Effect of external electric field on drug-guanine adduct: A conceptual density functional theory study

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Abstract

Interaction energy between mustine and guanine have been studied in presence of external electric field using conceptual density functional theory (DFT) at B3LYP/6-31+G(d) and B3LYP/6-311++G(d,p) level of theories. Apart from that effect of electric field on the ΔG and ΔH of the mustine-guanine adduct formation process was studied. Stability of the adduct was examined using DFT based reactivity descriptors in presence of electric fields.

Key words: Drug-DNA interaction, Density functional theory, reactivity descriptors, mustine.

1. Introduction

Interaction of anticancer drugs with DNA plays a predominant role in cancer chemotherapy. Most of these drugs target DNA and drug-DNA adduct formation becomes an important subject in cancer chemotherapy [1]. Many researchers have used different experimental techniques to study the binding pattern of these drugs with DNA [2]. Study of the drug-DNA adduct formation posture more significance towards drug designing and has been isolated and studied well by different groups [3]. Kinetics of drug-DNA interaction of different DNA targeted drugs were also studied extensively [4]. In an important work, Hartley et al. studied the effect of ionic strength on alkylation of N7 of guanine by nitrogen mustards [5].

Nitrogen mustards are well studied anticancer drugs and are known for their DNA alkylating ability. These drugs have been used in cancer chemotherapy since long and are well reviewed [6]. Mustine is the oldest member of this family and is being used in cancer chemotherapy since more than 50 years. This class of drug molecules exert their cytotoxic action through covalent bond formation with cellular nucleophilic centers especially in DNA. They interact with DNA via formation of aziridinium ion (Az^+) (Fig. I) and form mono-adduct which further leads to cross-linked adduct [1,6]. Detailed studies suggest that N7 of guanine is the most preferred position of these drug molecules for alkylation [7]. Recent theoretical studies have drawn attention of the scientists and a number of such studies have been made on drug-DNA adducts [8]. Stability of drug-DNA adducts play an important role in cytotoxicity of the drug molecules. It is important to mention that global hardness; a DFT based reactivity descriptor, is an efficient tool to describe the stability of a molecular species and have been tested well in recent years [9]. Moreover, it is observed that the stability of a species is sensitive to different factors such as external electric field, solvent polarity,

configuration of the species etc [10]. Alkylation of guanine by mustine takes place in highly polar medium (cell plasma). Therefore, it is expected that the polarity of the solvent medium and presence of metal ions in cell plasma might produce some electric field which affect stability of the adduct, interaction energy (between drug and DNA) and thermo chemistry of the adduct formation as well.

Here we have considered the mustine-guanine adduct (instead of a DNA chain we have considered one guanine molecule, glycosidic linkage is replaced by a methyl group) and studied the variation of interaction energy in presence of an external electric field using density functional theory. Apart from that we have performed thermodynamic analysis on the adduct formation process, Fig. I. Moreover effect of electric field on stability of the adduct have been observed.

2. Theoretical and Computational details:

The global hardness (η) [11] was calculated from the frontier orbital energies, HOMO (ε_{HOMO}) and LUMO (ε_{LUMO}) using the equation $\eta = \frac{(\varepsilon_{LUMO} - \varepsilon_{HOMO})}{2}$. Gas phase geometrical minima of the species was optimized using 6-31+G(d) basis set with Becke three parameter exchange and Lee, Yang and Parr correlation functional, B3LYP [12] and were confirmed by frequency calculation. Geometry optimization was followed by single point calculations at the same level of theory in presence of external electric field values in six different directions (along positive and negative directions of x, y and z axes). The electric field was varied from 0.000 a.u. to 0.020 a.u. [1a.u. of electric field=51.4 V/Å]. Further thermodynamic analysis have been carried out at B3LYP/6-31+G (d) level of theory. The interaction energies (ΔE_{int}) between mustine (Az^+ ion) and guanine were calculated using supermolecular approach, [ΔE_{int}= (E_{adduct}) − (E_{azi} + $E_{guanine}$)], where, E_{adduct} is the energy of the mustine-guanine adduct,

E_{azi} is the energy of the Az^+ ion and $E_{guanine}$ is the energy of the guanine molecule. Additionally, to check the consistency of our results we have performed single point calculations at B3LYP/6-311++G (d,p) level of theory. All calculations were performed using Gaussian09 package of programme [13].

3. Results and discussion:

3.1 Effect on interaction energy

To observe the effect of external electric field on interaction energy between mustine and guanine, initially we have calculated the interaction in absence of external electric field and then electric is applied along all six directions, shown in Fig. II.

Fig. II brings forth an interesting result on the effect of electric field on interaction energy. As we have applied electric field along negative direction of *x*-axis, high magnitude of electric field leads to a very high interaction energy, (for example, at – 0.02 a.u. field interaction energy = – 61.41 kcal/mol). As field strength decreases, interaction energy decreases and in absence of the field (field = 0.0 a.u.) interaction energy becomes low (= – 39.15 kcal/mol) and remain almost same as we increase the field strength along positive direction. However along y-axis, the pattern is observed to be quite different; interaction energy decreases as field strength decreases along negative direction and this decline in values continues as we go on increasing field strength along +y direction. The trend is exactly opposite in case of z-axis. During drug-guanine adduct formation, the drug molecule approaches guanine molecule along the *–x* direction; y and z axes are pointing perpendicular to the plane of the adduct (figure I) and hence results observed along z-axis is just opposite to that of y-axis. Thus, both field strength as well as direction of the applied field exerts strong

effect on interaction energy between mustine ion and guanine. Same results were observed with B3LYP/6-311++G (d,p) level of theory (Supplement Table 1).

3.2 Thermochemical analysis

Thermodynamic parameters play an important role in determining the direction of a chemical reaction; negative values of ΔG (change in Gibbs free energy) and ΔH (change in enthalpy) has always been sought for thermodynamic feasibility of a chemical reaction. To check the thermodynamic feasibility of the mustine-guanine adduct formation, we calculated ΔG and ΔH involved in the adduct formation process, Fig. I; ($\Delta G = G_{adduct} - (G_{aziridinium\ ion} + G_{guanine})$). Further, we have observed the effect of electric field on these two parameters by varying the field.

Fig. III shows that in absence of electric field (field = 0.0 a.u.), ΔG and ΔH of the adduct formation are – 38.99 and – 24.08 kcal/mol respectively which demonstrate that adduct formation is exothermic. From Fig. III(a), it has been observed that a very strong field (= 0.020a.u.) applied on the negative direction of x-axis results maximum (negative) ΔG and ΔH and as we decrease the field strength, these values decreases and further increasing the field strength along positive direction of x-axis, both ΔG and ΔH values remain almost constant. On the contrary y and z-axes results are quite different. Along y-axis, as we increase the field strength in negative direction, these values decrease and along positive direction it shows an increase with increasing field strength, Fig. II(b). Reverse trend is observed in case of z-axis, Fig. III(c). This indicates that field strength as well as direction of its applications are important for thermodynamic feasibility of the adduct formation. B3LYP/6-311++G (d,p) level of theory also give same results (supplement Table 2).

3.3 Variation of the global hardness:

Stability of the mustine-guanine adduct is observed from their global hardness (maximum hardness leads to maximum stability according to maximum hardness principle) by varying the electric field from 0.000 a.u. to 0.020 a.u in all six directions. The observed pattern along the three axes is summarized in Fig. IV.

It is observed that along x-axis, maximum hardness is found at around field value = 0.01 a.u. However, in case of y-axis this peak has shifted to field value = – 0.01 a.u. Perversely, no such minimum value is observed in the applied field range along z-axis. This clearly indicates that the stability of the mustine-guanine adduct depends on the direction of applied field. Thus, according to maximum hardness principle, the mustine-guanine adduct becomes stable in presence of strong external field along x-axis which may be exerted by polar media. Conclusively, it can be stated that application of different strength of electric field in different directions are obliged to impart extra stability to the adduct. Consistent results were found at B3LYP/6-311++G (d,p) level of theory (supplement Table 3).

Conclusion:

Our observations showed that stability of the mustine-guanine adduct is highly effected by external electric field. Further the pattern of variations obeys maximum hardness principle. Moreover electric field affect the interaction energy between Az^+ ion and guanine. External electric field applied in particular direction favours ΔG and ΔH of the mustine-guanine adduct formation process.

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References:

1. (a) R. B. Silverman, "The Organic Chemistry of Drug Design and Drug Action", 2nd ed., Elsevier Academic Press, 2004.
   (b) K. B. Lipkowitz and D. B. Boyd, Reviews in Computational Chemistry, 17 eds, Wiley-VCH, 2001.
2. (a) M. Colvin, R. B. Brundrett, M. N. Kan, I. Jardine, C. Fenselau, *Cancer Res.*, 1976, **36**, 1121-1126.
   (b) H. Robinson, Y. C. Liaw, G. A. van der Marel, J. H. van Boom, A. H. J. Wang, *Nucleic acid Res.* 1990, **18**, 4851-4858.
   (c) Q. Dong, D. Barsky, M. E. Colvin, C. F. Melius, S. M. Ludeman, J. F. Moravek, O. M. Colvin, D. D. Binger, P. Modrich, H. S. Friedman, *Proc. Natl. Acad. Sci.*, 1995, **92,** 12170-12174.
   (d) N. H. Hopcroft, A. L. Brogden, M. Searcey, C. J. Cardin, *Nucleic acid Res.* 2006, **34,** 6663-6672.
   (e) M. S. A. Majid, G. Smythe, W. A. Denny, L. P. G. Wakelin, *Mol. Pharmacol.* 2007, **71**, 1165-1178.
3. (a) M. J. Tilby, H. McCartney, K. A. Gould, C. C. O'Hare, J. A. Hartley, A. G. Hall, B. T. Golding, P. D. Lawley, *Chem. Res. Toxicol.* 1998, **11,** 1162-1168.
   (b) P. J. McHugh, R. D. Gill, R. Waters, J. A. Hartley, *Nucleic acid Res*. 1999, **27,** 3259-3266.
   (c) B. B. Bank, *Biochem. Pharmacol.* 1992, **44**, 571-575.
   (d) P. D. Lawley, D.H. Phillips, *Mut. Res. Fundamental Mol. Mech. Mutagen.* 1996, **355,** 13-40.
4. (a) L.P.G. Wakelin, M.J. Waring, *J. Mol. Biol.* 1980, **144,** 183-214.
   (b) K. W. Kohn, J. a. Hartley, W. B. Mattes, *Nucleic acid Res.* 1987, **15,** 10531-10549.
   (c) M. R. Osborne, P. D. Lawley, *Chem. Biol. Interact.* 1992, **84**, 189-198.
   (d) M. G. Bolton, J. Hilton, K. D. Robertson, R. T. Streeper, O. M. Colvin, D. A. Noe, *Drug. Metab. Dispos.* 1993, **21**, 986-996.
   (e) G. B. Bauer, L. F. Povirk, *Nucleic acid Res.* 1997, **25**, 1211-1218.
   (f) K. Lof, J. Hovinen, P. Reinikainen, L. M. Vilpo, E. seppala, J. A. Vilpo, *Chem. Biol. Interact.* 1997, **103,** 187-198.
5. J. A. Hartley, S. M. Forrow, R. L. Souhami, *Biochemistry*, 1990, **29**, 2985-2991.
6. (a) L. F. Povirk, D. E. Shuker, *Mutat. Res.* 1994, **318**, 205-226.

(b) S. Neidle, M. Waring, "Molecular Aspects of Anti-cancer Drug Action", (Eds.), Verlag Chemie: Weinheim, 1994.

(c) S. R. Rajski, R. M. Williams, *Chem. Rev.* 1998, **98**, 2723-2795.

(d) K.W. Kohn, in: "Anticancer Drugs", eds. H. Tapiero, J. Robert, T.J. Lampidis, INSERM, John Libbley Eurotext, London, Paris, 1989.

(e) D.M. Noll, T.M. Mason, P.S. Miller, *Chem. Rev.* 2006, **106,** 277-301.

7. (a) D. I. Niculescu, I. Baracu, A. T. Balaban, in "The chemistry of antitumour agents", eds, D. E. V. Wilman, Blackie, Glasgow 1990.

(b) P. D. Lawley, P. Brookes, *J. Biochem*, 1963, **89**, 127-138.

8. (a) P. K. Shukla, P.C. Misra, S. Suhai, *Chem. Phys. Lett.* 2007, **449**, 323-328.

(b) E. D. Scheeff, J. M. Briggs, S. B. Howell, *Mol. Pharmacol.* 1999, **56,** 633-643.

9. (a) R.G. Parr, W. Yang, "Density-Functional Theory of Atoms and Molecules", Oxford University Press, New York, 1989.

(b) P. Geerlings, F. De Proft, W. Langenaekar, *Chem. Rev.* 2003, **103**, 1793-1873.

(c) H.S. De, S. Krishnamurthy, S. Pal, *J. Phys. Chem. C*, 2009, **113,** 7101-7106.

(d) R. K. Roy, S. Krishnamurthy, P. Geerlings, S. Pal, *J. Phys. Chem. A*, 1998, **102** 3746 – 3755.

(e) G. Roos, P. Geerlings, J. Messens, *J. Phys. Chem. B*, 2009, **113,** 13465-13475.

10. (a) P. K. Bhattacharyya, R. Kar, *Comput. Theoret. Chem*. 2011, **967**, 5-11.

(b) B. Neog, N. Sarmah, R. Kar, P. K. Bhattacharyya, *Comput. Theoret. Chem.* 2011, **976,** 60–67.

(c) P. Pérez, R. Contreras, A. Aizman, *J. Mol. Struct. THEOCHEM*, 1997, **390**, 169–175.

(d) R. Kar, K. R. S. Chandrakumar, and S. Pal, *J. Phys. Chem. A*, 2007, **111,** 375–383.

(e) R. Kar, S. Pal, *Int. J. Quant. Chem.* 2009, **110,** 1642–1647.

11. (a) R.G. Parr, R.G. Pearson, *J. Am. Chem. Soc.*, 1983, **105,** 7512-7516.

(b) R. G. Pearson, *J. Am. Chem. Soc.*, 1985, **107**, 6801-6806.

12. (a) A.D. Becke, *J. Chem. Phys.*, 1993, **98,** 5648-5652.

(b) C. Lee, W. Yang, R.G. Parr, *Phys. Rev., B*, 1988, **37,** 785-789.

13. Gaussian 09, Revision B.01, Frisch et al. Gaussian, Inc., Wallingford CT, 2010.

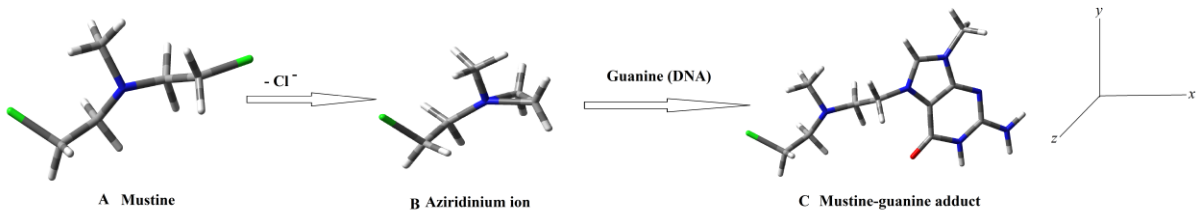

Fig. I. Formation of mustine-guanine adduct (mustine (**A**) form aziridinium ion (**B**) and then aziridinium ion interacts with guanine resulting mono-adduct (**C**)).

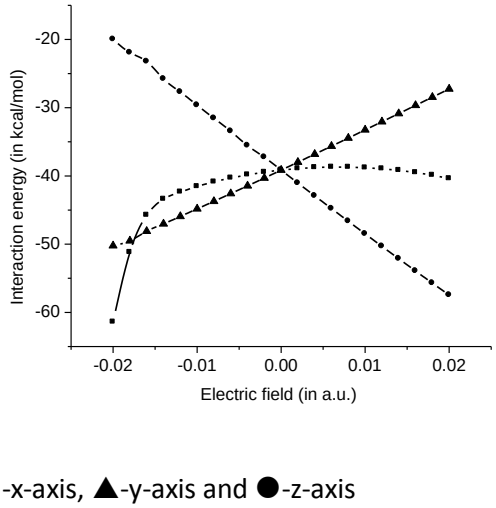

Fig. II: Variation of interaction energy (in kcal/mol) along three Cartesian axes at B3LYP/6-31+G (d) level of theory.

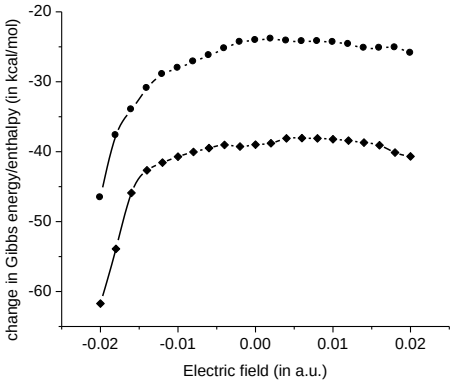

Fig. III (a): along x-axis.

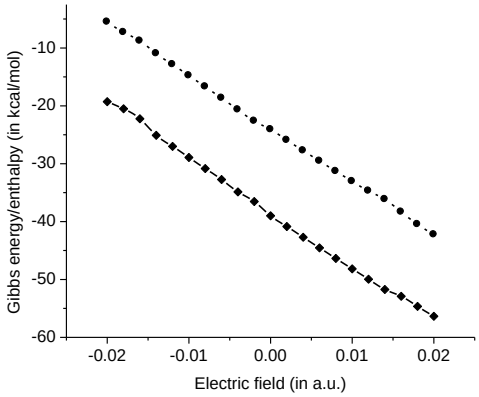

Fig. III (b): along y-axis

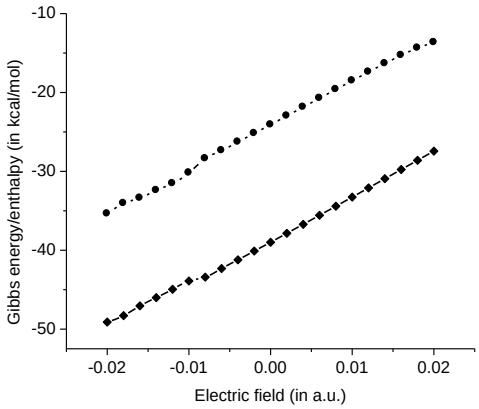

Fig. III(c): along z-axis

Fig. III. Variation of ΔG and ΔH (in kcal/mol) of the adduct formation with external electric field along three Cartesian axes at B3LYP/6-31+G(d) level of theory. (● - ΔH, ◆ - ΔG).

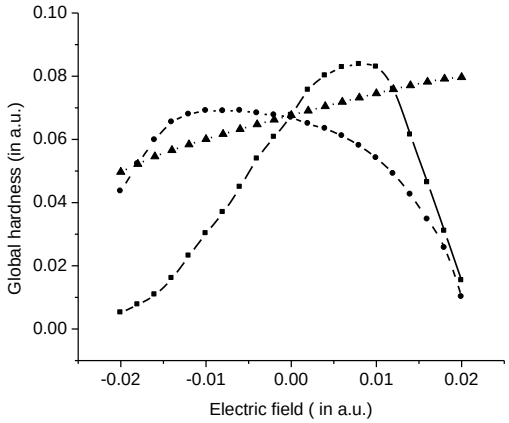

Fig. IV. Variation of global hardness along three Cartesian axes (■- along x-axis, ●- along y-axis, ▲- along z-axis).