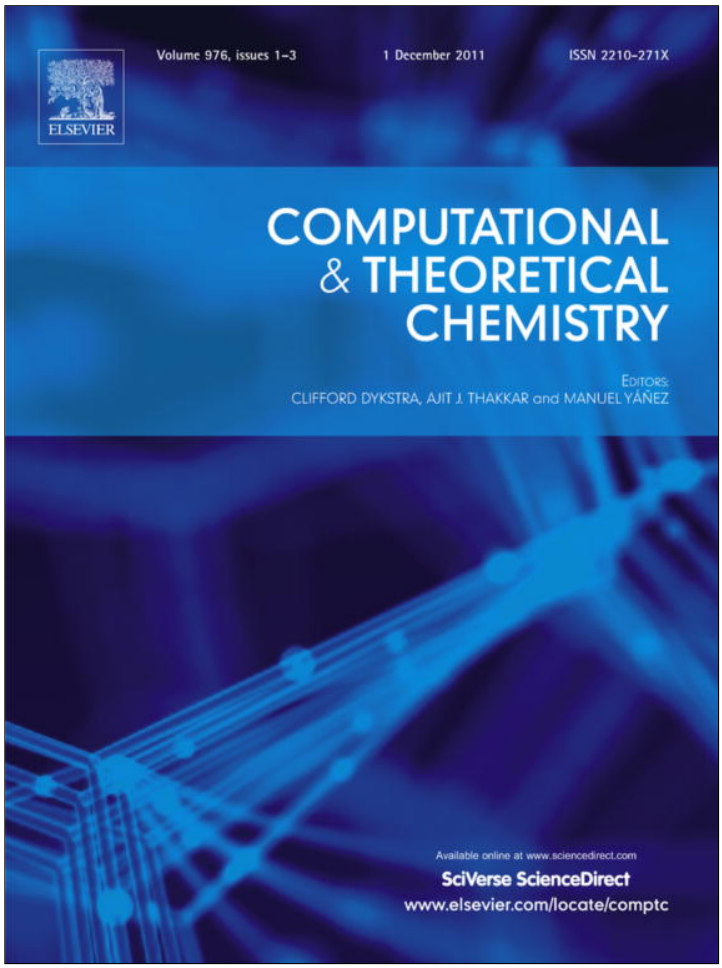

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Effect of external electric field on aziridinium ion intermediate: A DFT study

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ABSTRACT

We have analyzed the effect of external electric field on the aziridinium ion intermediate of mustine drug molecule using conceptual density functional theory based reactivity descriptors. The aziridinium ion intermediate is formed during the alkylation of DNA by mustine, a member of the nitrogen mustard family. This species experiences a field exerted by polarity of the solvent and metal ions present in body fluids (in extra- and intra-cellular fluids, blood etc.). The stability and reactivity of the aziridinium ion is monitored by studying some density based reactivity descriptors in the presence of external electric fields. Further, shifting of the reactive center (i.e., the LUMO) of the drug intermediate with variation in the electric field was observed. In addition, the maximum hardness and minimum electrophilicity principles were analyzed.

1. Introduction

DNA inter-strand cross-linking agents comprise an extremely important class of clinical agents in the treatment of cancer [1]. The nitrogen mustards represent the earliest and perhaps the most extensively studied DNA inter-strand cross-linking agents which have been used in cancer chemotherapy for last 50 years [2]. Despite its long history, mustine is the most heavily employed nitrogen mustard in use today [3]. Although nitrogen mustards have been studied and clinically exploited for over the last few decades, they still provide an area of extremely intense and progressive investigation. These drug molecules form a very reactive intermediate (aziridinium ion) and it reacts with nucleophilic centers in biomolecules [4]. It was suggested that the alkylation of the DNA bases is the favored mechanism of these drugs [5]. It was also reported that alkylation occur preferentially at the endocyclic nitrogen and exocyclic oxygen atoms of the DNA bases [6]. Each of the chloroethyl side chains of the nitrogen mustards (A) cyclizes spontaneously to form aziridinium ion (B) that binds to DNA covalently. The resulting mono-adduct (C) can form a second aziridinium ion (D) which can again bind to the second DNA strand to afford cross-linked product (E) as shown in Fig. 1 [7].

During its lifetime, the aziridinium ion intermediate has to pass through different environments ranging from non-polar (within the cell membrane) to polar environments (in extra- and intra-cellular fluids, blood etc.) before interacting with guanine [8]. These environments are expected to exert electric fields of different magnitude on the species present in them. Therefore, our interest is to study the effect of some external electric fields on aziridinium ion intermediate of mustine. For our purpose, we intend to exploit the density based reactivity descriptors to study the behavior of reactivity of aziridinium ion in presence of such external fields.

During the alkylation process, the aziridinium ion intermediate accepts electron density from the N7 center of the guanine base (in DNA). Therefore, the position as well as stability of the LUMO (lowest unoccupied molecular orbital) of the aziridinium ion becomes very important. Very recently, Bhattacharyya and Kar, observed the variation of the reactivity and stability of the tricyclic aziridinium ion intermediate of the mustine drug molecule with a variation of ∠NCC bond angle in gas as well as aqueous phase [9].

The reactivity descriptors, defined within the framework of density functional theory are global hardness, global electrophilicity, chemical potential, local softness, Fukui functions etc. [10]. 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 [11]. Geerlings et al. and Chattaraj et al. have reviewed the theoretical basis for these descriptors and their applications [12]. In general, the descriptors are classified to refer to the whole system, called "global reactivity descriptors", or to refer a local part of the system, called "local reactivity descriptors". Some of the recent developments and applications in this area of research are highly appreciable [13]. Since most of these descriptors are the derivatives of

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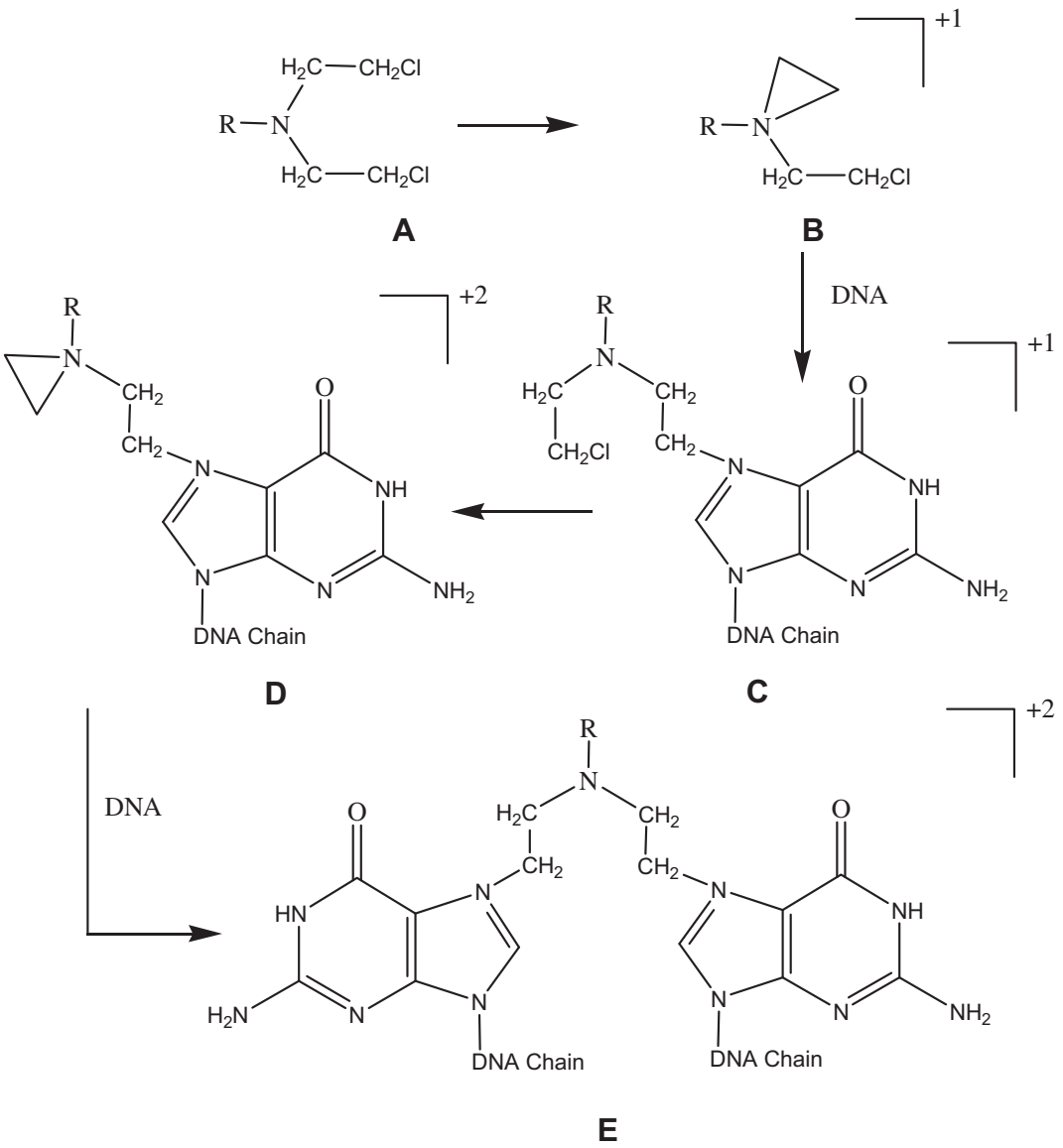


Fig. 1. Mechanism of alkylation of DNA by bisalkylating nitrogen mustard.

energy and electron density variables, it is expected that they will provide the modified reactivity information of the molecular systems in the presence of such external effects.

The effect of electric field on the chemical reactivity has been carried out in several earlier studies [14]. The chemical reactivity as a function of orientation in the electric field has been investigated in depth [15]. The influence of an external electric field on the *s* and *p* states of atoms and their compounds can affect their chemical properties, spectral, optical and magnetic resonance parameters [16]. Recently, Pal and co-workers have studied the behavior of these descriptors in presence of external electric field as well as solvent media [17]. Typically, in the case of electric field induced crystallization of ionic crystals, electric field strength of 105 V/m has been applied [18]. In the biological applications electric field strength of 1000 V/cm has been used [19]. Accordingly, introduction of electric field influences both physical and chemical properties of various molecular systems. Hence, in this article, we have made an effort to observe the variation in the shape of the LUMO and reactivity of the aziridinium ion in terms of global hardness, global electrophilicity and chemical potential in presence of external electric fields.

2. Theoretical details

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 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 ionization potential (IP) and electron affinity (EA) and therefore, μ and η, given below, can be used as working formulae

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

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

Approximations, involving the use of Koopmans' theorem, 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

$$\mathrm{IP} = -\varepsilon_{\mathrm{HOMO}} \tag{5}$$

$$\mathrm{EA} = -\varepsilon_{\mathrm{LUMO}} \tag{6}$$

and therefore, μ and η can be expressed as

$$\eta = \frac{\varepsilon_{\mathrm{LUMO}} - \varepsilon_{\mathrm{HOMO}}}{2} \tag{7}$$

and

$$\mu = \frac{\varepsilon_{\mathrm{LUMO}} + \varepsilon_{\mathrm{HOMO}}}{2} \tag{8}$$

Parr and his coworkers proposed electrophilicity index (ω) as a measure of electrophilicity of a species as [22]

$$\omega = \frac{\mu^2}{2\eta} \tag{9}$$

It is the measure of capacity of a species to accept an arbitrary number of electrons.

3. Computational details

The geometrical minima of the species are obtained using 6-311++G(d,p) basis set with Becke three parameter exchange and Lee, Yang and Parr correlation functional (B3LYP) [23] and is confirmed by frequency calculations. After locating the minima, single point energy calculations are carried out at different external electric field values in six directions (along positive and negative directions of *x*, *y* and *z* axis). The external electric field is applied along the direction of the Cartesian axes as shown in Fig. 2. The electric field is varied from 0.000 a.u. to 0.020 a.u. [1 a.u. of electric field = 51.4 V/Å]. The global reactivity descriptors (chemical potential, hardness and electrophilicity) are calculated using Eqs. (7)–(9). 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) basis set using B3LYP functional. All the calculations are carried out using Gaussian 09 [24].

4. Results and discussions

4.1. Shapes of LUMO of the aziridinium ion in presence of the field

The position of the LUMO of the aziridinium ion is observed by varying the electric field from 0.000 a.u.–0.020 a.u., along *z* axis using B3LYP/6-311++G(d,p) basis set and the observations are summarized in Fig. 3 (negative values of field means that it is applied in negative direction of the Cartesian axes). The variation of the LUMO when the field is applied along *z* axis is shown in Fig. 3b–f while Fig. 3g–k, shows the variation when the field is applied along negative direction of *z* axis.

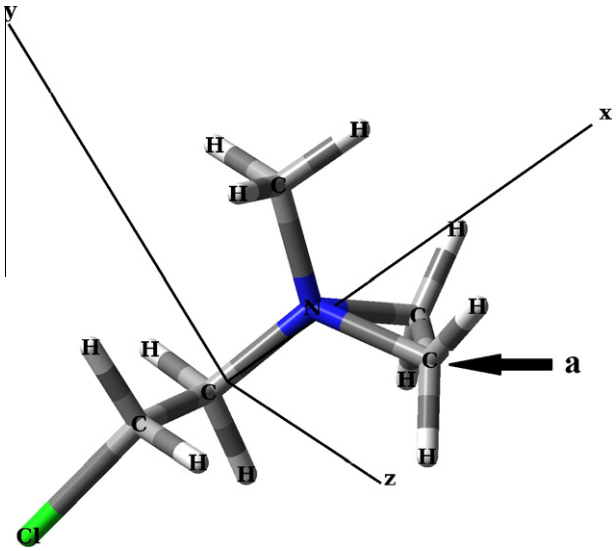


Fig. 2. Optimized structure of aziridinium ion intermediate at B3LYP/6-311++G(d,p) level of theory (cartesian axes are shown in the figure).

In absence of external electric field (field value = 0.000 a.u.), it is observed that the LUMO is located at the chloroethyl side chain, Fig. 3a. This position of the LUMO cannot explain the interaction of the ring carbon of the drug intermediate with guanine. When the electric field is applied, the position of the LUMO is shifted towards the direction of the applied field. For instance, at an applied field value of 0.002 a.u., Fig. 3b, the LUMO starts shifting towards the direction of external electric field and at a field value of 0.006 a.u., it is observed that a large portion of the LUMO is shifted, Fig. 3d. However, at higher field values, say greater than 0.01 a.u., almost complete shifting of the LUMO is observed, Fig. 3e. Thus, we have observed that when the strength of the external electric field is increased there is a significant shifting of the LUMO towards the direction of the applied field. Therefore, an external electric field applied in '*a*' direction, as shown in Fig. 2, will shift the LUMO significantly towards the ring carbon which would facilitate alkylation. This shifting in the position of the LUMO clearly indicates that, in the presence of an external electric field it is possible for the drug intermediate to interact with guanine base without any structural changes in it, as reported earlier [9].

When the external electric field is applied in negative direction of *z* axis, the LUMO is shifted in the direction of the external electric field, Fig. 3g–k. Similar results are observed when external field is applied along *x* and *y* axes and the results are consistent with another basis set, B3LYP/aug-cc-pVDZ (available as Supporting information).

4.2. Variation of LUMO energy

Now, we would like to examine the stability of the LUMO with the variation of external electric field strength along the three axes. The LUMO energy determines the electron acceptance capacity of the aziridinium ion and it is expected that the LUMO with more negative energy would facilitate electron acceptance which in turn facilitate alkylation. The variation of the LUMO energy with the external electric field at B3LYP/6-311++G(d,p) level of theory is shown in Fig. 4. In particular, Fig. 4a–c showing the variation of LUMO energy with external electric field values along *x*, *y* and *z* axes, respectively.

It is observed that as we go on increasing the field strength, the LUMO energy goes down (more negative energy) i.e., become more stable at higher field. When the magnitude of the field is in the

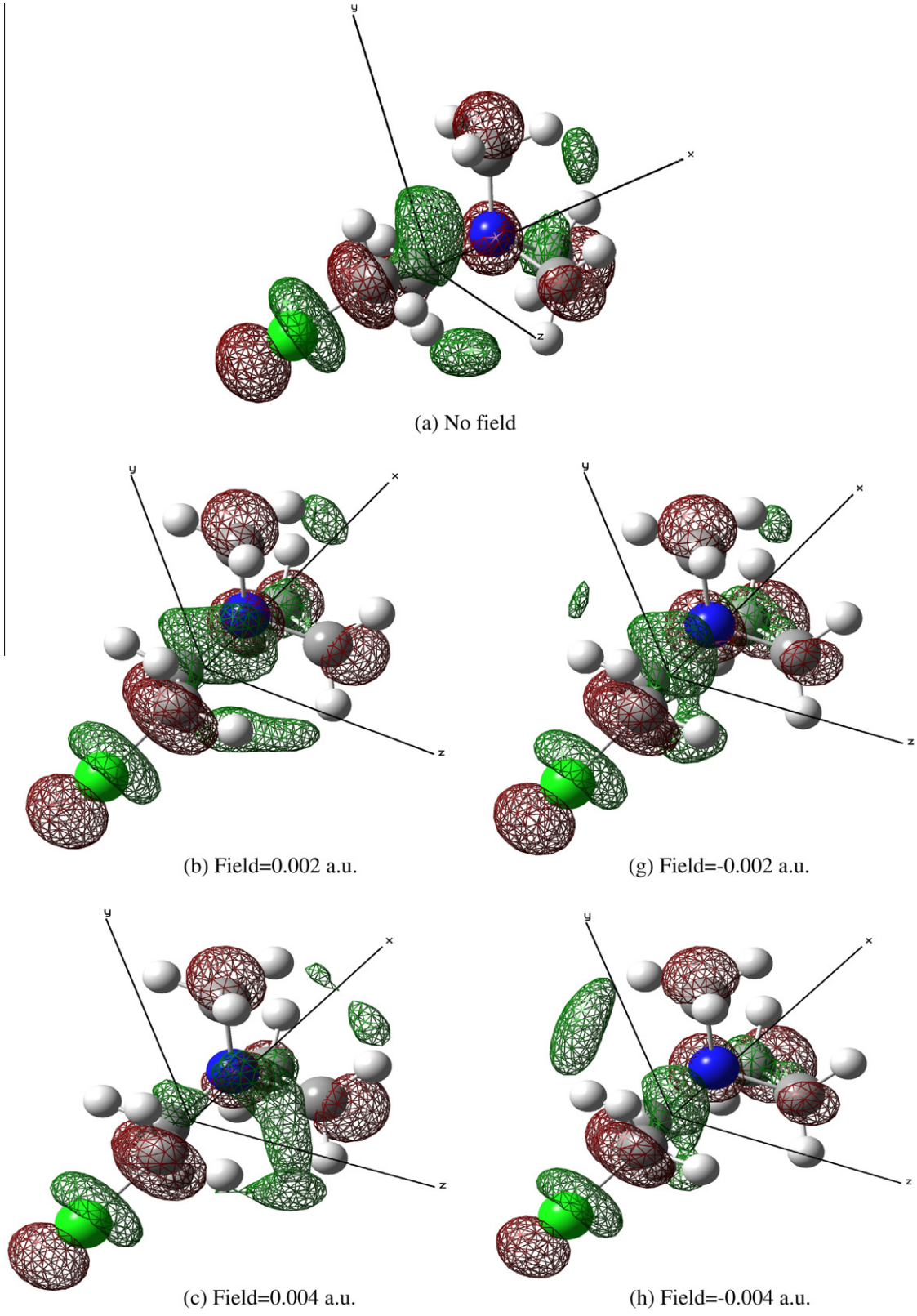


Fig. 3. Shapes of LUMO in the presence of external electric field applied along *z* axis.

range of 0.000 a.u. to 0.01 a.u., the LUMO is slightly stabilized however, at very high field the curve becomes steeper, Fig. 4. It means that at higher external electric field the LUMO will be more susceptible to accept electron density and hence, exhibit greater tendency towards guanine base. Thus, highly polar solvent (which would generate higher electric field) will make the aziridinium ion more reactive. It may also be noted that external field applied along *y* and *z* axes yields LUMO energy which are symmetrical about the zero field value, Fig. 4b–c. Similar trends are observed with B3LYP/aug-cc-pVDZ level (Supporting information).

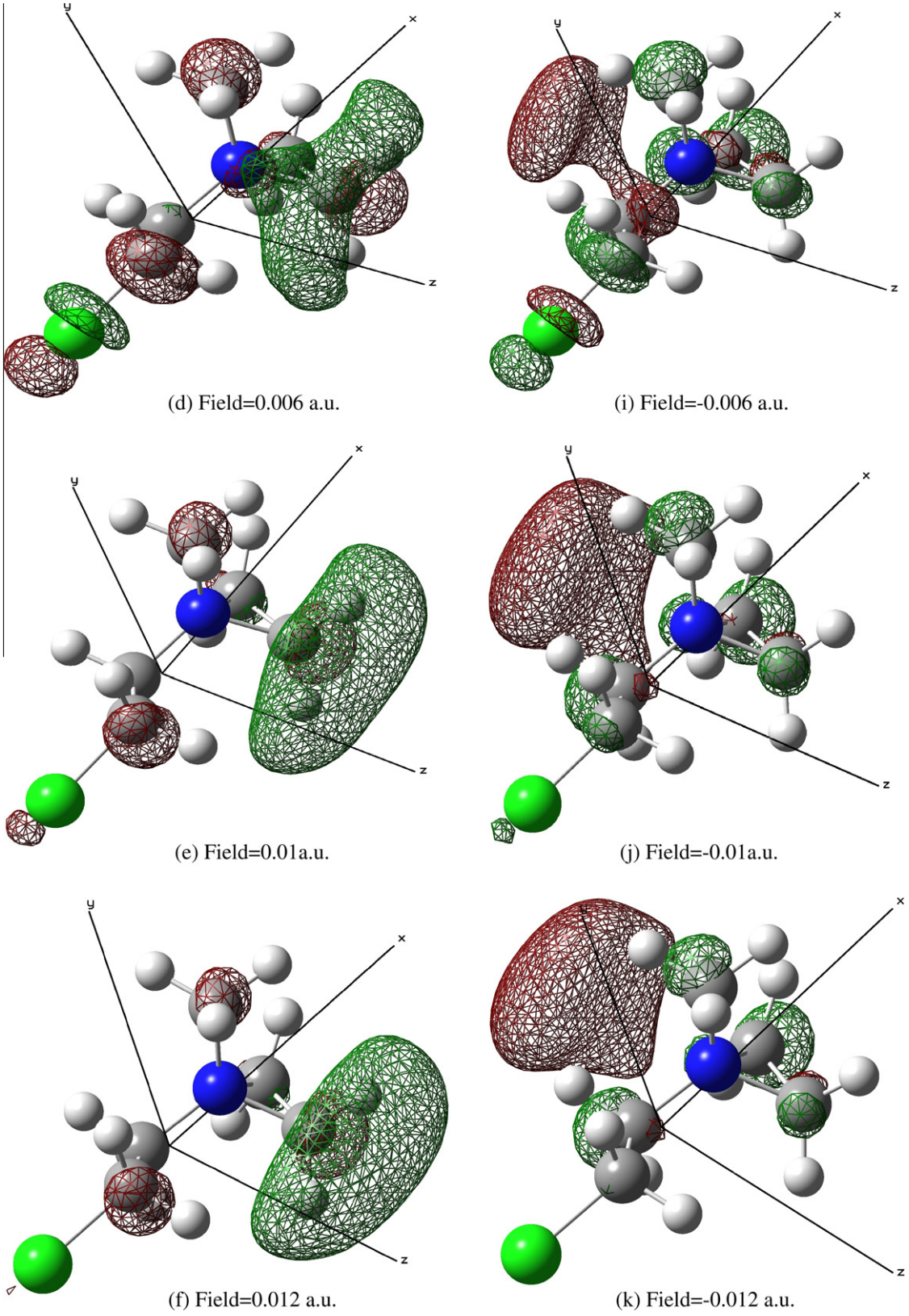
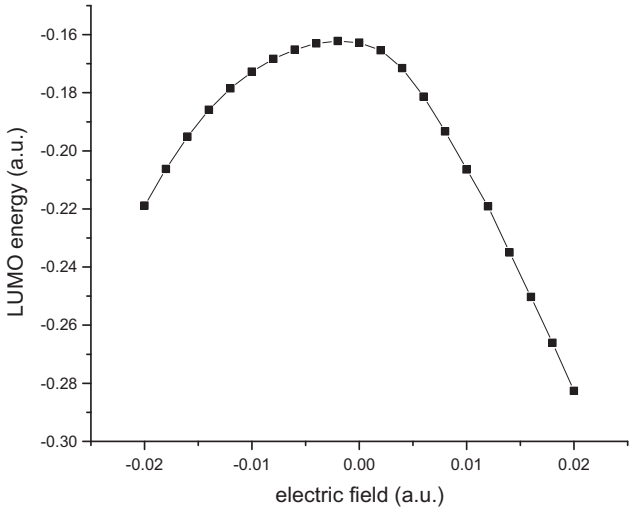


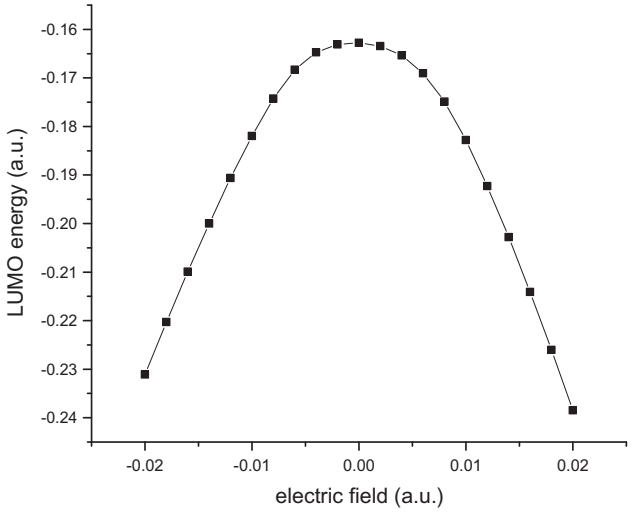
Fig. 3 (*continued*)

4.3. Variation of the global reactivity descriptors

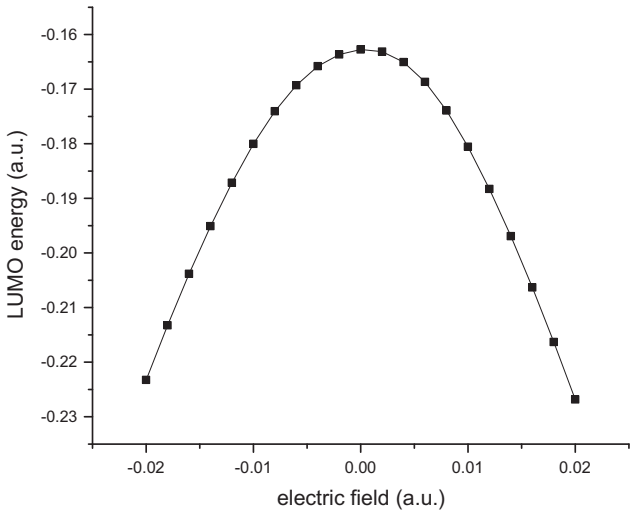
The variation of the density based reactivity descriptors such as chemical potential, global hardness and global electrophilicity with external electric field values along the three axes are shown in Figs. 5 and 6. Variation of hardness and electrophilicity with the external electric field along *z*, *y* and *x* axes are shown in Fig. 5a–c, respectively. However, the variation of chemical potential with electric field is shown in Fig. 6.



(a) along x-axis

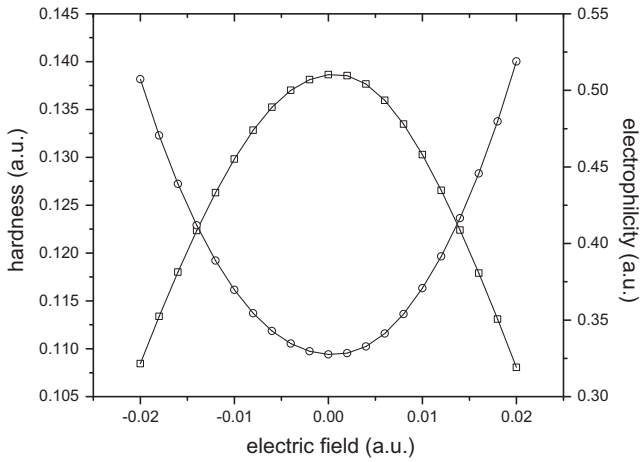


(b) along y-axis

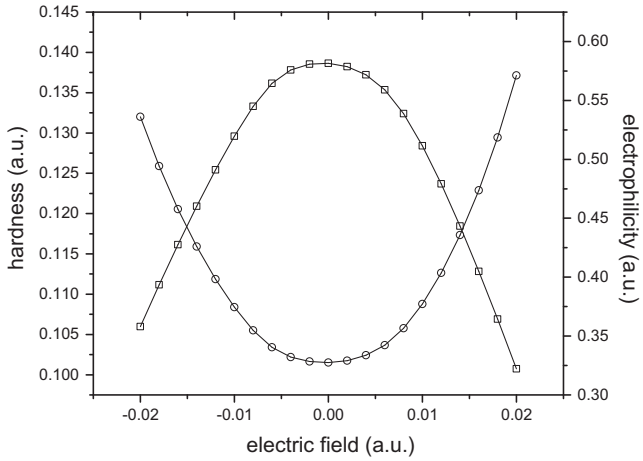


(c) along z-axis

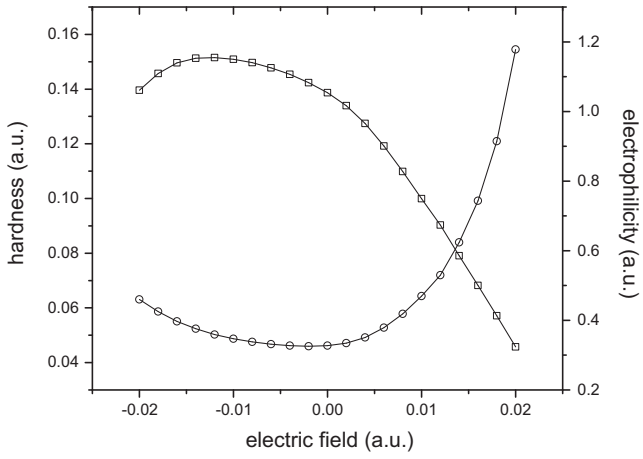
Fig. 4. Variation of LUMO energy (in a.u.) with external electric field at B3LYP/6-311++G(d,p) level.



(a) along z axis
[square=hardness; circle=electrophilicity]



(b) along y axis
[square=hardness; circle=electrophilicity]



(c) along x axis
[square=hardness; circle=electrophilicity]

Fig. 5. Variation of hardness, electrophilicity with external electric field at B3LYP/6-311++G(d,p) level.

It is observed that as the value of the external electric field increases, irrespective of the direction of the field, chemical potential and hardness decreases, Figs. 5 and 6. It can also be observed from

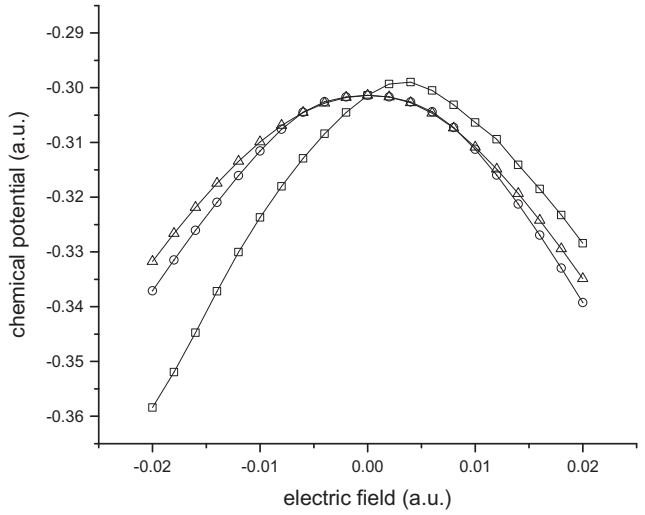


Fig. 6. Variation of chemical potential along *x*-axis (square), *y*-axis (circle), *z*-axis (triangle) with external electric field at B3LYP/6-311++G(d,p) level.

Fig. 6 that chemical potential has a maximum at around zero external electric field and decreases on increasing the field strength. The hardness, similarly, passes through a maximum when the external electric field is varied from −0.02 a.u. to +0.02 a.u. Fig. 5a–c and the maxima occurs at around zero field value. Thus, according to maximum hardness principle, the aziridinium ion intermediate attains maximum stability when the external field is absent. This clearly indicates that the aziridinium ion becomes more reactive in presence of external electric field. On the other hand, as the value of external electric field increases, irrespective of the direction of the field, global electrophilicity of the drug intermediate increases, Fig. 5a–c. It is also observed that the electrophilicity passes through a minimum when the external electric field is varied (Fig. 5a–c) and the minima occurs at around zero field value. Again, in order that the aziridinium ion intermediate accepts electron density from the guanine base, the electrophilicity of the drug intermediate must be maximum. It is observed that at high field value the electron acceptable tendency is more. Moreover, the minimum electrophilicity principle is satisfied. In a solvent media, the ions exert field in all directions and field exerted in a particular direction may be useful for the stability or reactivity of the species. It should, however, be noted that the maxima of hardness shift away from the zero field value when the external electric field is applied along the *x*-axis. It may be due to the extra stabilization of LUMO in that direction. Similar trends are observed using different basis set, B3LYP/aug-cc-pVDZ (Supporting information).

5. Conclusions

We have studied the behavior of the aziridinium ion intermediate of mustine drug molecule in presence of external electric field. Our study focused on the variation of energy and shape of the LUMO with the variation of external electric field from −0.020 a.u. to +0.020 a.u. Additionally, we have analyzed the variation in the stability and reactivity of the drug intermediate using the density based reactivity descriptors. It can be concluded that the aziridinium ion would be more reactive in environments, which exerts higher field and such an environment may facilitate the alkylation process. Our studies satisfy the minimum electrophilicity principle along with the maximum hardness principle. Even though, this study is performed on a particular drug molecule it is expected that the conclusions will hold in general.

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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.2011.08.002.

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