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An Analysis of Structural, Electronic and Reactivity Properties of MetforminChloride using XRD and DFT Approach

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ABSTRACT. In this work, crystallization of first-line antidiabetic drug MetforminChloride has been done by slow evaporation method and the structure has been re-determined at 100K and the most thermodynamically stable phase A has been obtained. Experimentally and theoretically obtained structures and their parameters match well. With the goal of understanding the nature and reactivity of the molecule, some reactivity descriptors such as ionization energy, electron affinity, HOMO-LUMO energy gap, chemical potential, molecular softness, hardness and electrophilicity index has been calculated using Density functional theory with the basis set B3LYP/6-311++G(d, p). In order to get insight into the electronic charge distribution in a molecule, Mulliken, AIM and Natural charges have been calculated and electrostatic potential has been visualized to identify the sites of electrophilic and nucleophilic regions where the molecular interactions likely to happen. The dipole moment has been calculated to predict the shape and polarity of the molecule. The NBO analysis has been carried out to obtain information about the hyper conjugative interaction and electron density transfer from the filled lone pair electron to the bonding orbitals. The docking study of Metformin cation with the 1FM9 protein has been carried out to better understand the drug-receptor interaction.

Introduction. MetforminChloride(MET/Cl) is known as potent drug in the treatment of type2 non-insulin-dependent diabetes mellitus[1]. The mechanism of the drug is alleviating hepatic glucose production as well as increasing insulin sensitivity. This is also known as anti-hyperglycemic drug as it reduces the risk of cardiovascular mortality without inducing hypoglycemia[2]. The investigation on the structural, electronic, nature and reactivity of the MET/Cl molecule leads us not only to obtain better knowledge about the existing drug but also paves way for the design of new potential and efficient drugs. In that sense this study throws light into the structure related things, charges, HOMO(Highest occupied molecular orbital)-LUMO(Lowest unoccupied molecular orbital) analysis, NBO analysis, electrostatic potential and dipole moment in order to obtain better interpretation on the character and reactivity properties of the MET/Cl molecule.

Methodology

Experimental. Crystallization of MET/Cl has been done using slow evaporation technique and needle shaped crystal have been harvested. The structure has been re-determined at 100K and the most thermodynamically stable phase A has been obtained.

Theoretical details. Using GAUSSIAN09 [3] software, the optimization of structure of MET/Cl has been done at B3LYP level with the basis set 6311G++(d, p) to obtain minimum energy structure. The equilibrium structure has been achieved with the absence of imaginary frequency.

Results and discussion

Structural details. The optimization yields the results that MET/Cl molecule has 22 atoms and it has 60 degrees of freedom. The structure has one Metformin cation and one Chlorine anion. Especially the metformin cation consists of three amine(-NH₂) groups and two methyl(-CH₃) groups linked

through alternate C-N bonds. The optimized structure clearly shows the occurrence of delocalization among the C-N bonds. The nuclear repulsion energy has been found to be 661.70 Hartrees. The optimized structure of MET/Cl was shown in figure 1.

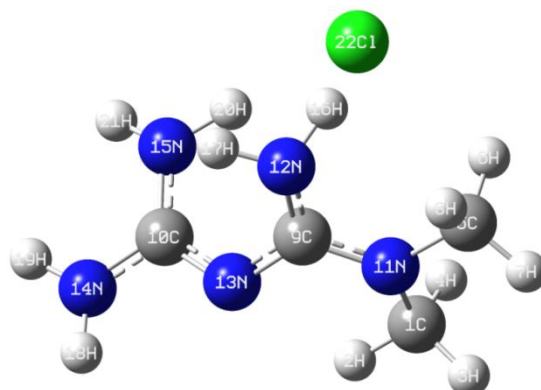


Fig. 1. Optimized Structure of MET/Cl.

Atomic charges

Analysis on the atomic charges provides information on charge distribution in the molecule and this describes the process of electronegativity equalization and charge transfer in chemical reactions. In order to get better perspective on charge distribution the comparison of Mulliken charges[4], AIM[5] and Natural population analysis[6] has been done and is given in Fig.2. Mulliken Population Analysis [4] based on the linear combination of atomic orbitals is the study of charge distribution within molecules, which partitions the total charge among the atoms in the molecule with its sign and magnitude while AIM charges[5] are based on charge density distribution. According to the results of the three analyses, all nitrogen N11, N12, N13, N14, N15 and Cl22 atoms carry negative charges.

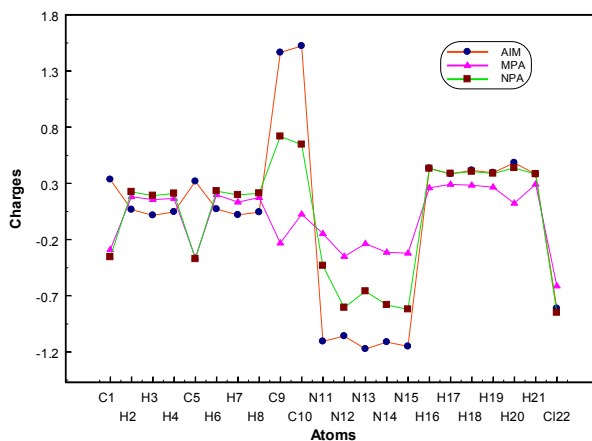


Fig. 2. Plot of atoms and charges from AIM, MPA and NPA analysis.

Nature and chemical reactivity

Frontier molecular orbital theory is an application of Molecular Orbital theory which describes the HOMO (Highest occupied molecular orbital) and LUMO (Lowest unoccupied molecular orbital) interactions and the bonding nature in terms of wave characteristics of electrons. Notably the HOMO-LUMO analysis has been carried out to explain the charge transfer within the molecule. The HOMO and LUMO energies were calculated by the standard basis set B3LYP/6-311G++ (d, p) where HOMO

state is found at -0.214a.u. and LUMO is found at -0.039a.u. The HOMO-LUMO isosurface maps and energy level graph of the molecule is given in Fig.3.

DFT has become an efficient tool to provide theoretical insights into the chemical reactivity and site selectivity in terms of popular qualitative chemical concepts like electronegativity (χ), chemical hardness (η), softness(S), chemical potential (μ), and electrophilicity index (ω). By Koopmans' theorem [7] ionization potential (I)[8], electron affinity(A)[9], electronegativity(χ)[10], hardness (η)[11], softness(S)[12] which are based on the energy of the HOMO and the LUMO.

$$\eta = \frac{1}{2}(I - A) = \frac{1}{2}(\varepsilon_{HOMO} - \varepsilon_{LUMO})$$

$$\mu = -\frac{1}{2}(I + A) = -\frac{1}{2}(\varepsilon_{HOMO} + \varepsilon_{LUMO})$$

$$\chi = \frac{I + A}{2}$$

where $I = -\varepsilon_{HOMO}$ and $A = -\varepsilon_{LUMO}$

Where I and A are the ionization potential and electron affinity of the molecules respectively.

The DFT method predicts that the HOMO – LUMO energy gap of MET/Cl is 0.175a.u. which is found to be very low and it leads to less stability of the molecule and it is more polarizable as the frontier orbital gap is small and is associated with low kinetic stability, high chemical reactivity.

The low ionization energy 0.214a.u. of MET/Cl shows that the molecule is highly reactive. Electronegativity measures the power of an atom to attract electrons to it. The target molecule has electronegativity of 0.126a.u. and so it has low capacity of attracting electrons from the neighboring molecules. Softness is used to measure the extent of chemical reactivity and is the measure of the capacity of an atom or group of atoms to receive electrons [12]. It is the reciprocal of hardness.

$$S = 1/2\eta$$

The calculated softness value for this molecule is very high and is found to be 5.715a.u. and this states that the molecule is very soft. Notably if the HOMO and the LUMO are close together, the absolute hardness is low and the atoms or molecules are ready to share the electrons to create the covalent bond. The title molecule has very low HOMO – LUMO energy gap of 0.175a.u. which forms a strong bond with other polarizable molecule. This is the most desirable property for any possible intermolecular interaction between a pharmaceutical compound and a bio molecule and a tool to forecast whether the molecule is a fast interacting drug or not. Moreover MET/Cl has very less toxicity as the electrophilicity index [13] is very low (0.090a.u.).

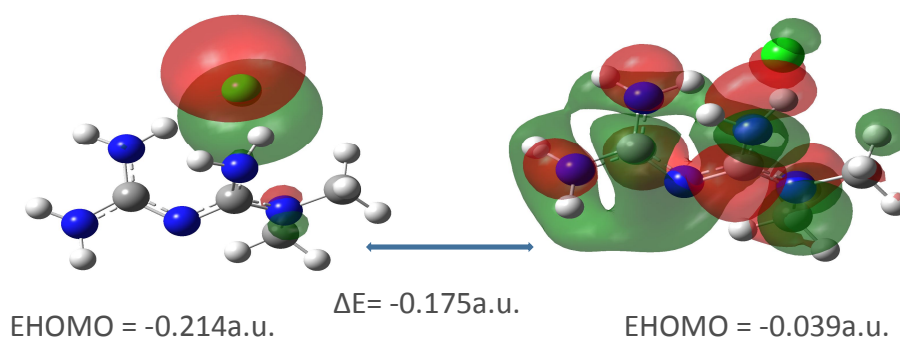


Fig. 3. Plots of HOMO, LUMO and energy gap of MET/Cl.

The reactivity descriptors have been listed in Table 1.

Table 1. Reactivity descriptors of MET/Cl molecule.

Reactivity descriptor	Energy(a.u.)	Reactivity descriptor	Energy(a.u.)
Electron affinity $A=[-E_{LUMO}]$	0.039	Electronegativity $\chi=(I+A)/2$	0.126
Ionization potential $I=[-E_{HOMO}]$	0.214	Electrophilicity index $\omega=\mu^2/2\eta$	0.090
Global hardness $\eta=(I-A)/2$	0.088	HOMO energy	-0.214
softness $S=1/2\eta$	5.715	LUMO energy	-0.039

Electrostatic potential and docking analysis

The electrostatic potential is very effective tool to predict the reactive sites of the molecule with the target molecule[14]. The Fig.4a clearly shows the electrophilic and nucleophilic regions of the MET/Cl molecule. The large electronegative region(red colour isosurface) is found in the vicinity of the Cl anion which is susceptible to electrophilic attack and large positive region(blue colour isosurface) is seen on the MET cation which is prone to nucleophilic attack.

The interaction of drug with protein(Fig.4b) can be understood through docking analysis. Interaction of the Metformin drug with the amino acid residues present in the 1FM9 protein. The N atoms are interacting with the amino acid residues such as Hn, Hg1, Hz2 present in the 1FM9.

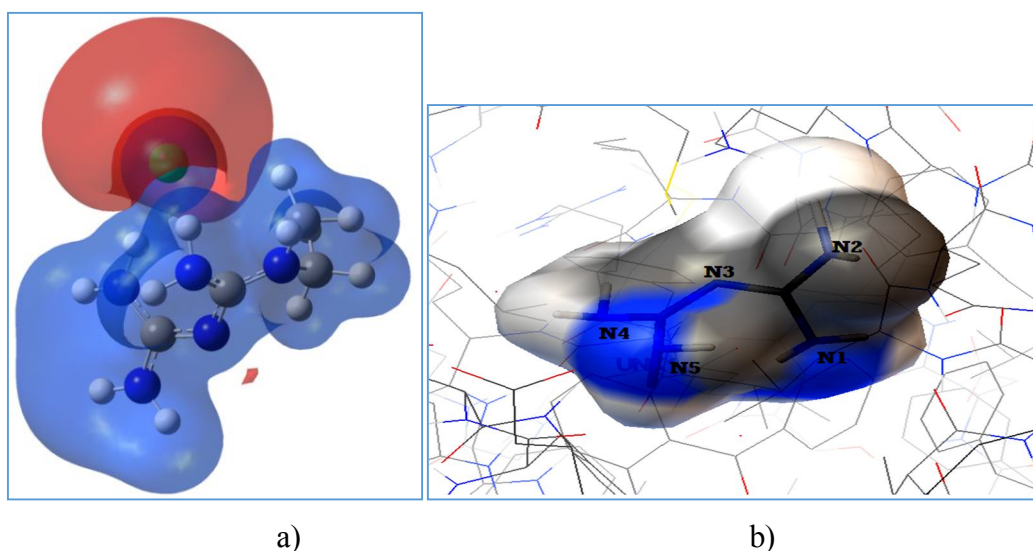


Fig. 4. a) View of electrostatic potential of MET/Cl b) Interaction of metformin cation with the amino acid residues of 1FM9 protein.

NBO Analysis

The NBO analysis provides information on the intermolecular interactions of the molecule and it plays vital role in interpreting the hyper conjugative interaction and electron density transfer from the filled lone pair electron[15]. The condition for occurring intra-molecular charge transfer is the orbital overlap between bonding(σ) and non-bonding(σ^*) orbital which stabilizes the system. Table2 gives

the Second order perturbation theory analysis of Fock matrix in NBO basis corresponding to the intramolecular of the MET/Cl compound. The interaction of $\sigma(\text{C1} - \text{H2})$ with the $\sigma^*(\text{C5} - \text{N11})$ takes the highest hyperconjugative energy and is found to be 3.72kcal/mol. The interaction between the bonding $\sigma(\text{C5} - \text{H6})$ and anti-bonding $\sigma^*(\text{N11})$ takes the lowest hyper conjugative energy, 0.51kcal/mol.

Table 2. Donor and acceptor NBO and energy details of MET/Cl.

Donor NBO(i)	Acceptor NBO(j)	E ^{(2)a} kcal/mol	E(j)-E(i) ^b a.u.	F(i,j) ^c a.u.	Donor NBO(i)	Acceptor NBO(j)	E ^{(2)a} kcal/mol	E(j)-E(i) ^b a.u.	F(i,j) ^c a.u.
$\sigma(\text{C1} - \text{H2})$	$\sigma^*(\text{C5} - \text{N11})$	3.72	0.85	0.050	$\sigma(\text{C9} - \text{N13})$	$\sigma^*(\text{C10})$	2.59	1.95	0.064
$\sigma(\text{C1} - \text{H3})$	$\sigma^*(\text{C9} - \text{N11})$	2.74	1.02	0.048	$\sigma(\text{C10} - \text{N1})$	$\sigma^*(\text{N13})$	0.82	1.61	0.033
$\sigma(\text{C1} - \text{H4})$	$\sigma^*(\text{N11})$	0.68	1.32	0.027	$\sigma(\text{C10} - \text{N15})$	$\sigma^*(\text{N13})$	0.53	1.62	0.026
$\sigma(\text{C1} - \text{N11})$	$\sigma^*(\text{C5})$	0.76	1.48	0.030	$\sigma(\text{N12} - \text{H16})$	$\sigma^*(\text{C9})$	0.55	1.86	0.029
$\sigma(\text{C5} - \text{H6})$	$\sigma^*(\text{N11})$	0.51	1.31	0.023	$\sigma(\text{N12} - \text{H17})$	$\sigma^*(\text{C9})$	1.95	1.87	0.054
$\sigma(\text{C5} - \text{H7})$	$\sigma^*(\text{C9} - \text{N11})$	3.38	1.02	0.053	$\sigma(\text{N14} - \text{H18})$	$\sigma^*(\text{C10})$	0.84	2.25	0.039
$\sigma(\text{C5} - \text{H8})$	$\sigma^*(\text{C1} - \text{N11})$	3.21	0.85	0.047	$\sigma(\text{N14} - \text{H19})$	$\sigma^*(\text{C10})$	1.43	1.80	0.045
$\sigma(\text{C5} - \text{N11})$	$\sigma^*(\text{C1})$	0.78	1.52	0.031	$\sigma(\text{N15} - \text{H20})$	$\sigma^*(\text{C10})$	1.78	1.75	0.050
$\sigma(\text{C9} - \text{N11})$	$\sigma^*(\text{C1})$	0.75	1.65	0.032	$\sigma(\text{N15} - \text{H21})$	$\sigma^*(\text{C10})$	0.93	1.77	0.036
$\sigma(\text{C9} - \text{N12})$	$\sigma^*(\text{C1} - \text{N11})$	3.61	1.17	0.058					

E^{(2)a} refers energy of hyperconjugative interaction;

E(j)-E(i)^b refers energy difference between donor and acceptor i and j NBO orbitals;

F(i,j)^c refers the Fock matrix element between i and j NBO orbitals.

Summary. This study gives clear picture about the structure, electronic properties, nature, chemical reactivity and molecular electrostatic potential of the biguanide MET/Cl. The three analyses of charges report that all the N atoms have negative charges and especially the Cl anion has the highest negative charge. The molecule is very soft in nature and highly polar molecule, less toxic when compared to the other biguanides, highly chemically reactive and a fast interacting drug. The Cl anion is susceptible to electrophilic attack and the MET cation is susceptible to nucleophilic attack. The NBO analysis lists out the highest and lowest interaction of hyperconjugative energy. The docking analysis reveals the interaction of metformin cation with the amino acid residues present in the 1FM9 protein.

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