Theoretical study of the regioselectivity of the interaction of molecules isolated from *Siphonochilus aethiopicus* with water

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Abstract: Computational methods are used to predict the most favorable site of furano sesquiterpenoids (FNTP) towards attack by a water molecule. The energetic of the various complexes are presented as well as their geometries, including Density Functional Theory (DFT) reactivity descriptors such as; Molecular electrostatic potential, Natural Bond Orbital (NBO), Mulliken Electrostatic Charges, Fukui functions HOMO-LUMO gaps data and interactions energies between FNTPs and water acting as simultaneous proton donor and acceptor, predict the reactivity of different basic sites in the following decreasing sequence: CO17> CO14> O19>O13 for FNTP-1 and CO16> O13 for FNTP-2.
Keywords: regioselectivity, interaction, S*iphonochilus aethiopicus,* furano sesquiterpenoids, Water.

INTRODUCTION

Many research groups are interest to *S. aethiopicus* because of its widespread use in the therapy of several diseases in African southern countries (South Africa, Zimbabwe, Malawi and Zambia) [1-6].

Some previous studies showed the presence of furano sesquiterpenoids (FNTP) endowed with anti malarial and antibacterial activities [1-5]. The most active ones had the IC_{50} of 3.4 μg/mL against chloroquine sensitive strains and 1.5 μg/mL against chloroquine resistant strains of *plasmodium falciparum* [2, 3].

The FNTP molecule is characterized by a polyfunctional three fused cyclic rings with four asymmetric centers for FNTP-1 and three asymmetric centers for FNTP-2 that can give 16 and 8 isomers respectively (Fig-1). Because of the presence of many hetero atoms, these molecules can be involved in none covalent interactions (NCIs) such as Hydrogen Bonds (HBs) [7-11]. These NCIs may serve to enhance bioactivity potency of FNTP.

In spite of biological importance of FNTP, the literature contains neither theoretical works predicting the reactivity and the regioselectivity of FNTP molecule in its interaction with proton acceptor or proton donor molecules such as water.

In the present work, we examine the reactivity and regioselectivity of FNTP molecules using reactivity descriptors such as Molecular electrostatic potential [12-15], Natural Bond Orbital (NBO), Mulliken Electrostatic Charges, Fukui functions [16-20] HOMO-LUMO gaps and their interaction with the molecule of water (all possible FNTP- sites of H_2O attachment are examined, and a rank order of stability of the complexes are calculated).

METHODS

Figure-1 give optimized structure at B3LYP/6-311++G (3d, 2p) level of FNTP-1 and FNTP-2.
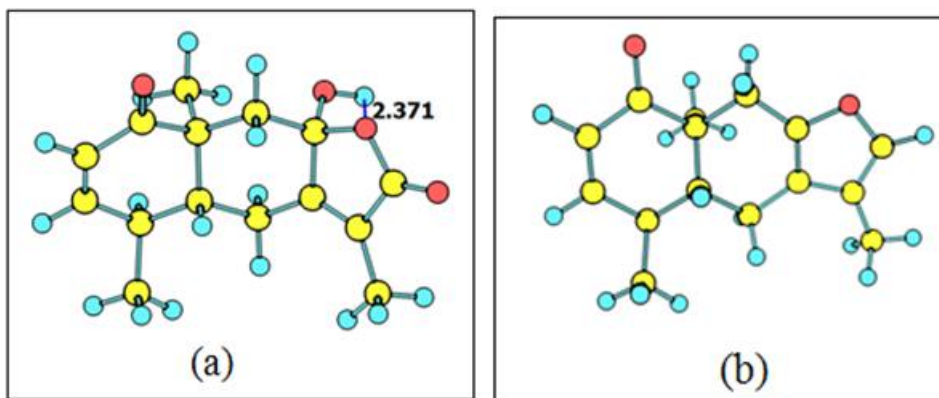
Fig-1: Optimized structure at B3LYP/6-311++G (3d, 2p) level of FNTP-1(a) and FNTP-2 (b)

The equilibrium geometries of the complexes formed between water with FNTP-1 and FNTP-2 where obtained using B3LYP-D3BSSE; WB97-D3BSSE and M0-62X BSSE methods [21-26]. The interaction energy of each complex was computed as the difference between the energy of the complex and the sum of the energies of the isolated FNTP and water monomers. These result where corrected for the Basis Set Superposition Error (BSSE) [25] using the Boys-Bernardi counterpoise correction [27-30].

The Molecular Electrostatic Potential (M.E.P), the interaction of a unit positive charge at given point $\vec{r}$ with reference to a molecular charge distribution, is evaluated by [12]

$$v(r) = \sum_A \frac{z_A}{|R_A - r|} - \int \frac{\rho(r)}{|r' - r|}\, dr$$

Where, $\rho(r)$ is the molecular electron density function; the summation over A runs over all nuclei with charge Z_A and the distance R_A. All calculations where performed using Gaussian 09 software package.

Atomic charges and charge transfer energies where assessed by NBO and Milliken atomic charges as implemented in Gaussian 09 [31]. Gauss View and Chemcraft [32-35] programs were used for visualization [34].

Fukui functions were calculated as the change in electron density of a molecule at a given position when the number of electron have been changed [18-20].

$$f(r) = \left(\frac{\partial \rho(r)}{\partial N}\right)_{v(r)} = \left(\frac{\delta \mu}{\delta v(r)}\right)_N$$

When, $\rho(r)$ is the electron density at a position r, and N the number of electrons.

$$f^+(\vec{r}) = \rho_{N+1}(\vec{r}) - \rho_N(\vec{r})$$
$$f^-(\vec{r}) = \rho_N(\vec{r}) - \rho_{N-1}(\vec{r})$$

RESULTS AND DISCUSSION
Molecular Electrostatic Potential (MEP)
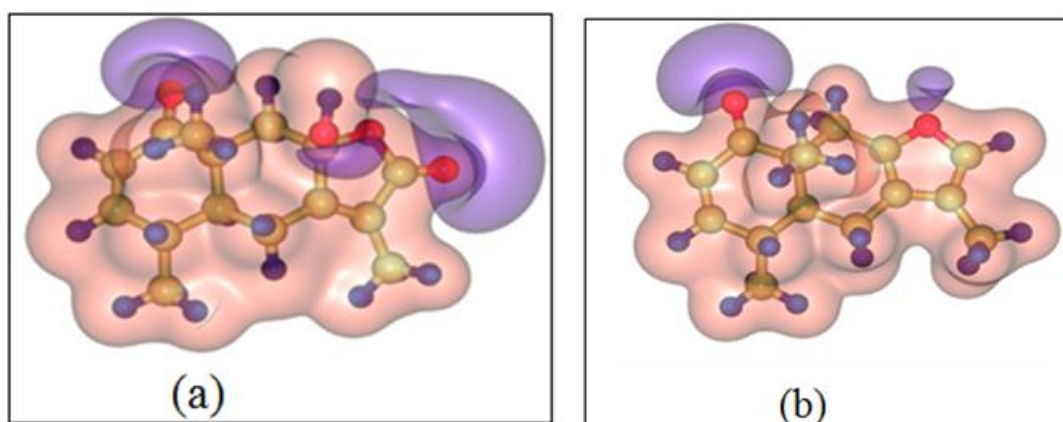The Molecular Electrostatic Potentials of FNTPs are displayed in the figure-2.

Fig-2: The Molecular Electrostatic Potential (MEP) of FNTP-1 (a) et FNTP-2 (b)

FNTP-1 MEP map shows two different regions of active sites for the reactions of electrophilic attack, shown in blue; the first region, widest extending from the oxygen -19 to oxygen-14 atoms. The second

region is located on oxygen-17 atom. The remaining portion (in purple) of the molecule is a low electron density region susceptible to nucleophilic attack.

FNTP MEP-2 card has two areas of active sites electrophilic attack; the first larger situated on oxygen

16 would be the prime center of electrophilic attack, the second is less extensive localized on oxygen 13.

Natural bonds orbitals (NBO)

The NBO charges on the atoms of isolated FNTP-1 and FNTP-2 molecules are shown in figure-3.
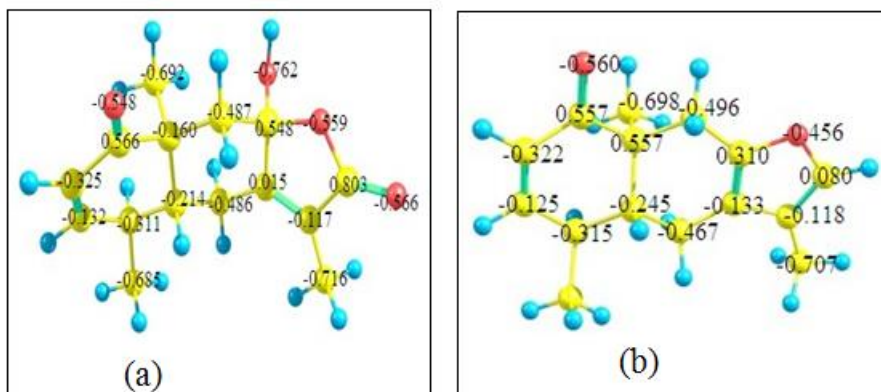

Fig-3: NBO atomic charges of (a) FNTP-1 and (b) FNTP-2

The analysis of natural bond orbital is in agreement with the MEP of FNTP-1 in relation to the oxygen atoms 19, 13, and 14 which have the higher electronic densities and make this region the preferred site of electrophilic attack (respective atomic charges of -0762, -0559, -0566). The molecule-1 FNTP would rather acidic character (protogenic) from its alcohol function.

The results of atomic charges Mulliken are similar to those of NBO and MEP according to the higher values of electron density on the oxygen atoms

19, 13 and14. Like to the molecule FNTP-2, the net atomic charge is essentially concentrated on the O16 atom with -0560 and to a lesser extent on O13 with -0456. In addition, NBO Mulliken attributes, on the back of the above oxygen atoms, the densities of electronic charges for different carbon atoms.

Fukui functions

In order to identify the most reactive molecular sites, the functions of positive and negative Fukui are shown in the figures below.
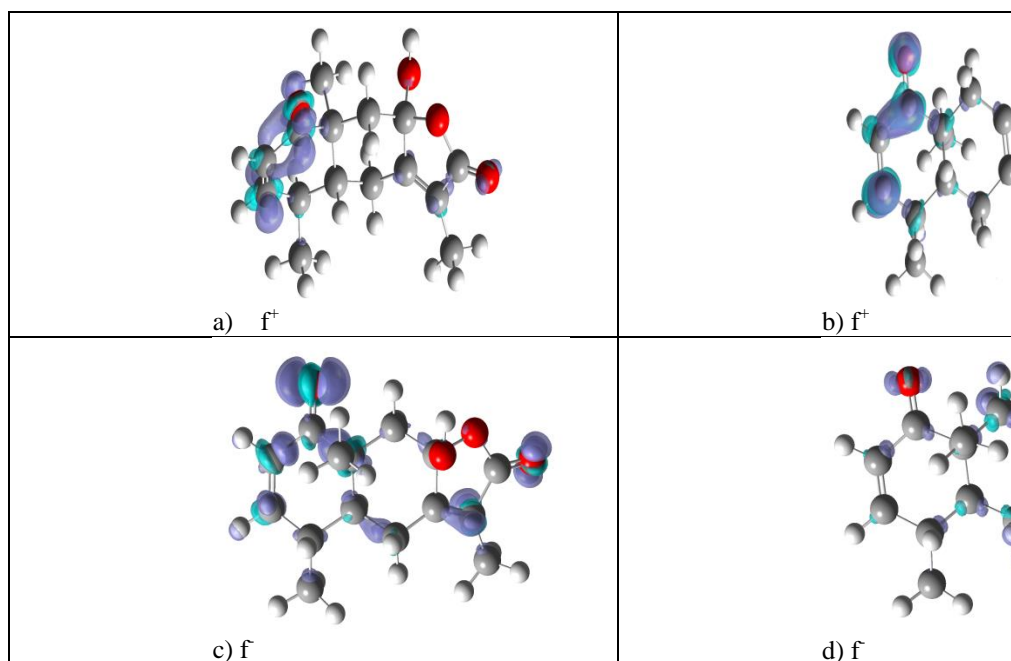

a) f^+

b) f^+

c) f

d) f

Fig-4: Positives and negative Fukui function of FNTP-1(a, c) and FNTP-2 (b, d)

For both molecules, the positive Fukui functions show that the most reactive sites are located at levels ethylenic double bonds and carbonyl in conjugation(resonance), namely C7 = C8 and C9 = O17 for the FNTP-1, and C7 = C8 and C9 = O16 for FNTP-2. Indeed, the resonance brings up a positive charge on the double bonds and a negative charge on the oxygen. It follows that electrophilic attack would be possible on the O17 and O16 oxygen while a nucleophilic attack is focused on the tail positively charged.

This is confirmed by the negative Fukui functions revealing carbonyl sites of FNTP-1 and FNTP-2 and conjugated double bonds in FNTP-2.

The results of MEP, NBO charges and Mulliken agree to fix oxygen carbonyl as the preferred region of electrophilic attack. In order to sit this observation from the abnormally high charge density of the alcoholic oxygen O19 of FNTP-1, the calculations of interaction energy with the proton donors are needed to predict the intrinsic regioselectivity FNTP- 1 and compare with that of FNTP-2.

Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO)
The HOMO and LUMO molecular orbitals are generally used to predict the reactivity of the molecule. The figures 5 (a-d) present the HOMOs and LUMOs orbitals of the two molecules of FNTP-1 and FNTP-2.
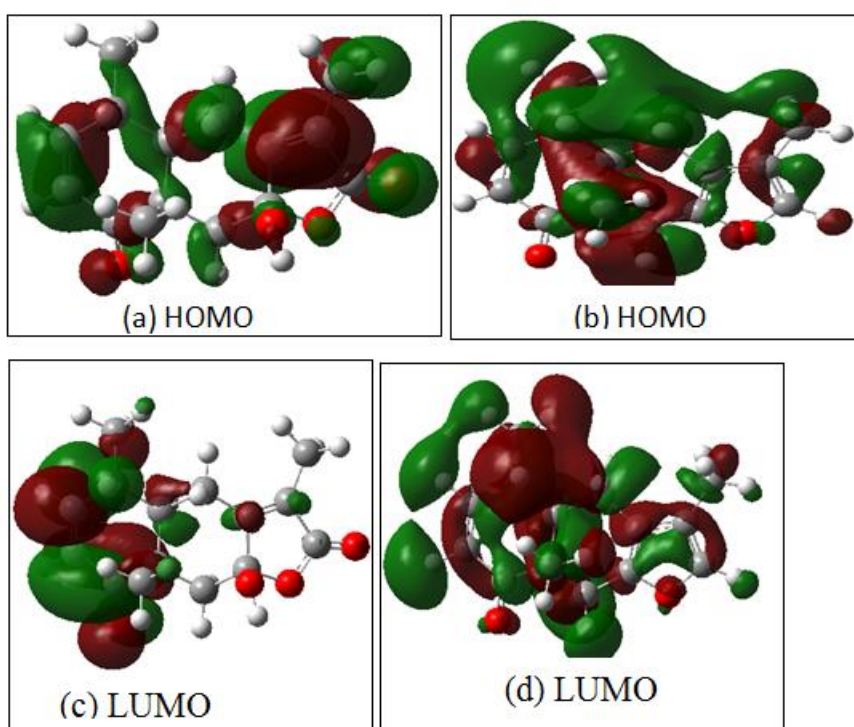

Fig-5: Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) for FdNTP-1 (a and c) and FNTP-2 (b and d)

These antiliant orbitals type π * cover several atoms and it is difficult to say which atoms have the greatest contribution. It can also be seen on the images of the HOMOs and LUMOs as presented in this figure, that the benzene ring has a great contribution in these two orbitals. This may lead to suggesting that this cycle is more reactive than the other cycles present in the molecule.

As it can be seen, the results of these descriptors of chemical reactivity proposed by conceptual DFT are really confused. Not easy to know what is the appropriate descriptor for these systems.

So, to get an idea on the preferential sites of interaction of these two molecules with water, the interaction energy was calculated and compared the various complexes from the standpoint of stability. The results are shown in the figures and tables below.

Interaction of FNTP-1 and FNTP-2 with water
Figure-6 shows the equilibrium geometries of the complexes obtained between FNTPs and water. The water molecule is oriented on different O atoms able to form hydrogen bonds. The interaction energies between water and FNTPs, as well as the distances of hydrogen bonds H-O ... O in the different complexes are also presented to gauge the strength of these hydrogen bonds at the different sites.
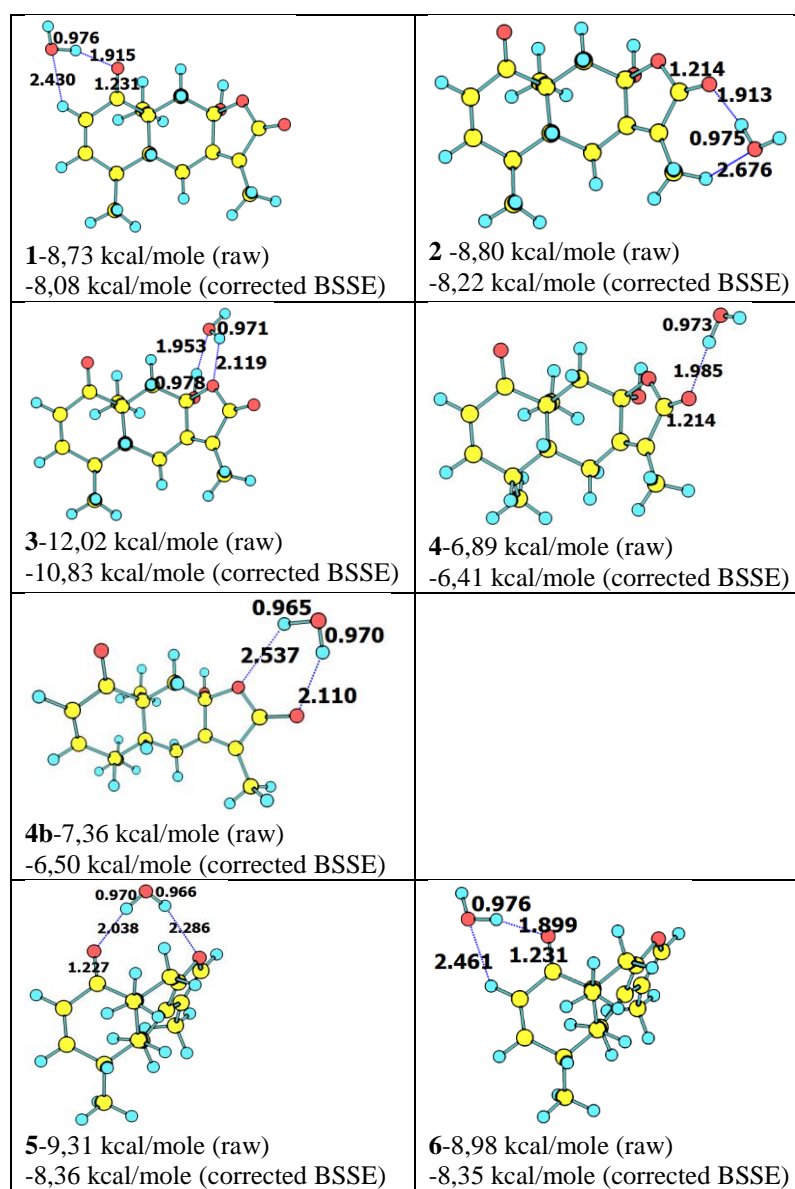
Fig-6: Geometric structure and interaction energies of the water-FNTP-1 (1-4) and water-FNTP-2 (5-6) complexes calculated with the B3LYP-D3 / 6-31 + G (d, p) method

The interaction energies between the water molecule and the FNTPs corrected and not corrected by the basic superposition error show that the water molecule prefers to form two hydrogen bonds with FNTPs so that it can play at the same time, the role of donor and acceptor of proton. This tendency of the water molecule to act as both acid and base (donor proton and acceptor of proton) has also been observed in the study of the interaction of temozolomide with water by Kasende *et al*., [21, 22]. In FNTP-1 the most stable complex is observed when the water molecule forms the hydrogen bonds O ... H-O19 and OH ... O13 with the furanol ring with a BSSE corrected interaction energy of -10 83 kcal / mole.

In contrast, in FNTP-2, furanol is replaced by furan, the water prefers to interact with the carbonyl group on the benzene ring, forming the hydrogen bonds OH ... O16 and O ... H-C7 characterized by an interaction energy of -8.35 kcal / mol. The bond O-H..O is generally known to be stronger than the bond of the type C-H ... O. This may justify the stability of 3 compared to 1, 2 or 6. The fact that 6 interacts more strongly with water than 1 may lead to the suggest that the carbonyl group of the FNTP-2 of benzene ring is more active towards water than that of FNTP-1.

In other words the oxidation of furan tends to decrease the basicity of the carbonyl attached to benzene. In addition to the complexes studied here (1, 2, 3), the water molecule acts as a proton donor and

acceptor, whereas in structures 4 and 5, the molecule acts only as a proton donor (acid). In 5, the water molecule forms the hydrogen bonds OH...O17 (2,038A) and OH ... O13 (2,286 A), whereas in structure 4, the water forms a single OH hydrogen bond. OH…O14, of length 1,985 A, obtained using the method B3LYP-D3 / 6-31 + G (d, p). An orientation of the water molecule in 4 leads to a complex of the same relative stability 4b with slightly higher interaction energy than 4 of -6.50 kcal / mol, in which the water molecule forms two hydrogen bonds , OH ... O14 and OH ... O13 of 2.10A

and 2.537A, similar to 5. The complexes 5 and 6 have the same interaction energy estimated at ~ -8.35kcal / mol at the same level of B3LYP theory -D3.

The table-1 compares the influence of ZPE and BSSE on the relative stabilization energies of the complexes and the interaction energies of the water molecules with FNTPs. The comparison between the relative energies and the complexing energies of FNTP-Water is described in Table-2.

Table-1: Total electronic energy of FNTPs- Water complexes corrected and no-corrected obtained with B3LYP-D3 / 6-31 + G (d, p).

Complexes	TotE	TotE+BSSE	TotE+ZPE	TotE+ZPE +BSSE	BSSE
1	-959.88346	-959.88242	-959.55227	-959.55123	0.00104
2	-959.88354	-959.88262	-959.55106	-959.55106	0.00091
3	-959.88847	-959.88658	-959.55667	-959.55478	0.00189
4	-959.87687	-959.87611	-959.54568	-959.54491	0.00076
4b	-959.87758	-959.87620	-959.54628	-959.54491	0.00137
5	-809.39724	-809.39573	-809.07424	-809.07274	0.00151
6	-809.39690	-809.39589	-809.07442	-809.07340	0.00102
FNTP-1	-883.43570		-883.12879		
FNTP-2	-732.94876		-732.65063		
Eau	-76.434057		-76.412774		

Generally, except the structure 3 whose correction energy due to the base error is slightly greater than 1kcal / mol, all other FNTPs-water complexes have an error due to weak base overlay, not exceeding 1kcal / mol. The order of stability is affected in the complexes by the various corrections made in particular ZPE and BSSE, this is the case of the complexes 1 and 2 formed between water and FNTP-1, and complexes 5 and 6 formed by the FNTP- 2. The total energy of 5 (2) is lower than 6 (1) when no

correction is considered, however, when this total energy is corrected by basis set superposition errors (BSSE) and the zero point energy (ZPE), it is found that the structure 6 (1) becomes lower in energy than the structure 5 (2).

Therefore, not correcting the total energies by BSSE and ZPE in some cases can lead to erroneous prediction of active reaction sites.

Table-2: Relative energies (RE in kcal / mol) of the complexes and binding energy (BE) between water and FNTPs calculated with B3LYP-D3 / 6-31 + G (d, p)

Complexes		E	E +BSSE	E +ZPE	E+BSSE +ZPE	E	E +BSSE	E +ZPE	E+BSSE +ZPE
FNTP-1	1	3.14	2.61	2.76	2.23	-8.60	-7.95	-6.72	-6.06
	2	3.10	2.48	2.95	2.33	-8.65	-8.07	-6.53	-5.96
	3	0.00	0.00	0.00	0.00	-11.7	-10.56	-9.48	-8.29
	4	7.28	6.57	6.90	6.19	-4.46	-3.99	-2.58	-2.10
FNTP-2	5	-0.21	0.10	0.11	0.42	-9.05	-8.19	-6.80	-5.85
	6	0.00	0.00	0.00	0.00	-8.84	-8.28	-6.91	-6.27

The water molecule can react as an acceptor and proton donor in interaction with FNTPs with oxygen and hydrogen atoms. The proton donor interactions of water with the different FNTP proton acceptor sites make it possible to compare their regioselectivity.

A strong interaction of water with a proton acceptor site goes hand in hand with a decrease in

electron energy (Table-3). The complex 3 is 2.33 kcal / mol more stable than complex 1 after correction of BSSE and ZPE. The complex 4 is the least stable of this sequence and is 6.19 kcal / mol above 3 on the potential energy surface of the FNTP-1-water complex. For FNTP-2, the complex 6 is the most stable and differs from 5 by 0.11 kcal / mol. This difference is very small and lies within the accuracy limit of DFT and may lead

to suggest that 5 and 6 have similar thermodynamic stabilities.

The binding energy (binding energy) of the FNTP-2 water molecule is lower for 6 (-6.25 kcal / mol) than 5 (-5.85 kcal / mol). These results show that the water molecule will tend to bind as a donor proton to give the complexes 5, or donors and acceptors in the case of 6. It is clear that 6 is the preferred complex taking into account the different corrections (BSSE and ZPE). As in the case of interaction energy, binding

energy of the complex 3 formed by FNTP-1 with water is the lowest.

Relative and complexation energies were calculated using also different methods to see the influence of the calculation method used on the results obtained. Table 4 compares the relative energies and interaction energies between FNTP molecules and water obtained with different methods, such as B3LYP-D3, wB97XD and M062X.

Table-3: Relative energies of FNTP-water complexes calculated using different methods with 6-31 + G (d, p) base including BSSE and ZPE and in bracket interaction energies with BSSE correction: (a) B3LYP-D3, (b) wB97XD, (c) M062X

Complexes		(a)	(b)	(c)
FNTP-1	1	2.23(-8.08)	2.64(-7.36)	3.27(-7.45)
	2	2.33(-8.22)	2.57(-7.65)	3.11(-7.75)
	3	0.00(-10.83)	0.00(-10.33)	0.00(-11.19)
	4	6.19(-6.41)	6.08(-5.90)	7.18(-5.99)
	4b	6.20(-6.50)	6.08(-5.86)	7.19(-5.99)
FNTP-2	5	0.42(-8.36)	0.30(-7.71)	-0.03(-7.73)
	6	0.00(-8.35)	0.00(-7.65)	0.00(-7.63)

In fact, the data analysis of the complexes formed between FNTP-1 and water shown in Figure 6 reveals that the complexation of water with the O13 site of interaction energy -10.83 -10.33 and -11.19 kcal / mol at B3LYP-D3 calculations, wB97XD and M062X is much more stable than with the O17 site of interaction energy-8.08; -7.36 and -7.45 kcal / mol calculated with B3LYP-D3, wB97XD and M062X (Table-3). This suggests a stronger interaction of water with O13 and H-O19 than with O17 carbonyl.

The interaction energies calculated by B3LYP-D3 are slightly higher than those obtained by M062X and by WB97D (Tab. 3). Since water is an amphiphilic molecule, the complexations involving the proton and the oxygen in the water involve the formation of a main hydrogen bond with the proton of the water as well as a secondary interaction by its oxygen which further stabilizes the water. Complex formed by the effect of cooperativity [36-38].

Thus, the interaction energy of water with O14 of FNTP-1 is -6.41 kcal / mole (OH..O14 bond of 1.985Å) without secondary interaction against -8.22 kcal / mole with an OH..O14 bond of 1.913Å and another secondary O ... H-C15 between the methyl group and the water oxygen of 2.676 Å at the B3LYP-D3 theory level. On the other hand, a destabilizing effect of anti-cooperativity [38] is observed in FNTP-1 when H_2O is doubly proton donor, as the case of complex 4a where O14 and O13 interact with H water (interaction energy ~ -6.52 kcal / mol to B3LYP-D3). This interaction energy is 0.37 kcal / mol higher than 4 in which the water forms a single bond O14 ... H-O. In contrast to 4a, the FNTP-2 complex in which O17 and

O13 form hydrogen bonds with H_2O gives rise to an interaction energy similar to the complex 6 resulting from an interaction where the water is both donor and acceptor ~ -8.36 kcal / mol.

Complexes 1 and 6 have the same mode of action of attacking water. In both complexes the molecule binds to the carbonyl group of the benzene ring and acts as a proton donor of C = O and maintaining as proton acceptor of C-H. The water interaction energy calculated between water and FNTP-1 in complex 1 is -8.08 kcal / mole whereas that for 6 for FNTP-2 is -8.35 kcal / mole at the same level of calculation B3LYP / 6-31 + G (d, p) thus indicating that the carbonyl site on benzene in FNTP-2 is more basic than that of its counterpart FNTP-1.

The same look is observed with M062X and wB97XD methods (Table-3). The complexation between water and FNTP-2 gives rise to two geometries (5 and 6) with energies slightly different from 0.42; 0.30 and -0.03 kcal / mol at the level of the B3LYP-D3, wB97XD and M062X theories. While B3LYP-D3 and wB97XD predict 6 to be more stable, M062X shows that both structures have the same thermodynamic stability.

Taking into account interaction energy values calculated with B3LYP-D3 and wB97XD, the stability of the water complexes with the FNTPs decreases in the following order: 3＞5＞6> 2> 1> 4.

Apart from complex 4, the complexing energies reveal that FNTP2 forms a stable complex with water than FNTP-1.

CONCLUSION

The calculated DFT descriptors are good indicators for the prediction of the regioselectivity of FNTP-1 and FNTP-2 molecules. Indeed, the prediction of the MEP-based reactivity and Fukui functions corroborate with the relative stabilities of the complexes formed between the FNTP molecules with the water calculated using the DFT.

Complexation between FNTP molecules and water shows that water prefers to bind to FNTP molecules as a proton donor and acceptor.

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