, in gas as well as in aqueous phase. However, in case of Az_2^{2+} ions, uracil mustard shows the highest reactivity. We observed a similar trend at B3LYP/6-311++G(d,p) level of theory (Supplement Table 2).

4.3. Gibbs free energy of solvation of Az_1^+ and Az_2^{2+}

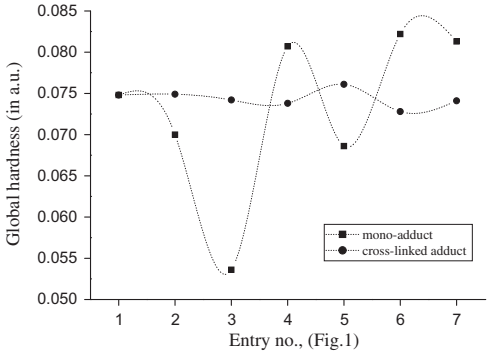
In solvent phase, stability of a chemical species is governed by solvation, and ΔG_{sol} (Gibbs free energy of solvation using SMD model) is a widely used scale to observe stability of a species in a particular solvent medium [48–50]. ΔG_{sol} values in aqueous phase for Az_1^+ and Az_2^{2+} ions were observed at the two levels of theory. It is interesting to note that for Az_1^+ ions, ΔG_{sol} at B3LYP/6-31+G(d) level follows the order: uracil mustard (−74.02) > melphalan (−69.23) > phosphoramide mustard (−67.01) > bendamustine (−66.08) > spiromustine (−64.33) > chlorambucil (−61.29) > mustine (−61.22). For Az_2^{2+}, the order is found to be: uracil mustard (−166.31) > phosphoramide mustard (−161.16) > mustine (−156.88) > melphalan (−156.11) > bendamustine (−155.95) > spiromustine (−154.39) > chlorambucil (−154.12), (values in kcal/mol are shown in bracket). It is seen that, both Az_1^+ and Az_2^{2+} ions of uracil mustard are well stabilized in aqueous phase; Az_1^+ ion of mustine is the least stabilized in aqueous phase. This facilitates Az_1^+ ions of mustine to react instantly with nucleophilic centres. Our observation is consistent with earlier findings [13,14,24]. Higher ΔG_{sol} values of Az_2^{2+} ions are attributed to high charges (+2), they carry and a high value of ΔG_{sol} make Az_2^{2+} ions more stable thereby preventing the formation of cross-linked adducts. Unexpectedly, ΔG_{sol} does not show any linear relationship with dipole moment of the respective species (Supplement Fig. 1). Calculations at B3LYP/6-311++G(d,p) level of attested the results observed at B3LYP/6-31+G(d) level of theory (Supplement Table 3).

4.4. Interaction energy and free energy of solvation of mono- and cross-linked adducts

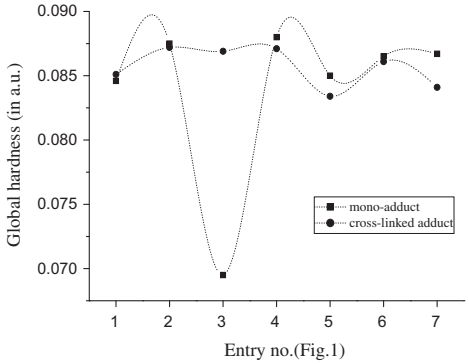
Although many experimental works comprising the interaction of drug molecules with the guanine residue of DNA has been successfully done [15–17], only few quantified results presuming the

Table 2
Interaction energies (in kcal/mol) of mono and cross-linked adducts in gas and aqueous phases (within bracket) at B3LYP/6-31+G(d) level of theory.

Drug molecule	$\Delta E_{int\text{-}mono}$	ΔG_{sol}	$\Delta E_{int\text{-}cross}$	ΔG_{sol}
Mustine	−46.83 (−21.11)	−57.73	−62.39 (−21.43)	−138.32
Melphalan	−47.86 (−23.96)	−66.48	−64.67 (−27.12)	−140.58
Chlorambucil	−48.74 (−29.41)	−63.88	−61.07 (−27.49)	−141.90
Bendamustine	−43.54 (−24.37)	−69.49	−60.74 (−26.73)	−141.56
Phosphoramide mustard	−57.89 (−37.55)	−69.79	−79.17 (−38.99)	−141.76
Uracil mustard	−55.61 (−26.94)	−66.32	−71.61 (−30.14)	−146.29
Spiromustine	−51.27 (−25.72)	−59.12	−68.69 (−29.40)	−134.04



(a) Hardness of mono- and cross-linked adduct in gas phase



(b) Hardness of mono- and cross-linked adduct in aqueous phase

Fig. 4. Global hardness of mono-and cross-linked adduct in gas and aqueous phases at B3LYP/6-31+G(d) level of theory.

interaction energies has been reported [13,22]. Interaction energy happens to be of cardinal importance for a drug molecule. Hence, we have analysed interaction energy between the drug molecules and GC base pairs, in mono- as well as in cross-linked adducts, using super molecular approach. Interaction energies in mono- and cross-linked adducts in gas and aqueous phases, along with ΔG_{sol} in aqueous phase at B3LYP/6-31+G(d) level are summarised in Table 2.

It is apparent from the results that, among the chosen set of drug molecules, phosphoramide mustard shows maximum interaction energy, in case of mono- as well as cross-linked adduct in gas and aqueous phases. Moreover, it is worth mentioning that the aqueous phase interaction energies are comparatively less than the gas phase values, and this is due to extensive solvation in the aqueous phase. Another important inference that can be made from the results is that, the interaction energies in cross-linked adducts are not double than that in mono-adducts, as is usually expected. This also suggests lower probability for formation of cross-linked adduct compared to mono-adducts. We found consistent results with B3LYP/6-311++G(d,p) level of theory (Supplement Table 4).

The observed trend of ΔG_{sol} in case of mono-adducts is: phosphoramide mustard > bendamustine > melphalan > uracil mustard > chlorambucil > spiromustine > mustine and in case of cross-linked adducts, this trend changes to: uracil mustard > chlorambucil > phosphoramide mustard > bendamustine > melphalan > mustine > spiromustine. Results inferred that, in aqueous phase, among the drug molecules, cross-linked adduct of uracil mustard is the most stable one. In this case also, ΔG_{sol} cannot be correlated with the dipole moments (Supplement Fig. 1).

4.5. Stability of mono- and cross-linked adduct: global reactivity perspective

Stability of mono-adducts and cross-linked adducts are monitored in terms of global hardness, in gas phase as well as in aqueous phase at both the level of theories, shown in Fig. 4. Hardness of mono-adducts of phosphoramide mustard, uracil mustard and spiromustine exhibit higher values compared to the rest of the drug molecules. In case of cross-linked adducts we observed almost similar values.

5. Conclusion

An effort to examine the reactivity of the first and the second aziridinium ions and adducts formed with GC base pair, in gas as well as in aqueous phases has been made. Our results suggest that:

1. Though global reactivity parameters fail to predict the reactivity pattern among the drug molecules, yet, local reactivity parameters proved their applicability.
2. Local parameter, f^+ value of Az_1^+ ions satisfactorily explains the highest reactivity of mustine in the chosen set of drug molecules. The corresponding Az_2^{2+} ion of uracil mustard is found to have the maximum reactivity. Local reactivity of the Az_2^{2+} ions is remarkably lower compared to that of Az_1^+ ions.
3. Considerably higher values of free energy of solvation of Az_2^{2+} ions (compared to Az_1^+ ions) granted higher stability to Az_2^{2+} ions and is responsible for slower cross-linked adduct formation.
4. All the drug molecules exhibit considerable interaction energies with GC base pair. The aqueous phase interaction energies are lower compared to gas phase values because of solvation and high values ΔG_{sol} advocating a higher degree of solvation in aqueous phase.
5. Global hardness suggests that phosphoramide mustard forms the most stable cross-linked adduct.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.comptc.2013.06.002.

References

[1] D.M. Noll, T.M. Mason, P.S. Miller, Chem. Rev. 106 (2006) 277–301.
[2] S.R. Rajski, R.M. Williams, Chem. Rev. 98 (1998) 2723–2795.
[3] A. Gilman, F.S. Philips, Science 103 (1946) 409–436.
[4] L.S. Goodman, M.M.J. Wintrobe, J. Am. Med. Assoc. 132 (1946) 126–132.
[5] P. Kapoor, S.V. Rajkumar, A. Dispenzieri, M.A. Gertz, M.Q. Lacy, D. Dingli, J.R. Mikhael, V. Roy, R.A. Kyle, P.R. Greipp, S. Kumar, S.J. Mandrekar, Leukemia 25 (2011) 1523–1524.
[6] F. Bergel, J.A. Stock, J. Chem. Soc. (1954) 2409–2417.
[7] J.L. Everett, J.J. Roberts, W.C.J. Ross, J. Chem. Soc. (1953) 2386–2392.
[8] P. Hillmen, J.G. Gribben, G.A. Follows, D. Milligan, H.A. Sayala, P. Moreton, D.G. Oscier, C.E. Dearden, D.B. Kennedy, A.R. Pettitt, A. Nathwani, D. Cohen, A. Rawstron, C.F. Pocock, Ann. Oncol. 22 (2011) 123.
[9] A.E. Glode, A. Jarkowski, Pharmacotherapy 11 (2009) 1375–1384.
[10] M. Colvin, R.B. Brundrett, M.N. Kan, I. Jardine, C. Fenselan, Cancer Res. 36 (1976) 1121–1126.

[11] W.B. Mattes, C.S. Lee, J. Laval, T.R. O'Connor, Carcinogenesis 4 (1996) 643–648.
[12] D.D. Shoemaker, P.J. O'Dwyer, S. Marsoni, J. Plowman, J.P. Davignon, R.D. Davis, Invest New Drugs 4 (1983) 303–308.
[13] P.K. Sukla, P.C. Misra, S. Suhai, Chem. Phys. Lett. 449 (2007) 323–328.
[14] B. Pullman, in: H. Weinsteins, J.P. Green (Eds.), Quantum Chemistry in Biomolecular Science, The New York Academy of Science, New York, 1981.
[15] G.B. Bauer, L.F. Provirk, Nucleic Acid Res. 25 (1997) 1211–1218.
[16] B. Singer, Nature 264 (1976) 333–339.
[17] W.B. Mattes, J.A. Hartley, K.W. Kohn, Nucleic Acids Res. 14 (1986) 2971–2987.
[18] R.B. Silverman, The Organic Chemistry of Drug Design and Drug Action, Elsevier Academic Press, USA, 2004.
[19] P.G. Baraldi, R. Romagnoli, P.M. Giovanna, C.N.M. Del, J.P. Bingham, J.A. Hartley, Bioorg. Med. Chem. 10 (2002) 1611–1618.
[20] P.G. Baraldi, I. Beria, P. Cozzi, C. Geroni, A. Espinosa, M.A. Gallo, A. Entrena, J.P. Bingham, J.A. Hartley, R. Romagnoli, Bioorg. Med. Chem. 12 (2004) 3911–3921.
[21] B. Marvania, P.C. Lee, R. Chaniyara, H. Dong, S. Suman, R. Kakadiya, T.C. Chou, T.C. Lee, A. Shah, T.L. Su, Bioorg. Med. Chem. 15 (2011) 1987–1998.
[22] A. Polavarapu, J.A. Stillabower, S.G.W. Stubblefield, W.M. Taylor, Mu-Hyun Baik, J. Org. Chem. 77 (2012) 5914–5921.
[23] D.J. Mann, J. Phys. Chem. A 114 (2010) 4486–4493.
[24] K.W. Kohn, Anticancer Drugs, in: H. Tapiero, J. Robert, T.J. Lampidis (Eds.), INSERM, John Libbley Eurotext, London, Paris, 1989.
[25] P. Brookes, P.D. Lawley, J. Biochem. 80 (1961) 496–503.
[26] P.D. Lawley, D.H. Phillips, Mutat. Res., Fundam. Mol. Mech. Mutagen. 355 (1996) 13–40.
[27] R.J. Goldacre, A. Loveless, W.C.J. Ross, Nature 163 (1949) 667–669.
[28] P. Geerlings, F.D. Proft, W. Langenaekar, Chem. Rev. 103 (2003) 1793–1873.
[29] P.K. Chattaraj, U. Sarkar, D.R. Roy, Chem. Rev. 106 (2006) 2065–2091.
[30] H.S. Dey, S. Krishnamurty, S. Pal, J. Phys. Chem. C. 113 (2009) 7101–7106.
[31] N. Sablon, P.W. Ayers, F.D. Proft, A. Borgoo, P. Geerlings, J. Chem. Phys. 126 (2007) 224108–224113.
[32] R.G. Parr, R.A. Donnelly, M. Levy, W.E. Palke, J. Chem. Phys. 68 (1978) 3801–38017.
[33] R.G. Parr, R.G. Pearson, J. Am. Chem. Soc. 105 (1983) 7512–7516.
[34] R.G. Pearson, J. Am. Chem. Soc. 107 (1985) 6801–6806.
[35] P.K. Chattaraj (Ed.), Chemical Reactivity Theory: A Density Functional View, CRS press, Boca Raton, 2009.
[36] T.A. Koopmans, Physica 1 (1933) 104–113.
[37] R.G. Parr, L.V. Szentpaly, S. Liu, J. Am. Chem. Soc. 121 (1999) 1922–1924.
[38] P.K. Chattaraj, B. Maiti, U. Sarkar, J. Phys. Chem. A. Commun. 107 (2003) 4973–4975.
[39] B. Mennucci, J. Tomasi, J. Chem. Phys. 106 (1997) 5151–5158.
[40] V. Marenich, C.J. Cramer, D.G. Truhlar, J. Phys. Chem. B 113 (2009) 6378–6396.
[41] Gaussian 09, Revision B.01, Gaussian, Inc., Wallingford CT, 2010.
[42] M.F. Torrent-Sucarrat, F.D. Proft, W. Ayers, P. Geerlings, Phys. Chem. Chem. Phys. 12 (2010) 1072–1080.
[43] R.G. Parr, P.K. Chattaraj, J. Am. Chem. Soc. 113 (1991) 1854–1855.
[44] P.W. Ayers, R.G. Parr, J. Am. Chem. Soc. 122 (2000) 2010.
[45] R.G. Parr, W. Yang, J. Am. Chem. Soc. 106 (1984) 4049–4050.
[46] K. Fukui, Science 218 (1987) 747–754.
[47] W.B. Mattes, J.A. Hartley, K.W. Kohn, Nucl. Acids Res. 14 (1986) 2971–2987.
[48] F.R. Raphael, A.V. Marenich, C.J. Cramer, D.G. Truhlar, Phys. Chem. Chem. Phys. 13 (2011) 10908–10922.
[49] G. Scalmania, M.J. Frisch, J. Chem. Phys. 132 (2010) 114110.
[50] A.D. French, G.P. Johnson, C.J. Cramer, Carbohydr. Res. 350 (2012) 68–76.