



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.

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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 $\angle\text{NCC}$ 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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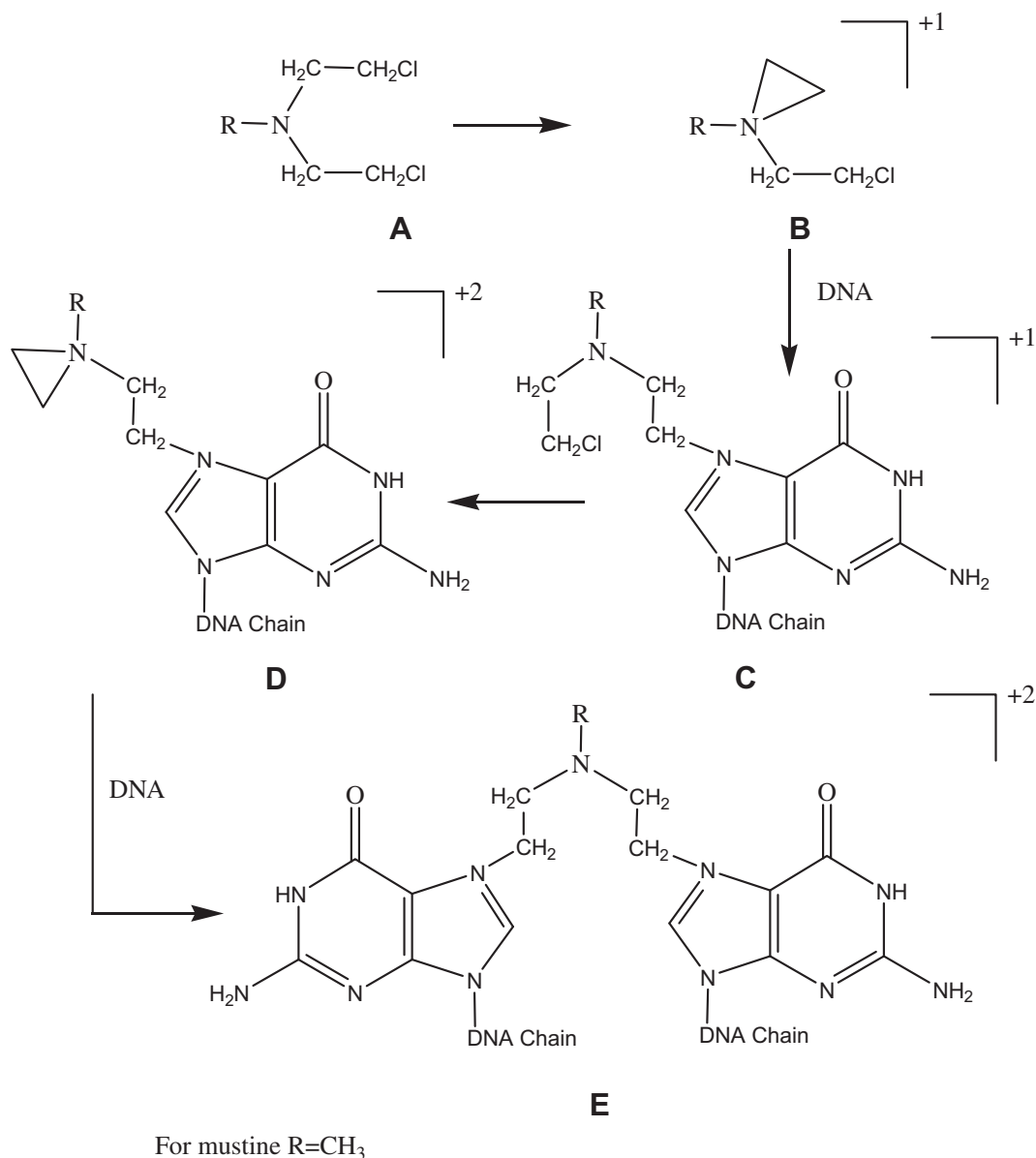


Fig. 1. Mechanism of alkylation of DNA by bisalkylating nitrogen mustard.

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]

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

and hardness (η) [21]

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

where E is the energy and N is the number of electrons of an electronic system at constant external potential, $v(\vec{r})$.

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