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Research Article

Theoretical Study of the Regioselectivity of some Monomers: Chitin and Chitosan

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ABSTRACT

Biopolymers have become more and more attractive nowadays for both experimental and theoretical studies because of their importance in our daily life. In this contribution, the electronic properties and reactivity behavior of some biomonomers; chitin and chitosan have been thoroughly investigated theoretically using density functional theory (DFT) B3LYP/6-31G(d) level of theory. The regioselectivity of these molecules has been rationalized by using both Fukui and Parr indices in order to explain and show the most probable sites to be attacked towards nucleophiles and electrophiles. For the three studied monomers, the oxygen and nitrogen atoms were found to be the most reactive sites. Parr functions and Fukui functions found to be complementary while explaining the possible regioselectivity.

Keywords: DFT, Monomers, Fukui and Parr functions, Regioselectivity.

1. INTRODUCTION

Chitosan (CTS), is a biopolymer, it is a deacetylated product of the polysaccharide chitin, obtained from various organisms, including the exoskeleton of crustaceans, like crabs, crawfish, prawns, lobsters, shrimps, and the cell walls of some fungi such as *Aspergillus*.[1,2]

Chitin, the second most abundant natural polysaccharide, after cellulose, is the major component of the exoskeleton of crustaceans, it is a linear biopolymer, composed of repeating *N*-acetyl-2-amido-2-deoxy-D-glucose units linked by β-(1 → 4) bonds.[3]

Chitosans, the partially *N*-deacetylated analog of chitin, are linear heterocopolymers of two different substituted D-glucopyranose which are derived from chitin by either homogeneous or heterogeneous chemical means.[4-7]

Generally, chitosan can be distinguished from chitin by the degree of acetylation (DA), with chitosan having lower than 50% of DA values, and chitin having higher percentages. Note that there is no unique polymer structure for chitosan (it is not a single polymer), but a family of polymers with differences in their composition; depend on its DA, and its molecular weight. Chitosan has attracted the attention of both scientists and industrials in various domains such as pharmaceutics, biomedicine, biotechnology, packaging, cosmetics, food processing, nutritional enhancement, and wastewater treatment, among others. Chitosan is a natural resource with many interesting properties such as, excellent film-forming, high biocompatibility, easy degradability, and thus is very useful for preparing films for food packaging, and more importantly their major use is as an edible coating to preserve food as long as possible, fresh fruits and vegetables. Moreover, chitosan has met a specific interest as a coating material, because of its significant film-forming properties coupled with its antifungal properties and antimicrobial activity.[8,9] The development of synthetic membranes based on chitosan as biocompatible polymers has been a promising point of research recently because of its multiple and several applications such as biochemical, environmental separations, artificial organs and controlled drug delivery devices, mainly using the swelling/deswelling phenomenon of chitosan.[10-12] The mucoadhesive properties of chitosan make of it a considerable component used for nasal drug and vaccine delivery applications.[13-15]

The modification of saccharides according to the regioselectivity of saccharides is persistently interesting for scientists since 1991 to our days.[16-22]

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Regioselectivity of glycosylation reactions of galactose saccharide acceptors have been studied, and it was successfully rationalized; they evaluated the model of D-galactose and analyzed the reactivity of the OH-3 and OH-4 attached to methyl groups of saccharide.[17] The experimental and computational studies of the regioselective acetal protection of saccharide-based diols using chiral phosphoric acids (CPAs) and their immobilized polymeric variants, as the catalysts, have been successfully developed.[18] In a previous paper, Ieng Chim (Steven) Wan et al. investigated the origin of regioselectivity of metal catalyzed oxidation of glucopyranosides on the basis of density functional theory.[20]

The aim of this paper is to present a DFT elucidation of the regioselectivity of chitosan and chitin monomers and shed light on their reactivity using different theoretical approaches such as Fukui and Parr indices.

2. MATERIALS AND METHODS

The calculations were carried out with Gaussian09 suit of program.[23] DFT calculations were done using the B3LYP functional in conjunction with basis set 6-31G.[24-26] Optimizations were performed using Berny's method.[27] The obtained structures were checked by frequency calculations. Fukui indices were calculated using natural population analysis (NPA),[28,29] whereas Parr functions were produced using Mulliken population analysis (MPA).[30-32]

2.1. Theoretical Studies

Electrophilicity Fukui index (f^{+}) of a given atom A in molecule M (of N electrons)

$$f_A^+ = P_A(N+1) - P_A(N) \qquad (1)$$

Nucleophilicity Fukui index (f^{-}) of a given atom A in molecule M (of N electrons)

$$\mathbf{f_A^- = P_A(N) - P_A(N-1)} \qquad (2)$$

where P_A is the population of atom A in molecule M.
Global electronic properties such as chemical electronic potential **μ**, hardness **η**, electrophilicity ***ω***, and nucleophilicity ***N*** were calculated using the expressions:[33-35]

$$\mu = \frac{1}{2}(E_{HOMO} + E_{LUMO}) \qquad (3)$$

$$\eta = \frac{1}{2}(I - A) \qquad (4)$$

$$\omega = \frac{\mu^2}{2\eta} \qquad (5)$$

$$N = E_{HOMO} - E_{HOMO(TCE)} \qquad (6)$$

where E_{HOMO} is the HOMO energy of the system and $E_{HOMO(TCE)}$ is the HOMO energy of tetracyanoethylene (TCE) taken as reference where $E_{HOMO(TCE)}$= -0.34427a.u.

Local electrophilicity ω_k and local nucleophilicity N_k are defined by the equations:

$$\omega_k = \omega f_k^+ \qquad (7)$$

$$N_k = N f_k^- \qquad (8)$$

where ω and N are the electrophilicity and nucleophilicity indexes.
In order to calculate Parr indices, the following expressions were used:[35]

$$\boldsymbol{P_k^- = \rho_s^{rc}(k)} \text{for electrophilic attack} \qquad (9)$$

$$P_k^+ = \rho_s^{ra}(k) \text{ for nucleophilic attack} \qquad (10)$$

where $\rho_s^{rc}(k)$ is the cation atomic spin density (ASD), and $\rho_s^{ra}(k)$ is the anion atomic spin density (ASD). Each ASD provides local nucleophilic and electrophilic Parr functions of the neutral system.
Using $P^-(k)$ and $P^+(k)$, it is possible to define the local electrophilicity ω_k and the local nucleophilicity N_r indices as follow.[31,32,35]

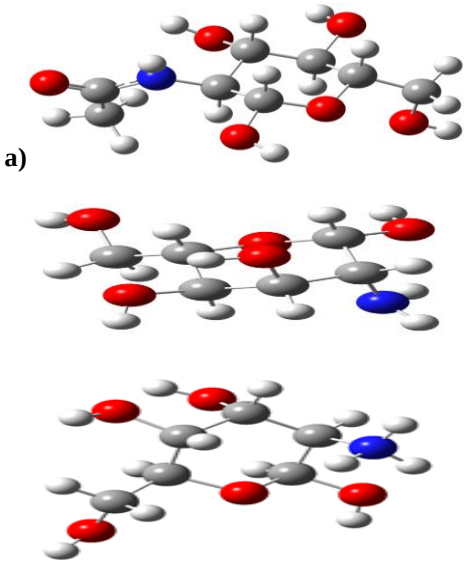
$$\omega_k = \omega \rho_k^+ \qquad (11)$$

$$N_k = N \rho_k^- \qquad (12)$$

3. RESULTS AND DISCUSSION

3.1. Structural and Electronic Properties

The molecular structures of the three studied monomers are given below in Figure 1.



a)

b)

c)

Figure 1. Molecular structures of (a) chitin, (b) chitosan and (c) protonated chitosan optimized at B3LYP/6-31G.

Table 1. Global electronic properties (eV) of the studied molecules at B3LYP/6-31G level.

Molecule	E_{HOMO}	E_{LUMO}	μ	η	ω	N
Chitin	-6.61	0.80	-0.11	0.14	1.14	2.76
Chitosan	-6.01	1.24	-0.09	0.13	0.78	3.42

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Protonated Chitosan	-10.49	-3.86	-0.26	0.12	7.77	-1.12

From **Table 1**, it can be seen that, for chitin and chitosan, the nucleophilicity index is much greater than the electrophilicity index. This means that these molecules act more likely as nucleophiles rather than electrophiles. However, the protonated chitosan shows a reverse behavior where the electrophilicity index value is much greater than the nucleophilicity one. Hence, the protonated chitosan will act as electrophile. This gives a clear idea about the impact and effect of protonation on chitosan.

The frontier molecular orbitals (HOMO and LUMO) energy gap is very useful parameter to predict reactivity of a given molecule. For this purpose, the HOMO and LUMO schemes as well as the corresponding gaps for the three studied monomers have been calculated and presented in Figure 2.

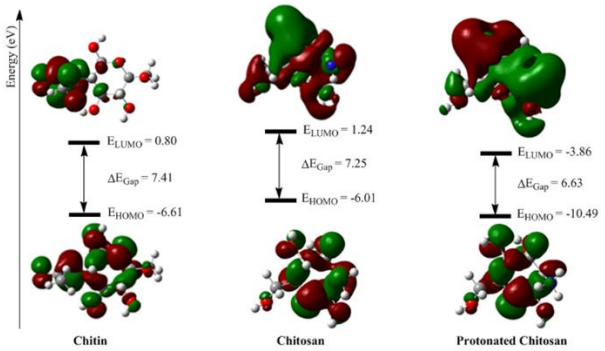

Figure 2. HOMO and LUMO plots.

It is well known that the smaller gaps correspond to greater reactivity. The descending order of gaps is given as: ΔE_{GAP} (Chitin) > ΔE_{GAP} (Chitosan) > ΔE_{GAP} (Protonated chitosan). This shows that the order of reactivity is: Protonated chitosan > Chitosan > Chitin. Looking to the charge distribution, the electron density is found to be more localized on the heteroatoms especially the ones belonging and surrounding heterocyclic ring.

3.2. Fukui and Parr study

In order to predict and localize the most nucleophilic and the most electrophilic sites for each molecule, the Fukui and Parr indices have been investigated. The obtained results are listed in the following Tables 2-5.

In Table 2, the most important quantities of N_k are in bold with red color for Fukui indices and black for Parr functions. It can be seen that all oxygen atoms of chitin exhibit a nucleophilic character. The five atoms **O11**, **O15**, **O19** and **O24** show a value of around 0.1 for Fukui N_{kF} and variable values of Parr N_{kP}. **O17** has a remarkable value of 0.25 for N_{kF} and 0.33 for N_{kP}. However, **O24** which belongs to the acetyl group is the most nucleophilic oxygen atom of this molecule (Figure 3). The same thing is seen for the nitrogen atom **N21** that presents a very pronounced N_{kF} value after the **O24**. It is worthy to note, here too, that the nitrogen atom is directly bonded to the acetyl group. The order of reactivity for oxygen atoms using Fukui indices N_{kF} is: **O24 > O17 > O15 > O11 ≡ O19 > O29**. On the basis of Parr functions N_{kP}, the order can be given as: **O24 > O17 > O15 > O29 > O11 > O19**.

Table 2. Fukui indices f^-, f^+, Parr functions P_k^+, P_k^-, local electrophilicity ω_k^+, and nucleophilicity N_k for chitin at B3LYP/6-31G.

	Fukui Indices				Parr Functions			
Atom k	f_k^+	f_k^-	ω_{kF}^+	N_{kF}	P_k^+	P_k^-	ω_{kP}^+	N_{kP}
C1	0.03	-0.01	0.02	-0.02	0.08	0.01	0.09	0.02
C2	-0.01	-0.01	0.00	-0.01	0.00	0.02	-0.01	0.05
C3	0.02	0.00	0.01	-0.01	0.05	0.05	0.06	0.14
C4	0.00	0.00	0.00	-0.01	0.00	0.02	0.00	0.04
C5	0.00	-0.01	0.00	-0.03	0.03	0.00	0.03	-0.01
O11	0.02	0.05	0.01	**0.12**	0.01	0.05	0.01	**0.14**
C12	0.01	-0.01	0.01	-0.02	0.02	0.00	0.03	-0.01
O15	0.01	0.06	0.01	**0.14**	-0.02	0.09	-0.02	**0.25**
O17	0.02	0.10	0.01	**0.25**	0.00	0.12	0.00	**0.33**
O19	0.03	0.05	0.02	**0.12**	-0.01	0.05	-0.01	**0.13**
N21	0.02	0.17	0.01	**0.43**	0.02	0.31	0.02	**0.86**
C23	0.13	-0.01	**0.08**	-0.02	0.25	-0.10	**0.28**	-0.29
O24	0.10	0.21	0.06	**0.52**	0.09	0.30	0.10	**0.84**
C25	-0.01	0.00	-0.01	0.00	-0.03	0.03	-0.03	0.08
O29	0.01	0.04	0.00	**0.10**	-0.01	0.06	-0.01	**0.15**

Both Fukui and Parr indices results agree well on the most nucleophilic site O24 followed by O17 and O15. On the other hand, the most electrophilic site (highest ω_{kF}^+ and ω_{kP}^+) which is **C23** is highlighted in blue. Hence, this carbon atom is part of the acetyl group.

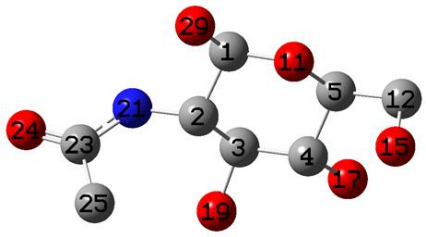

Figure 3. Atomic numbering of chitin molecule

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Table 3. Fukui indices f_k^-, f_k^+, Parr functions P_k^+, P_k^-, local electrophilicity ω_k^+, and nucleophilicity N_k for chitosan at B3LYP/6-31G.

	Fukui Indices				Parr Functions			
Atom k	f_k^+	f_k^-	ω_{kF}^+	N_{kF}	P_k^+	P_k^-	ω_{kP}^+	N_{kP}
C1	0.01	-0.01	0.00	-0.02	0.03	0.02	0.03	0.08
C2	0.06	-0.01	0.02	-0.02	0.08	0.02	0.07	0.07
C3	0.01	-0.01	0.00	-0.03	0.05	0.00	0.04	0.02
C4	0.01	-0.02	0.01	-0.05	0.02	-0.01	0.02	-0.02
C5	0.01	-0.02	0.00	-0.06	0.03	0.01	0.03	0.03
O11	0.01	0.13	0.00	**0.42**	0.00	0.21	0.00	**0.73**
O12	0.03	0.02	0.01	0.06	-0.01	0.00	-0.01	0.01
N14	0.00	0.30	0.00	**0.95**	-0.02	0.46	-0.01	**1.59**
O17	0.03	0.06	0.01	**0.18**	0.00	0.07	0.00	**0.22**
O19	0.05	0.02	0.02	0.06	-0.03	0.00	-0.03	0.01
C21	0.02	-0.01	0.01	-0.04	0.04	0.00	0.03	-0.02
O24	0.02	0.10	0.01	**0.31**	-0.01	0.14	-0.01	**0.48**

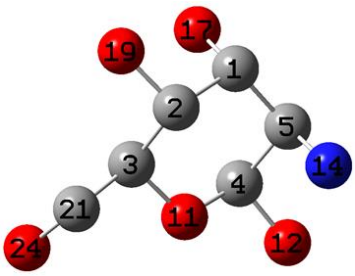


Figure 4. Atomic numbering of chitosan molecule.

As shown in Table 3 and Figure 4, the most nucleophilic sites are given in the order: **N14 > O11 > O24 > O17** and this is the same order found by Fukui and Parr. Here, for the chitosan molecule, the nitrogen atom **N14** is the most nucleophilic site followed by the most nucleophilic oxygen atom **O11**. This latter is comprised between two carbon atoms **C3** and **C4** belonging to the six membered heterocyclic ring. Overall, the chitosan molecule tends to be more nucleophilic rather than electrophilic since no electrophilic site is observed concerning the carbon atoms.

The results presented in Table 4, the local nucleophilicity N_{kF} shows that the most nucleophilic sites are the oxygen atoms **O11**, **O12**, **O14**, **O16** and **O21** and the nitrogen atom **N26**. Here, only Fukui indices give a good interpretation of nucleophilic sites with respect to Parr functions where no site found to be nucleophilic enough to be mentioned. However, both indices, Fukui and Parr, agree well on the fact that carbon atoms **C1**, **C2**, **C3**, **C4** and **C5** are found to be very good electrophilic sites when reacting with a nucleophilic agent.

Table 4. Fukui indices f_k^-, f_k^+, Parr functions P_k^+, P_k^-, local electrophilicity ω_k^+, and nucleophilicity N_k for protonated chitosan at B3LYP/6-31G.

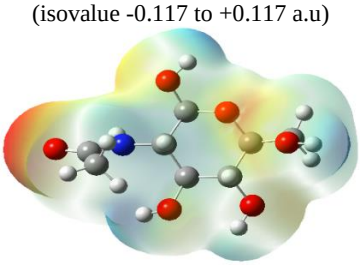
	Fukui Indices				Parr Functions			
Atom k	f_k^+	f_k^-	ω_{kF}^+	N_{kF}	P_k^+	P_k^-	ω_{kP}^+	N_{kP}
C1	0.01	-0.01	**0.10**	0.02	0.04	-0.01	**0.35**	0.01
C2	0.03	0.00	**0.25**	0.00	0.05	0.05	**0.40**	-0.05
C3	0.01	-0.01	0.07	0.01	0.02	0.03	**0.19**	-0.03
C4	0.01	-0.01	**0.10**	0.02	0.02	-0.01	**0.15**	0.01
C5	0.04	-0.01	**0.32**	0.01	0.12	0.02	**0.92**	-0.02
O11	0.00	-0.48	-0.01	**0.66**	0.00	0.20	0.00	-0.23
O12	0.00	-0.74	-0.02	**1.01**	-0.01	0.02	-0.10	-0.02
O14	0.03	-0.66	**0.23**	**0.90**	0.01	0.17	0.06	-0.19
O16	0.03	-0.71	**0.21**	**0.97**	0.00	0.10	0.01	-0.11
C18	0.00	-0.16	-0.03	0.22	0.00	-0.01	0.02	0.02
O21	0.00	-0.51	0.04	**0.69**	0.00	0.35	0.00	-0.40
N26	0.05	-0.87	**0.39**	**1.19**	-0.15	0.00	-1.15	0.00

Figure 5. Atomic numbering of protonated chitosan molecule.

3.3. Molecular electrostatic potential

Moreover, Figure 6 depicts the molecular electrostatic potential (MEP) maps. This kind of representation is used to show and analyze the most susceptible regions of the molecule to an electrophilic and nucleophilic attacks. The red color denotes the nucleophilic (negative) part of the molecule; whereas the blue color exhibits the electrophilic (positive) parts of the molecule.[36-39]

(isovalue -0.117 to +0.117 a.u)



Chitin

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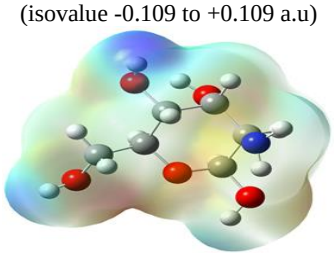
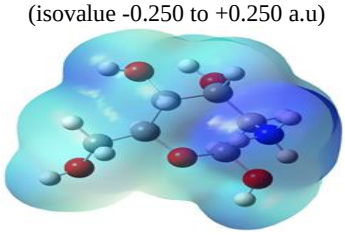
(isovalue -0.109 to +0.109 a.u)



Chitosan

(isovalue -0.250 to +0.250 a.u)



Protonated Chitosan

Figure 6. MEP of the three studied compounds.

As presented in Figure 6, the red zones encounter the oxygen atoms for both chitin and chitosan. This means that these parts are nucleophilic and then will react with electrophilic sites of another molecule. It is worth to note that, for chitin, the red color is more pronounced on the oxygen atom of the carbonyl group which leads to say that it is the most nucleophilic region of this molecule. However, the protonated chitosan barely shows a red region and instead of this the blue color is more abundant through the skeleton of this molecule. The blue color is very dark on the region surrounding the nitrogen atom. This is the most electrophilic part of the protonated molecule.

4. CONCLUSION

In this work, we have conducted a theoretical study at B3LYP level and the 6-31G basis set on chitosan, chitin and protonated chitosan using Gaussian 09 suit of program. The higher values of nucleophilicity of chitin and chitosan show that both molecules exhibit a strong nucleophilic character; whereas the higher value of electrophilicity of protonated chitosan offers this molecule a remarkable electrophilic character. This result has been shown by exploring the MEP surfaces. For chitin, the reaction of this molecule toward a nucleophilic attack will mostly take place on the C23 atom of the carbonyl group. In contrary, during an electrophilic attack, the reaction will take place on the N21 and O24 sites. For chitosan, the reaction of this molecule toward an electrophilic attack will take place at the N14 site followed by oxygen atoms O11 and O24. Finally, for protonated chitosan, a possible electrophilic attack will take place on the atoms O11, O12, O14, O16, O21 and N26 while, during a nucleophilic attack, the reaction will take place on the C5 site.

The oxygen of acetyl group is found to be the most nucleophilic site whereas the carbon atom directly linked to it is the most electrophilic site. This finding is in good agreement with the experimental outcomes.

The ASD analysis at the radical anion and radical cation of the reagents provides a useful characterization of the most electrophilic and nucleophilic centers. The study of most reactive sites using Fukui and Parr indices was very fruitful and complementary and it would be very interesting taking into account both of them when dealing with such investigation.

Conflict of interest

The authors declare that they have no conflict of interests.

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