Comparative study of GO289 and 5-bromo-4-formylguaiacol using DFT and MD calculations

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Abstract

We investigated the reactivity of the Schiff base GO289 **2**, and 5-bromo-4-formylguaiacol **1** by performing quantum chemical calculations using the density functional theory method. First, we employed this method to predict the reliable orbital molecular energies. Next, we calculated the quantum chemical parameters. Electrophilicity index increases with the various electrodifictary sites of GO289 **2**. This one is greater than this of 5-bromo-4-formylguaiacol **1**. The calculated data confirm that the fraction of electrons for GO289 **2** is large. We have also evaluated the conformations of these molecules in solution using the molecular dynamics simulation. The calculations confirm that the GO289 **2** has a spatial conformation state. Molecular dynamic simulations give us very good results in the prediction of reactivity and inhibition effect. Our theoretical results complete very well the experimental data.

Keywords GO289 · Guaiacol derivatives · Density functional theory · Molecular dynamics simulation

1 Introduction

Guaiacol compounds are extensively used in different area. Bromoguaiacol derivatives are precursors of lignin with high biological activities such as, antioxidant [1, 2] and cytokinin-like [3, 4]. Many authors have prepared the 4-bromoguaiacol from guaiacol [5–9]. Other reactions have been carried out on guaiacol, in particular deoxygenation. Several experimental and theoretical studies have been carried out on the deoxygenation of guaiacol [10–15]. Nowadays, authors have investigated to studying the conformations of the phenolic hydroxyl and methoxy groups in guaiacol using Ab Initio calculation methods [16].

Guaiacol was also studied theoretically with the density functional theory (DFT). This study reveals important conversion to main intermediates such as phenol, anisole and catechol [17]. Recently, Oshima et al. have converted arylhydrazide **A** to amino triazole **B** using closing reaction

with hydrazine followed by alkylation. Then, the condensation reaction between triazole **B** and 5-bromo-4-formyl-2-methoxyphenol **1** furnished the Schiff base compound: GO289 **2** (Fig. 1) [18].

In this work, we compared the structure activity relationship of GO289 **2** and 5-bromo-4-formylguaiacol **1** using the quantum chemical methods (DFT). We have also evaluated the conformations of these molecules using the molecular dynamics simulation in solution. Next, we compared our calculated results.

2 Methodology

2.1 Quantum chemical calculations

The molecular quantum optimisation calculations are performed by density functional theory DFT B3LYP method using 6–31G basis set implemented in Gaussian

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Fig. 1 Synthesis of (E)-5-Bromo-2-methoxy-4-(((3-(methylthio)-5-phenyl-4H-1,2,4-triazol-4-yl)imino)methyl)phenol **2** [18]

03 W programme [19–22]. The following quantum chemical results are considered: total energy (E_t), ionisation potential (IP), energy of the highest occupied molecular orbital (E_{HOMO}), energy of the lowest unoccupied molecular orbital (E_{LUMO}), energy gap ($\text{EG} = E_{\text{LUMO}} - E_{\text{HOMO}}$), dipole moment (μ), chemical hardness (η), Mulliken electronegativity ($\chi = -(E_{\text{LUMO}} + E_{\text{HOMO}})/2$), electrophilicity index ($\omega = \chi^2/2\eta$), and the fraction of electrons (ΔN).

2.2 Molecular dynamics (MD) simulation

All MD simulations were performed with the AMBER force field using Polak-Ribiere conjugate gradient algorithm with a gradient of 0.01 kcal/mol (RMS). In vacuum, the system was simulated using Molecular Dynamics with 0.0001 ps step. Temperature was kept constant at 300 K. The starting temperature was taken at 100 K and the step at 20 K. In water simulations, the system was placed in a box ($20 \times 20 \times 20 \text{ \AA}$) containing one molecule of studied compound and 240 water molecules and cut-off 4 Å. Optimisation of the molecule was realised in periodic boundary conditions (PBC). The compounds were solvated by added water molecules. The systems were first energy minimised steps with the conjugate gradient algorithm. Then, the position-restrained MD simulation was run 0.5 ps.

3 Results and discussion

To our knowledge, no paper has been made to study the comparative structure–activity relationship of the following compounds: 5-bromo-4-formyl-guaiacol **1** and GO289 **2** using the DFT B3LYP method and molecular dynamics simulation.

Table 1 Quantum chemical parameters for: 5-bromo-4-formyl-2-methoxyphenol **1** and GO289 **2** with DFT B3LYP method

Entry	Parameter	5-bromo-4-formyl-guaiacol 1	GO289 2
1	E_t (eV)	−84,517.906	−108,721.636
2	μ (D)	3.727	5.107
3	IP (eV)	6.410	6.013
4	HOMO (eV)	−6.410	−6.013
5	LUMO (eV)	−1.970	−2.122
6	EG (eV)	4.440	3.891
7	η (eV)	2.220	1.946
8	σ (eV ^{−1})	0.450	0.514
9	χ (eV)	4.190	4.067
10	ω (eV)	3.954	4.252
11	$\Delta N_{(110)}$	0.142	0.194

3.1 Quantum chemical parameters

In this paper our objective is to study the structure–activity relationship of the GO289 **2** compound then to make a comparative study of the reactivity of 5-bromo-4-formyl-2-methoxyphenol **1** using the DFT method. From the density functional theory method, we have evaluated: (1) molecular orbital (HOMO and LUMO), (2) chemical hardness (η), (3) electrophilicity index (ω) and (4) the fraction of electrons ΔN .

The energy gap between the HOMO and LUMO describes an important stability factor [23–25]. Large gap involves high stability which leads weak chemical reactivity. However, small gap implies low stability indicating high chemical reactivity. The chemical hardness is the combination of both the chemical reactivity and the stability of a molecule.

The calculated hardness (η) indicates that the value of 5-bromoguaiacol **1** is greater than that of GO289 **2** (Table 1, entry 7, **2**: 1.946; **1**: 2.220). According to the data in Table 1, there is a relationship between the IP values of reactant/substrate structures and the imine forming reaction. GO289 **2** has all ring atoms hybridised sp^2 , and its six π -electrons are delocalized between triazole and phenyl rings via the imine bond. 5-Bromoguaiacol **1** is considered as electrophile due to the formyl group. Consequently, we conclude that GO289 **2** is more reactive if compared to 5-bromoguaiacol **1**. In the case of GO289 **2**, the obtained gap value is lesser than that of 5-bromoguaiacol **1**. Therefore, its chemical reactivity is high if compared to compound **1**.

In 5-bromoguaiacol **1**, the activating groups: OH, OMe and Br are necessities for the stabilization of the aromatic ring by resonance donor effect (M+) (donating electrons to the system). The electron density of these groups is distributed into the aromatic ring. Therefore, the electron deficiency is located on formyl group precisely on carbon atom.

The formyl site attack is greatly favored because the steric hindrance between electrophile **1** and nucleophile **B** does not exist. Therefore, the condensation reaction between triazole **B** and 5-bromophenol **1** gives the resulted product GO289 **2**. Scheme 1 reveals a consistent reactivity where electron-rich nitrogen amine **B** attacks the electrophile **1**. So, the best interaction HOMO–LUMO would preferentially occur. Our theoretical results complete very well the experimental data of literature [18].

3.2 Global reactivity descriptors

We have calculated the electrophilicity index (ω) from the Mulliken electronegativity (χ) and the chemical hardness (η). Maynard et al. [26] have demonstrated that this electrophilicity index provide a relationship of an electrophile and the electrophilic power of the inhibitor. In the present study, ω defined the electrophile character in the condensation reaction. The calculated data show very well that the electrophilicity index increases with withdrawing effect on formyl group in the electrophile **1** (Table 1, entry 10).

Scheme 1 Frontier molecular orbitals. Triazole **B** and 5-bromophenol **1**. Hydrogens are omitted for clarity

By analogy to electrophilicity index describe by Maynard, the electrophilicity index (ω) was also defined by Parr et al. as a descriptor to quantify the global electrophilic power of a molecule [27]. Here, the global electrophilic power of GO289 **2** is specially localized on imine group and substituted phenol. The electrophilicity index raises with the various electrodeficitary sites of this molecule. As a consequence, ω is more important for GO289 **2** than 5-bromoguaiacol **1**.

Pearson has reported that the fraction of electrons ΔN transferred between inhibitor molecules and the metal surface can be estimated according to the following equation [28]:

$$\Delta N = \frac{(\chi_{\text{met}} - \chi_{\text{inh}})}{2(\eta_{\text{inh}} + \eta_{\text{met}})} \quad (1)$$

Kokalj has reported that the use of metal work function $\phi_{\text{Fe}(110)} = 4.82$ eV rather than χ_{Fe} is more suitable for an adsorbate–metal surface interaction [29]. Authors have preferred $\phi_{\text{Fe}(110)}$ because it has a packed surface and high stability [30]. Thus, using it in the place of χ_{Fe} and putting $\eta_{\text{Fe}} = 0$, the above Eq. (1) becomes:

$$\Delta N = \frac{(\phi_{\text{Fe}(110)} - \chi_{\text{inh}})}{2\eta_{\text{inh}}} \quad (2)$$

From Table 1, we note that ΔN is great for GO289 **2** because the molecular system is highly unsaturated, and contains three resonance-stabilized aromatic rings. Moreover, hydroxyl group and bromine atom are an electron donor types that can provide their charges to the imine bond through the aromatic ring. As a result, they are increasing its nucleophilic effect. 5-Bromoguaiacol **1** has only a withdrawing effect in the formyl group (Fig. 2). As consequence, we can order the fraction of electron as follows: **2** > **1**.

Fig. 2 Electronic effects for 5-bromo-4-formylguaiacol **1** and GO289 **2**

The fraction of electrons ΔN increases when:

- (i) The nucleophilicity increases with non-binding doublets, charge and polarizability.
- (ii) The molecular system is highly unsaturated and stabilized by resonance.
- (iii) The aromatic ring is substituted by mesomer donor groups (M^+) OH and Br.

3.3 Mulliken charges

For GO289 **2**, we note that the HOMO is located over two rich aromatic rings (Bz and triazole), sulfur and nitrogen atoms (Fig. 3a₂). In LUMO orbital, we observe that the charge density (CD) is situated principally around imine bond and slightly on the third aromatic ring (Fig. 3b₂, c₂). In HOMO, CD is essentially delocalised over the two rings (Bz and triazole) through the imine bond. These situations seem to be the same in the context of 5-bromo-4-formylguaiacol **1** (Fig. 3/a₁, b₁, c₁). So, the reactivity has been estimated on the aromatic moiety and on the electronegative atoms of these compounds. The Mulliken charges are given in Table 2.

We conclude that the inhibition is more efficient if the electron transfer from the target molecule to the Fe metal is large. Therefore, GO289 **2** is an inhibitor of choice. This compound can better reduce the corrosion of iron. This result indicates that inhibition depends on the structure of the molecule. Here, inhibition and reactivity increase with the presence of mesomer donor groups and highly unsaturated and stabilized aromatic systems. We can conclude that the fraction of electrons ΔN and the electrophilicity index ω vary in same direction for the two compounds **1** and **2**. For compound **2** the fraction of electrons ΔN is higher than compound **1** because of the electrophile character of this compound.

3.4 Molecular electrostatic potential

Molecular electrostatic potential (MEP) provides valuable information concerning the polarity of the compounds [31, 32]. The electrostatic potential (ESP) contour of compounds **1** and **2** illustrates the two-dimensional charge distribution of these molecules computed at the 0.004 a. u. isovalue diagrams. The electrostatic potential representation clearly shows that the σ -withdrawing properties of the oxygen on the methoxy, hydroxyl and formyl groups reduce the π -donating and deactivate the ring. In 5-bromo-4-formylguaiacol **1**, formyl has a large charge

compared to GO289 **2**. Therefore, this molecule becomes polar due to the presence of the triazole group and the imine bond. Polarizability is increased because of the presence of nitrogen and sulfur atoms. Therefore, these atoms reveal the molecular interactions between molecules. The green colour region depicts the neutral electrostatic region. The red colour regions in ESP indicate the positive potential region which is the favourable site for nucleophilic attack.

The negative regions are associated to: oxygen atoms in methoxy, hydroxyl and formyl groups, and nitrogen atoms in triazole group and imine bond (Fig. 4). The oxygen atom in hydroxyl with electrostatic potentials ranging from -4 to -2×10^{-2} a. u. has been unchanged in both compounds but bromine atom decreases in compound **2** rather than **1**. The electrostatic potentials of nitrogen atoms in triazole group and imine bond vary from -4 to -0.8 and -4 to -2×10^{-2} a. u.

3.5 Molecular dynamic simulation

Molecular dynamics method has been widely used to understand the interaction and adsorption behavior of an inhibitor on the metal surface [31–34].

In the present study, we have used this efficient method to investigate the adsorption behavior of GO289 **2** and compound **1**. The binding energy (E_{bind}) was used to estimate the adsorption intensity of the inhibitor molecules on the metal surface when the simulation system reaches thermal and energetic equilibrium. The interaction and binding energies in solution simulation system can be calculated by Eq. 3 [35]

$$E_{\text{bind}} = -E_{\text{int}} = -(E_{\text{Total}} - (E_{\text{Solvent}} + E_{\text{Molecule}})) \quad (3)$$

where E_{Total} represents the energy of the entire system, E_{Solvent} represents the entire energy of water solution and E_{Molecule} represents the whole energy of target molecule.

To simulate the interaction behaviour of the GO289 **2** and compound **1**, we have proceeded as follows:

- (i) First, the 3-D periodic box (PB) ($20 \times 20 \times 20$ Å) containing 240 water molecules was equilibrated at 300 K using MD simulations. So, the resulted total energy of PB is $E_{\text{TH2O}} = -2387.480$ kcal/mol.
- (ii) Then one molecule of each studied molecule (**2** and **1**) was added to 3-D PB containing 240 water molecules and the system was equilibrated at 300 K using MD simulations.

Fig. 3 Quantum parameters of a) 5-bromo-4-formylguaiacol **1** and b) GO289 **2**: **a** Mulliken charges, **b** HOMO and **c** LUMO by the DFT method. Hydrogens are omitted for clarity

Table 2 Mulliken charges for 5-bromo-4-formylguaiacol **1** and GO289 **2** using the DFT method

Compound	Type/Charge
GO289 2	N ₁ − 0.313, N ₂ − 0.303, C ₃ 0.171, N ₄ − 0.601, C ₅ 0.378, S 0.353, C _{MeS} − 0.607, N _{imino} − 0.212, CH 0.027, HO − 0.611, MeO − 0.602, C _{ME} − 0.170, Br 0.168, C ₁ 0.267, C ₂ 0.284, C _{3'} − 0.138, C _{4'} 0.097, C _{5'} − 0.360, C _{6'} − 0.079
5-bromo-4-formyl-guaiacol 1	HO − 0.61, MeO − 0.602, C=O − 0.407, Br 0.168, C ₁ 0.267, C ₂ 0.287, C ₃ − 0.131, C ₄ 0.063, C ₅ − 0.341, C ₆ − 0.074, CH 0.151, C _{ME} − 0.170

We used the MD simulation to predict configuration of the inhibitory molecule adsorbed at the metal interface when equilibrium is reached. In the present work, we have determined the total energy of each molecule in the gas state, the total energy of the system and the energy of interaction. The obtained values of the energies are summarized in Table 3 and the best configurations in the solution are shown in Fig. 5a, b.

From Fig. 5a, we observe that the molecule **1** have a planar structure and can move to the Fe surface as parallel as possible. The GO289 **2** can be adsorbed on the metal surface with a folded configuration (Fig. 5b). We think that spatial and non-parallel adsorption is due to type interaction between inhibitory GO289 **2** and metal. The Schiff base **2** has a sufficient amount of N, O, Br and S donor heteroatoms as well as π electrons in its structure which provide enough electrons to the vacant orbital metal.

Table 3 Calculated MD parameters for 5-bromo-4-formylguaiacol **1** and GO289 **2**

Entry	Property	5-bromo-4-formylguaiacol 1	GO289 2
1	$E_{\text{molecule gas}}$ (kcal/mol)	37.428	84.027
2	E_{Total} (kcal/mol)	− 2393.550	− 2327.710
3	E_{int} (kcal/mol)	− 43.498	− 14.257

From Table 3, we note that the calculated interaction energy values of the adsorption systems at 300 K are − 43.498 and − 14.257 kcal/mol for **1** and **2**, respectively. These high values of negative energy suggest that the adsorption process is spontaneous in nature. We can suggest from this interaction energy value, that molecule **2** gives complex structure with water molecules and adsorb on the iron surface more spontaneously than that of **1**. As a consequence, we classify these molecules in the following order: **2** > **1**. In Fig. 6, we propose the complex structure and adsorption sites of GO289 **2** specie in water on the iron surface.

From literature, we note that corrosion takes place in acidic medium when using Schiff base, benzotriazole, quinazolinone and pyrimidinone because of the basic character of these compounds [28, 29, 34, 36]. Our results are in good agreement with those obtained from literature. We conclude that GO289 **2** has the lower chemical hardness η and lower binding energy E_{Bind} which are significant of high reactivity.

Fig. 4 ESP 2D representation of: **a** 5-bromo-4-formylguaiacol **1** and **b** GO289 **2**. Hydrogens are omitted for clarity

Fig. 5 Equilibrium configurations of organic inhibitor molecules in solution. **a** 5-bromo-4-formylguaiaicol **1**, **b** GO289 **2**

Fig. 6 Proposed complex structure and adsorption sites of GO289 **2** in water on the iron surface

4 Conclusion

We have studied the reactivity of the GO289 **2** and compound **1** using the DFT method. The results show that the electrophilicity index increases with various electrofidity sites of GO289 **2**. We note that the fraction of electrons ΔN is large for GO289 **2**. Consequently, the

inhibition is more efficient when using GO289 **2** rather than 5-bromo-4-formylguaiaicol **1**. We have also evaluated the conformations of the GO289 **2** and **1** using the molecular dynamics simulation in solution. We note that the 5-bromo-4-formylguaiaicol **1** reaches its high planar conformation state in the solution environment. GO289 **2** has a spatial and non-planar conformation and has the

highest interaction energy because of multiple hydrogen bonds with water molecules. We confirm that the combination of the active structure of 1,2,4-triazole with that of substituted phenol has effectively increased the chemical properties and therefore the structure–activity relationship has been demonstrated.

We conclude that GO289 **2** is a soft Schiff base with high chemical reactivity and strong tendency to adsorb on the metal surface. Our theoretical results complete very well the experimental data of literature.

Compliance with ethical standards

Conflict of interest There is no conflict of interest.

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