

Density functional theoretical studies on 2-methyl-4-chlorophenoxyacetic acid (MCPA)

R P Singh Grewal^{*a} & Girija Sharma^b

^a Applied Sciences Department, Guru Nanak Dev Engineering College, Ludhiana 141 006, India

^b I. K. Gujral Punjab Technical University, Kapurthala 144 603, India

E-mail: rpsinghchem@gmail.com; girijasharma05@gmail.com

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MCPA is a post-emergence herbicide for control of wild oats and annual grassy weeds found among several economically important crops. In the present work, the Eigen values and Eigen functions of the MCPA have been calculated using two basis sets of DFT. The Global DFT descriptors for the compound have also been calculated. The Fukui functions, local softness, and atomic charges for each center of MCPA have also been calculated. It has been found that all the reactivity centers of MCPA are not equal in chemical reactivity. The differences in chemical reactivity of different sites have been investigated in detail in this work.

Keywords: DFT, 2-methyl-4-chlorophenoxyacetic acid, post-emergence herbicide, The Fukui function, atomic charge

2-Methyl-4-chlorophenoxyacetic acid (MCPA) is a selective post-emergence herbicide for control of wild oats and annual grassy weeds found among brassicas, carrots, celery, field beans, French beans, broad beans, barley, wheat, parsnips, peas, potatoes, soy beans, oilseed rape, onions, sugar beet, and lettuce. The structure of MCPA includes a carboxylic acid group, and an ether linkage with chlorophenyl moiety. The acidic herbicide MCPA can resist biodegradation. The mechanism of action of MCPA is not well understood. MCPA is one of the top 10 herbicides used across the world, most extensively in the Canada, a very few theoretical studies have been done¹. Hence the study of reactivity of MCPA has been carried out in this work.

Now a day, Density Functional Theory² has been widely accepted as a useful tool to study the fundamental properties of atoms, molecules, and chemical reactions. Density functional theory is a quantum mechanical theory used in physics and chemistry to investigate the electronic structure of many-body systems like the atoms, molecules, and condensed phases. The DFT has provided some very important computational methods by which the activity of target molecule can be measure prior to their synthesis. Hence, it will help the experimental scientists to design some effective herbicides. It is well-known that the structure of a molecule determines many of its physicochemical properties³. It

is also well established that the activity of molecules is reliant on the molecular electronic wave function. Using the DFT methods we can compute many molecular reactivity descriptors like Global Hardness, Chemical Potential, Electronegativity, Electrophilicity etc which in turn can be used to explain several molecular properties. For its computational benefits, among physicists and chemists, density functional theory is one of the most popular and successful quantum mechanical approaches to matter and real life problems. DFT is applied in studying the band structure of solids, biological phenomenon and in mineralogy. It is also applied in the field of superconductivity, relativistic effect atomic nucleus, classical liquids, the magnetic properties of alloys and condensed matter physics etc. DFT based computational methods can also be applied in the agricultural field. The success of density functional theory (DFT) not only encompasses standard bulk materials but also complex materials such as proteins and carbon nanotubes.

DFT can also be applied to synthesize risk free herbicides. The commercial exploitation of a compound as a herbicide is likely to require, at some stage of its development, the determination of biological or chemical activities or properties related to the intended end use of the compound. It is desirable, therefore, to have at hand relatively straightforward and inexpensive procedures enabling

the efficient and accurate prediction of molecular activity or property especially when its direct measurement by experiment is to be avoided if at all possible. The procedures that are conventionally used for indirect determinations of activities make use of molecular “descriptors” which include suitable molecular properties and physical-organic constructs obtained from both experimental and computational sources. The aim of the present article is to find out the reactive centers of the chemical MCPA through computational techniques.

Molecular Global Reactivity Descriptors

The resistance power of a chemical species towards the deformation or polarization of the electron cloud of that species under small perturbation of charge cloud during chemical reaction is defined as the chemical hardness of that species⁴. In simple words, it describes the chemical stability of the compound.

The chemical potential of a species in a mixture can be defined as the slope of the free energy of the system with respect to a change in the number of moles of that species. It is a form of potential energy that can be absorbed or released during a chemical reaction. Parr *et al.*⁵ defined the electronegativity as negative of the chemical potential, “Although electronegativity is defined in many different ways, the most logical and rational definition of it is the electron holding power of the atoms or molecules”⁶.

The electrophilicity index is a global reactivity descriptor of a molecule that provides a quantitative classification of the global electrophilic nature of the molecule. According to Parr *et al.*⁷ the electrophilicity measures the electrophilic power of a ligand to “soak up” electrons.

Highest Occupied Molecular orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) also known as Frontier Molecular Orbitals (FMO). FMO play significant role in determination of reactivity of a chemical species. Energy gap between HOMO-LUMO explains the bioactivity from intra-molecular charge transfer⁸. HOMO-LUMO energy gap helps to explain the chemical reactivity and kinetic stability⁹. HOMO act as electron donor and LUMO act as electron acceptor. HOMO – LUMO energy gap explains the energy required for the charge transfer within the molecule.

In the present work the herbicide 2-Methyl-4-Chlorophenoxyacetic Acid (MCPA) is studied using DFT methods. This article aims to compute the global

and local descriptors using DFT method. This technique can also be extended to design some modified sprout inhibitors having reduce toxicity. The main advantage of adopting the theoretical technic is that it can reduce the inhibitor discovery cost, time and efforts.

Computational Method

In this present study, geometry optimization and vibrational frequencies for MCPA in gas phase are carried out at the 6-31G/ B3LYP and 6-31G++/ B3LYP level of theory^{10,11} with the help of Gaussian 03 package program¹².

HOMO-LUMO structures for MCPA obtained using DFT method and basis set 6-31G/B3LYP. The HOMO-LUMO orbital energies are used to calculate chemical hardness, Electronic chemical potential and electrophilicity using the following equations (Eqs 1-4) of CDFT.

The Hardness (η), Chemical Potential (μ), and Electronegativity (χ) are calculated using Pearson’s methods.

$$\eta = -(\epsilon_{\text{HOMO}} - \epsilon_{\text{LUMO}})/2 \quad \dots (1)$$

$$\mu = (\epsilon_{\text{HOMO}} + \epsilon_{\text{LUMO}})/2 \quad \dots (2)$$

$$\chi = -\mu = -(\epsilon_{\text{HOMO}} + \epsilon_{\text{LUMO}})/2 \quad \dots (3)$$

The electrophilicity index (ω) is calculated using the method suggested by Parr *et al.*¹⁵

$$\omega = \chi^2/2\eta \quad \dots (4)$$

The local reactivity descriptors

Fukui Functions

The Fukui functions¹³ play a prominent role in the field known as conceptual Density Functional Theory (DFT)¹⁴. Yang and Parr¹⁵ based on the original ideas of Fukui¹³, introduced Fukui function which reflect the response of a molecular system towards a change in the number of electrons (N_e) of the molecular system under consideration. The Fukui functions is a measure of local reactivity and defined as:

$$f(r) = (\partial \rho(r) / \partial N)_v \quad \dots (5)$$

Where $\rho(r)$ is the electron density.

In frontier orbital theory, the two orbitals, the HOMO and the LUMO, are the most important in correlating the molecular reactivity and suggesting orientation of a group in the molecule. It is a fact that the reaction takes between two reactants locally and

not globally. The algorithms used to define the Fukui functions are as follows:

For governing electrophilic attack,

$$f^-(r) = [\partial\rho(r) / \partial N]_{v(r)}^- \quad \dots (6)$$

For governing nucleophilic attack,

$$f^+(r) = [\partial\rho(r) / \partial N]_{v(r)}^+ \quad \dots (7)$$

For governing radical attack,

$$f^0(r) = [\partial\rho(r) / \partial N]_{v(r)}^0 \quad \dots (8)$$

Fukui function measures the response of the electron density at every point r and the sites with the largest value for the Fukui functions are those with the largest response, and as such the most reactive sites within the molecule. According to the "frozen core" approximation, the operational algorithms proposed⁴ to calculate the Fukui functions are as follows:

For governing electrophilic attack,

$$f^-(r) \approx \rho_{\text{HOMO}}(r) \quad \dots (9)$$

for governing nucleophilic attack,

$$f^+(r) \approx \rho_{\text{LUMO}}(r) \quad \dots (10)$$

for governing radical attack,

$$f^0(r) \approx \frac{1}{2} [\rho_{\text{HOMO}}(r) + \rho_{\text{LUMO}}(r)] \quad \dots (11)$$

The Fukui function has been used in several works as a natural descriptor of site selectivity. Within the Li and Evans reactivity and selectivity rules¹⁶, for soft-soft interactions, the preferred reactive site in a

molecule should have the highest value of the Fukui function, whereas the hard-hard interactions are supposed to be described through the minimum value of this local index often the reactivity in molecules with only one reactive site can be correctly characterized. However, for poly-functional systems where more than one site can be attacked, the Fukui function seems to fail predicting the selectivity of hard-hard interactions since hard-hard interactions are charge controlled and soft-soft interactions are frontier controlled, the Fukui function is not expected to describe well the hard-hard interactions. In a recent work, using the properties of Fukui function, more powerful descriptor of chemical reactivity and site selectivity have been proposed by Chattraaj *et al.*¹⁷

Results and Discussion

The IUPAC name and structure of MCPA are given in Table I.

The above structure of MCPA is used as input file in Gauss view 3.09. First calculation has been done for optimization and frequency. From here we get optimized structures of the chemical MCPA. Optimized structures are the most stable structure with minimum energy. Optimized structure for MCPA is shown in Figure 1.

HOMO-LUMO structures for MCPA obtained using DFT method and basis set 6-31G/B3LYP and B3LYP/6-31G++ are shown in Figure 2(a) and Figure 2(b) and Figure 3(a) and Figure 3(b) respectively.

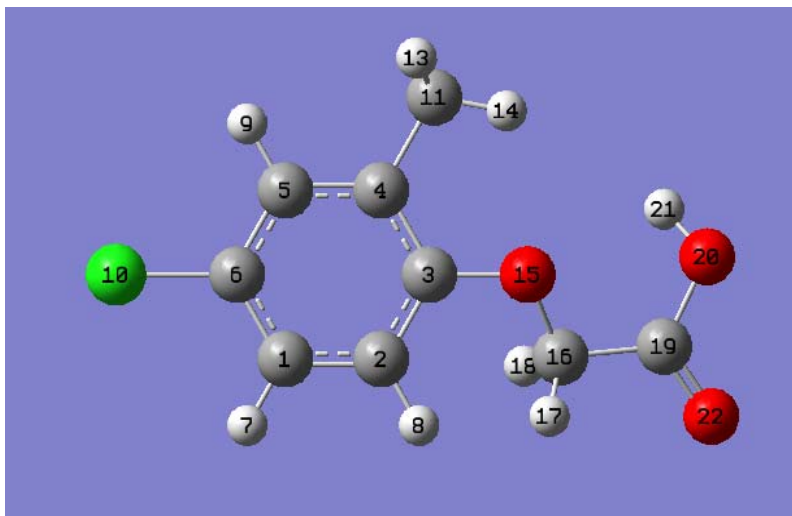
The calculated HOMO-LUMO orbital energies, HOMO-LUMO energy gaps and dipole moments are

Table I — IUPAC name and structure of MCPA

IUPAC name

2-Methyl-4-Chlorophenoxyacetic Acid

Structure



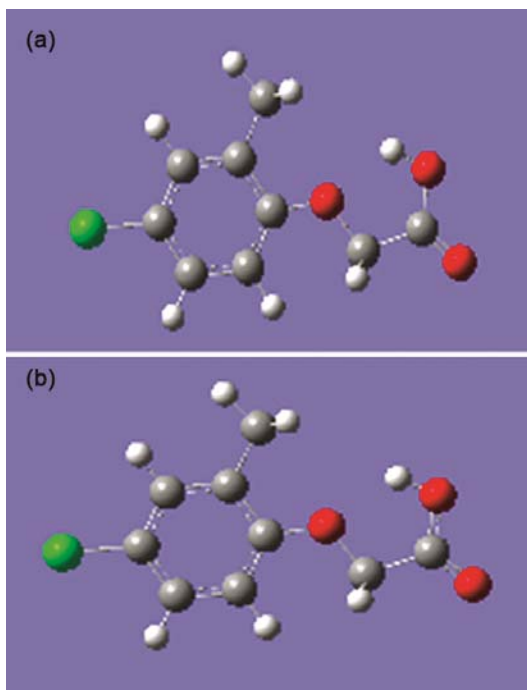


Figure 1 — (a): Optimized structure of MCPA with basis set B3LYP/6-31G++(DP), (b): Optimized structure of MCPA with basis set B3LYP/6-31G(DP)

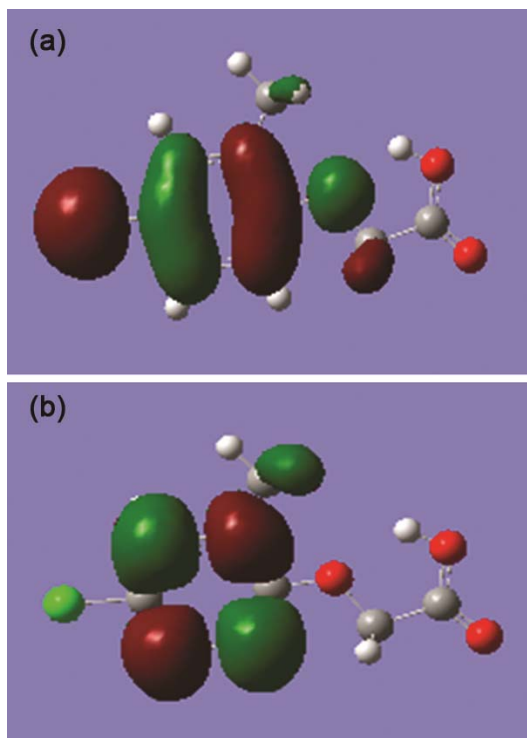


Figure 2 — (a): HOMO WITH B3LYP/6-31G(DP), (b): LUMO WITH B3LYP/6-31G(DP)

presented in Table II. Using the HOMO LUMO energies, the chemical hardness, the electronic

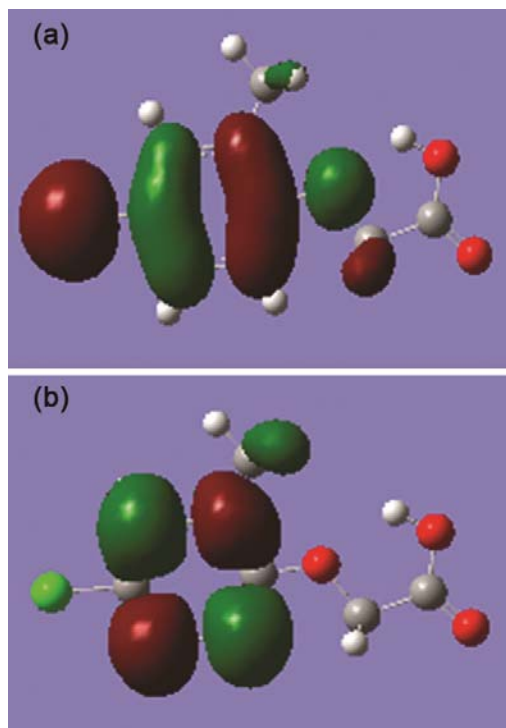


Figure 3 — (a): HOMO WITH B3LYP/6-31G++(DP), (b) LUMO WITH B3LYP/6-31G++(DP)

Basis Set	Dipole Moment (μ)	HOMO(eV)	LUMO	Energy Gap
6-31G++(d,p)	2.7478	-6.697158	-1.1156674	5.6055484
6-31G(d,p)	2.3626	-6.4491018	-0.7074964	5.7416054

chemical potential and electrophilicity of MCPA are computed using Eq. 1, Eq. 2, Eq. 3 and Eq. 4 respectively. The computed chemical hardness, electronic chemical potential and electrophilicity data of the two compounds are presented in Table III.

Atomic Charges (Mulliken atomic charge and Atomic charges with hydrogens summed into heavy atoms) are computed using B3LYP/6-31G++ (d,p) and B3LYP/6-31 (d,p) basis sets.

The NBO analysis has been done to calculate Fukui functions (f_k^+ , f_k^- , f_k^0).

It is well known that the Fukui function represents the response of the chemical potential of a system to a change in external potential and could thus be regarded as an important index of reactivity.

It is known that atomic charges and frontier orbital theory (FMO) are generally used to probe the regio-selective nature of a reaction. Thus, DFT-based

parameters that combine both charge and orbital information could emerge as a novel and alternative approach to the site selectivity problem in chemical reactions.

It should be stressed that local softness mainly accounts for the charge transfer terms of the interaction energy that can best be related to a soft acid – soft base affinity. Charge transfer is however not the sole factor responsible for site-selectivity.

The carboxyl group of 2-Methyl-4-chlorophenoxyacetic acid in aqueous environment deprotonated, and they become negatively charged. Usually the carboxyl group is deprotonated at $\text{pH} > 7$. The atomic charge on the C-11 will be high due to the so called inductive effect.

Hence our expectation is that the C-3, C-11, C-19, O-22, O-10, H-21, O-15 will be more reactive than others.

The results of calculation with basis set 6-31G++ are presented in Figure 4.

Figure 4 reveals that the center C-11 has maximum Mulliken charge density (negative). Mulliken charge density (negative) of the centers C-1, C-3, C-11, O-15, O-20 and O-22 are very high which indicates the sites are prone towards electrophile. This fact is supported by our common experience with the properties of Carboxylic acid group and Methyl group. The Mulliken charge densities (positive) of the centers C-2, C-19, and H-21 are high which indicates the sites are prone towards nucleophile.

Figure 5 reveals that the center O-15 has maximum Mulliken charge density (negative). Mulliken charge density (negative) of the centers C-3, C-11, O-20 and O-22 are very high which indicates the sites are prone towards electrophile. This fact is supported by our common experience with the properties of Carboxylic acid group and Methyl group. The Mulliken charge densities (positive) of the centers C-19, and H-21 are high which indicates the sites are prone towards nucleophile.

Table III — Electronegativity, chemical potential, Hardness, Softness, Electrophilicity index

Basis set	Electro negativity (χ)	Chemical Potential	Hardness (η)	Softness (s)	Electrophilicity index (ω)
6-31G ++(d,p)	3.918	-3.918	2.791	0.3583	2.750
6-31G (d,p)	3.578	-3.578	2.871	0.3483	2.229

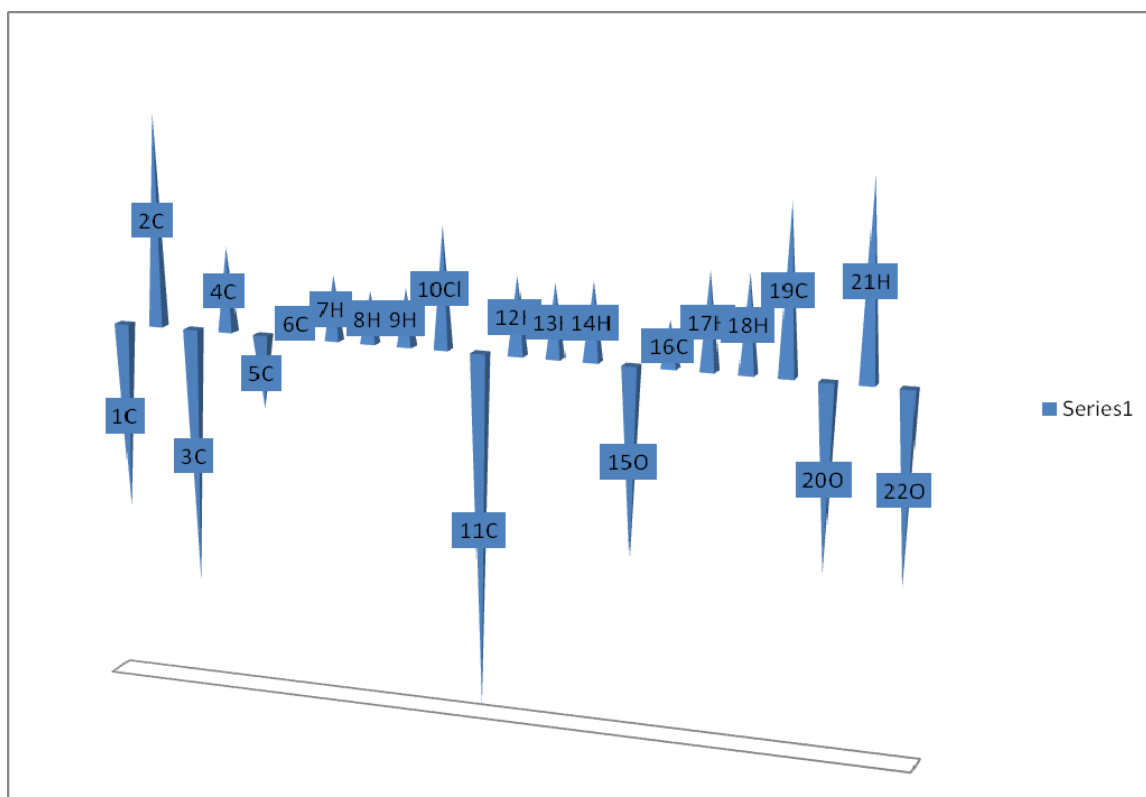


Figure 4 — Atomic Charges using B3LYP/6-31G++ (d,p)

Calculation of Fukui functions with basis set 6-31G++ and 6-31 G were done to check the reactivity of the above mentioned atomic centers. The results of calculation of Fukui functions with basis set 6-31G++ and 6-31 G are presented in the Figure 6 and Figure 7.

Figure 6 reveals that the center O-15 has the maximum f^+ value. The f^+ values of the centers C-3, C-11, O-20 and O-22 are very high which indicates the sites are prone towards electrophile. This fact is supported by our common experience with the

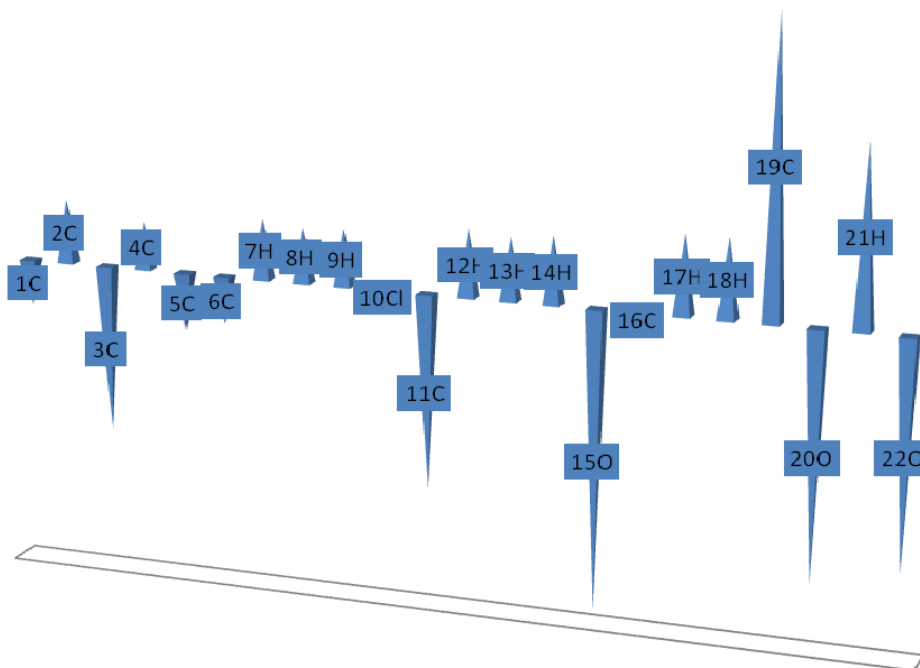
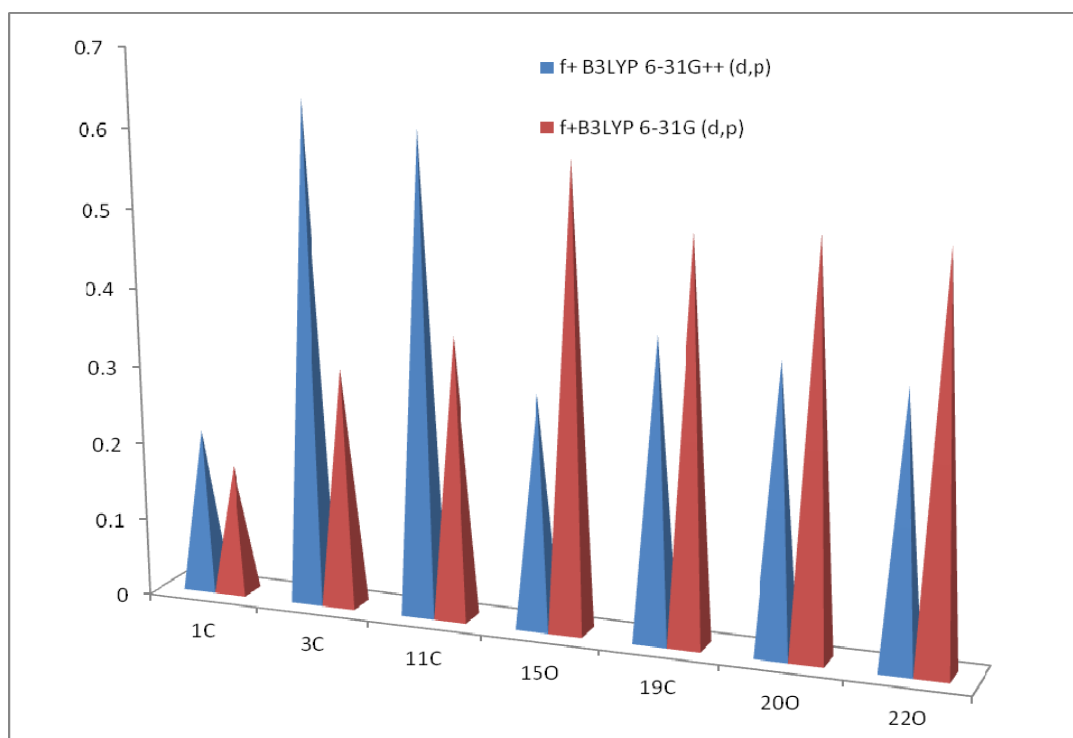


Figure 5

Figure 6 — Computed f^+ values

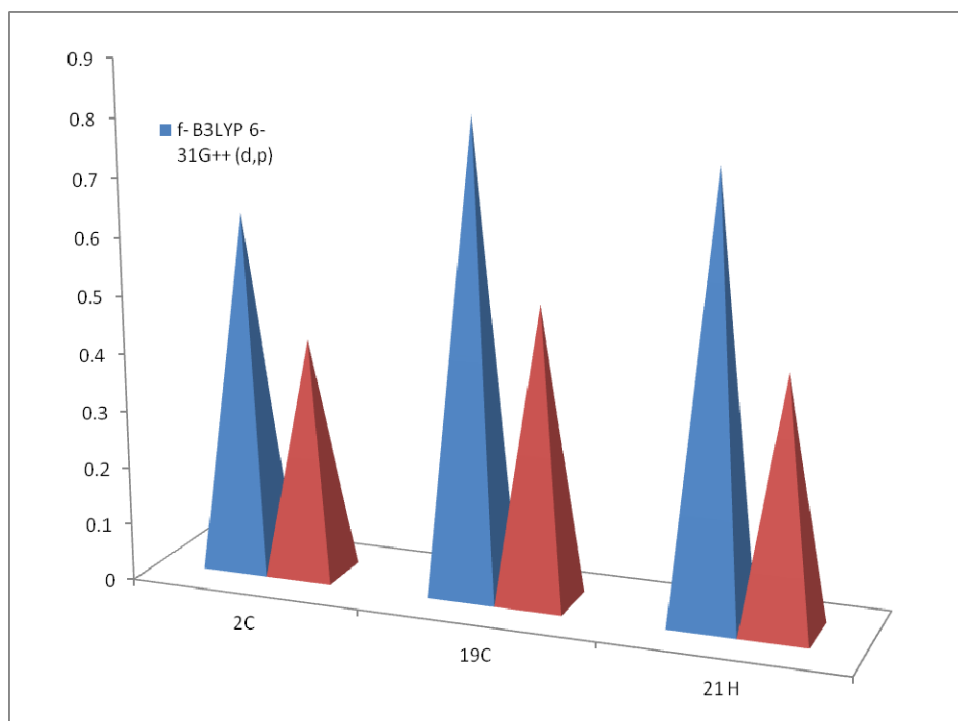


Figure 7 — shows that the f values of the centers C-19, and H-21 are high which indicates the sites are prone towards nucleophile. Actually the carboxylic H atoms can be easily abstracted by nucleophile and the anion is stabilized. The fact is supported by the computed Fukui function value of the H-21.

properties of Carboxylic acid group and Methyl group. The f^+ values of the centers C-19, and H-21 are high which indicates the sites are prone towards nucleophile.

Conclusion

MCPA is a post-emergence herbicide for control of wild oats and annual grassy weeds found among brassicas, carrots, celery, field beans, French beans, broad beans, barley, wheat, parsnips, peas, potatoes, soy beans, oilseed rape, onions, sugar beet, and lettuce. In this work, using two basis sets of DFT, we have calculated the Eigen values and Eigen functions of the MCPA. We have also calculated the Global DFT descriptors for the compound. The Fukui functions, local softness, and atomic charges for each center of MCPA are also calculated. It is well known fact that the donor- acceptor interaction is one of the key factors for selective chemical reaction. Hence to study the effectiveness of the MCPA we need to study the reactivity of the different sites of the compound. We have found that all the centers are not equal in chemical reactivity. Also we have pointed out the maximum reactive site(s) of the compound under study. The differences in chemical reactivity of different sites for are nicely represented in this work.

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