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Computational Studies of the Active Metabolite of Triflusal Molecular Orbitals and Spectroscopic Features; The Basis for Triflusal Phototoxicity Mechanism

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ABSTRACT

Triflusal is a prodrug used as a platelet antiaggregant agent (a platelet aggregation inhibitor). It has efficacy similar to that of aspirin specially in patients with cerebral and myocardial infraction. Chemically, triflusal is nothing except a derivative of acetylsalicylic acid (2-acetyl-3-trifluoromethylsalicylic acid). It is bio-transformed under the effect of a deacetylation process into the active metabolite (known as HTB) which is 2-hydroxyl-3-trifluoromethylbenzoic acid. During the triflusal uses the cutaneous phototoxic/photoallergic side effect is noted including rash, itching or allergic reactions. In order to study this side effect, we use a very excellent tool to study such reactions which is DFT and TD-DFT. The active metabolite of triflusal HTB molecular orbitals and UV-VIS spectroscopic features have been investigated herein. The obtained results show that there is a difference in the molecular orbitals (MOs) pattern between the two forms of HTB (protonated and deprotonated) especially the HOMOs of the deprotonated species. The HOMOs of this species localized on the carboxylic moieties, which is manifested in the Mulliken atomic charge distributions on the carboxylic moiety, where in the deprotonated species shows higher negative charge on carboxylic moieties compared with the neutral form. This is also reflexed in the results obtained for the UV-VIS spectrum of the neutral and deprotonated forms of HTB. The MOs and UV-VIS spectrum of the neutral and deprotonated species of HTB molecule and its excitations to the triplet state are investigated in more details in the present work.

KEYWORDS: *Triflusal, Phototoxicity, Photobinding, DFT, TD-DFT.*

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INTRODUCTION

Triflusal (Trade names: Triflux, Tecnosal, Disgren, Aflen) is a prodrug used as a platelet antiaggregant agent. In another word, it is a platelet aggregation inhibitor. Triflusal was discovered and commercialized in Spain since 1981. Nowadays, it is available in more than 25 countries distributed in Europe, Africa, Asia and United States. It has efficacy similar to that of aspirin specially in patients with cerebral and myocardial infraction. However, it has a reduced risk of haemorrhagic complications. Also, it has an important role in the primary prevention of cerebrovascular events in atrial fibrillation. Moreover, it is used in the secondary prevention of cerebral and myocardial infraction. In turn, it is an alternative to aspirin in patients whom aspirin is unsuitable [1].

Pharmacodynamically, triflusal inhibits the thromboxane-B2 production irreversibly in platelets through acetylating cyclooxygenase-1 enzyme. Many other targets are affected by triflusal such as NF kappa B, this is a gene expression regulatory factor for cyclooxygenase-1 and cytokines. The efficacy and safety profile comparison have been done in the previous various studies those show that there is no significant difference or a better efficacy and safety profile between triflusal and acetylsalicylic acid. Triflusal protects cerebral tissue because of its lipid peroxidation inhibition resulting from anoxia-reoxygenation. From metabolism point of view, deacetylation process in liver is the main pathway of triflusal metabolism in which the main metabolite 2-hydroxy-4-trifluoromethylbenzoic acid (HTB) is formed. In invitro the latter metabolite seems to have marked antiplatelet properties [2-6].

On the other hand, triflusal acts as a selective platelet antiaggregant via various mechanisms of actions; it blocks cyclooxygenase enzyme which in turn inhibiting thromboxane A2. It also prevents vascular prostacyclin producing antiaggregant effect. Moreover, it increases nitric oxide synthesis in neutrophiles. In addition, it blocks phosphodiesterase enzyme increasing cAMP concentration which is promoting antiaggregant action because of calcium metabolism inhibition. Lastly, it inhibits the nuclear factor KB activation which is responsible for regulation of the expression of the mRNA of vascular cell adhesion molecule-1 that required for platelet aggregation [2].

Chemically, triflusal is a derivative of acetylsalicylic acid, (i.e., a derivative of aspirin). In which a hydrogen atom that is in para-position to carboxylic moiety is replaced by a trifluoromethyl group. Indeed, triflusal is 2-acetyl-3-trifluoromethylsalicylic acid; as shown in Figure 1 (A). This chemical compound is metabolized or bio-transformed under the effect of a deacetylation process into what is known HTB which is 2-hydroxyl-3-trifluoromethylbenzoic acid as seen in Figure 1 (B) [1]. In other word, the triflusal is very close in its chemical structure to that of acetylsalicylic acid, whereas the HTB (its metabolite) is very close to that of salicylic acid as depicted in Figure 2, A, AA, B and BB, respectively.

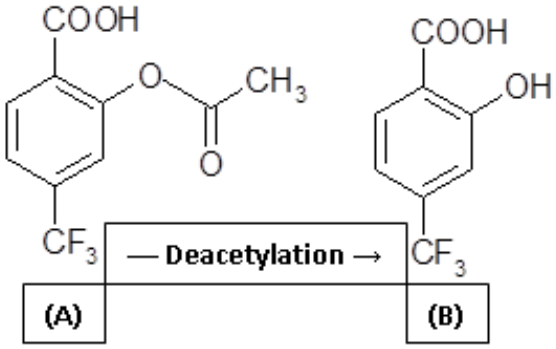

Figure 1. Chemical structure of triflusal (left; A) and its metabolite; HTB (right; B).

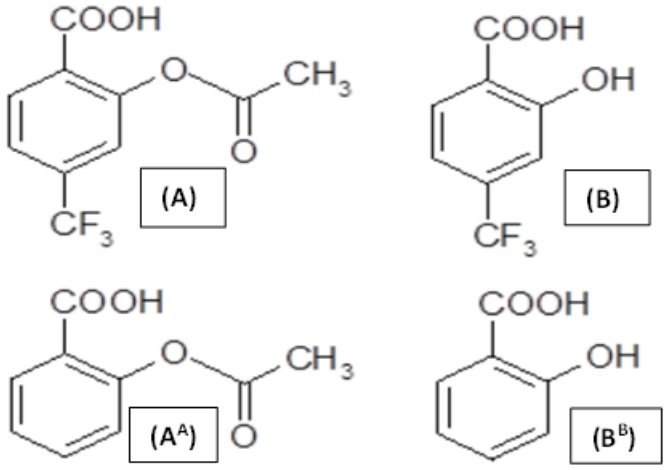

Figure 2. It clarifies that the chemical structure of triflusal (A) is very close to that of acetyl-salicylic acid (AA) and its metabolite; HTB (B) which also very close to salicylic acid (BB).

Beside the benefit medical uses of triflusal as it is prescribed to prevent blood clots especially in patients whom familiar with cardiovascular events history such as stroke or myocardial infraction, it has various side effects including gastrointestinal discomfort. This is considered as the most frequently reported side effect of triflusal. This is manifested as abdominal pain, diarrhea, nausea and/or vomiting. In addition, It may cause headache, dizziness or lightheadedness, and hematological side effects where the risk of bleeding is increased and could be presented as easy bruising, prolonged cuts bleeding, bleeding gums and nosebleeds. Furthermore, liver function abnormalities are noted with the long-term use of triflusal, so regular monitoring and liver function test may be recommended in such cases. Moreover, cutaneous phototoxic/photoallergic side effects are also noted with the use of triflusal including rash, itching and/or allergic reactions [7-13]. In the present work, we will discuss in details cutaneous phototoxic/photoallergic side effects.

COMPUTATIONAL METHODOLOGY

One form of HF-DFT frameworks is presented in the hybrid functional B3LYP is used [14-16], which applied with the middle size basis set 6-31G(d, p). This is used in order to obtain the HTB optimized structures which is shown in Figure 1 using the GAUSSIAN 03 package [17]. The basis set which used in the present work was investigated previously in one of our studies, where a similar molecular size drug (diclofenac) and its main photo-product have been investigated. We performed test calculations using a range of basis set (e.g., 6-31g(d,p) and 6-311g(d,p) with (and without) diffuse functions have been done [18]. Because of the results obtained from this test show that the effects on absorption spectra and transitions are within only a few nanometers, in addition to this and for computational reasons we have had used the B3LYP-6-31G(d,p) level of theory throughout this work.

Another very excellent tool in DFT framework named as Time dependent DFT (TD-DFT) [19-21] calculations were used herein in order to obtain the excitation energies of HTB in both the protonated (neutral) and deprotonated species, the obtained excitation energies are manifested in the form of UV-VIS spectra of HTB. We should intake in our consideration that the excitation energies tend to be overestimated by approximately 0.2 eV at this level of theory, leading to a slight blue-shift of the peaks in the computed spectra. Due to the solvent effects have very little influence on the HTB absorptions, under the methodology employed herein, subsequently they not included in the TD-DFT calculations. In Figure 3 we display the optimized structures of the triflusal and its active metabolite HTB in their singlet states, with the numbering of their atoms which will be used throughout the present work.

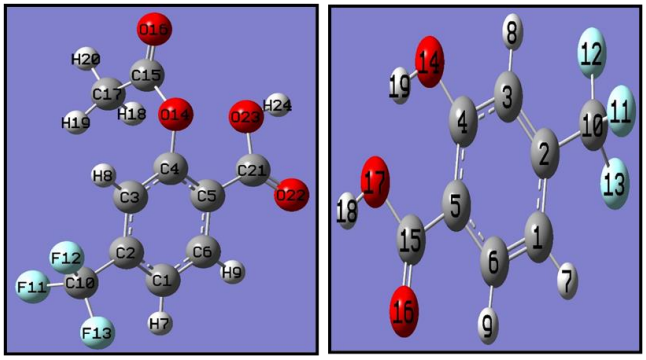

Figure 3. The optimized structures of the triflusal (left) and its active metabolite HTB (right) with numbering of their atoms which will be used throughout this study.

RESULTS AND DISCUSSION

In general, cutaneous photosensitivity diseases may be idiopathic. Nevertheless, they may be produced either by exogenous photosensitizers, or associated with endogenous photosensitizers. The former photosensitizers (exogenous agents) normally cause phototoxicity and photoallergy, as well as the exacerbation or induction of systemic disorders resulting in photosensitivity as a prominent clinical manifestation. The main difference between the phototoxic disorders and the photoallergic reactions is their incidences, the former one has a high incidence whereas, the later reactions are much less frequent. The action spectra for most phototoxins and photoallergens lie in the UVA range. Furthermore, the phototoxic and photoallergic reactions can be distinguished on the basis of diagnosis, pathogenesis, clinical characteristics, and management. Drugs such as antibiotic, porphyrins, psoralens, and NSAIDs are capable for causing phototoxic reactions. On the other hand, drugs like psychiatric medications and topical antimicrobial agents are capable to producing photoallergic reactions [22].

In this circumstance, Triflusal shows photoallergic side effects. Since this drug is prodrug, it is invivo metabolized to 2-hydroxy-4-trifluoromethylbenzoic acid (HTB), the pharmacologically active species. Under various conditions, HTB was found to be photolabile. The nucleophilic attack at the trifluoromethyl moiety is appeared to be major photodegradation pathway. This involves the triplet state in the photodegradation. Unequivocally, it is proved via direct detection of the triplet transient state in laser flash photolysis and also through quenching experiments with oxygen, cyclohexadiene and naphthalene. Which is turn, shows that the HTB is photo-binding to proteins, for example bovine serum albumin had been demonstrated using ultraviolet–visible (UV–Vis) and fluorescence spectroscopy. The responsible for the formation of covalent drug photo-adducts with protein is nucleophilic groups present in the protein, this is considered as the first step involved in the photo-allergy shown by triflusal [9].

MOLECULAR ORBITALS OF THE NEUTRAL AND THE DEPROTONATED FORMS OF HTB

The main aim of this work is to shed more light upon the photochemistry of triflusal agent and its main metabolite HTB. That is by depending upon the pervious experimental studies mentioned above and by using the excellent tool applied herein as mentioned in the methodology part. More and deep investigations about molecular orbitals studies have been depicted herein for the main photolabile species HTB which is responsible for the photo-binding with macromolecules subsequently leading to the phototoxicity side effects.

We in Figure 4 show the computed highest occupied and lowest unoccupied molecular orbitals (HOMOs and LUMOs) of the neutral (protonated) and deprotonated HTB species through TD-DFT/B3LYP level of theory with 6-31g (d,p) basis set. The results show that the HOMO, HOMO-1 and HOMO-2 of the protonated (neutral) species localized mainly on aromatic phenyl ring and the attached hydroxyl moiety, totally localized on the carboxylic group of the molecule, and on the aromatic phenyl ring and the oxygen atom of the carboxylic acid moiety, respectively. On the other hand, the LUMO and LUMO+2 of the neutral form are almost localized for both overall the molecule. Whereas, LUMO+1 is localized mainly and only on the aromatic ring system. In contrast to the protonated species, the deprotonated form of HTB show a different orbital pattern. Since all HOMO, HOMO-1 and HOMO-2 are all localized on the carboxylic moieties of the compound. Instead, the LUMO of the deprotonated form is localized mainly on the aromatic system and with lesser

extend to both carboxylic moiety and trifluoromethyl group of the active metabolite HTB molecule. Whereas, the LUMO+1 of the same species show that it localized on the aromatic ring system and the connected hydroxyl group. Lastly the LUMO+2 of the deprotonated species is localized on the hydroxyl moiety with very lesser extend to adjacent two carbons of the aromatic system.

The molecular orbitals (MOs) pattern difference between the two forms of HTB (protonated and deprotonated) specially the HOMOs of the deprotonated species in which they localized on the carboxylic acid moieties is also noted with various NSAIDs of our pervious various studies [23-27]. This is manifested in the Mulliken atomic charge distributions on the carboxylic acid moiety where in the deprotonated species shows higher negative charge on carboxylic acid moieties compared with the neutral form. They accounted to be -0.741 e- and 0.092 e-, respectively, as seen in the Table-1. The MO distributions difference of the neutral versus deprotonated of HTB plays an important role in their photochemical behaviors.

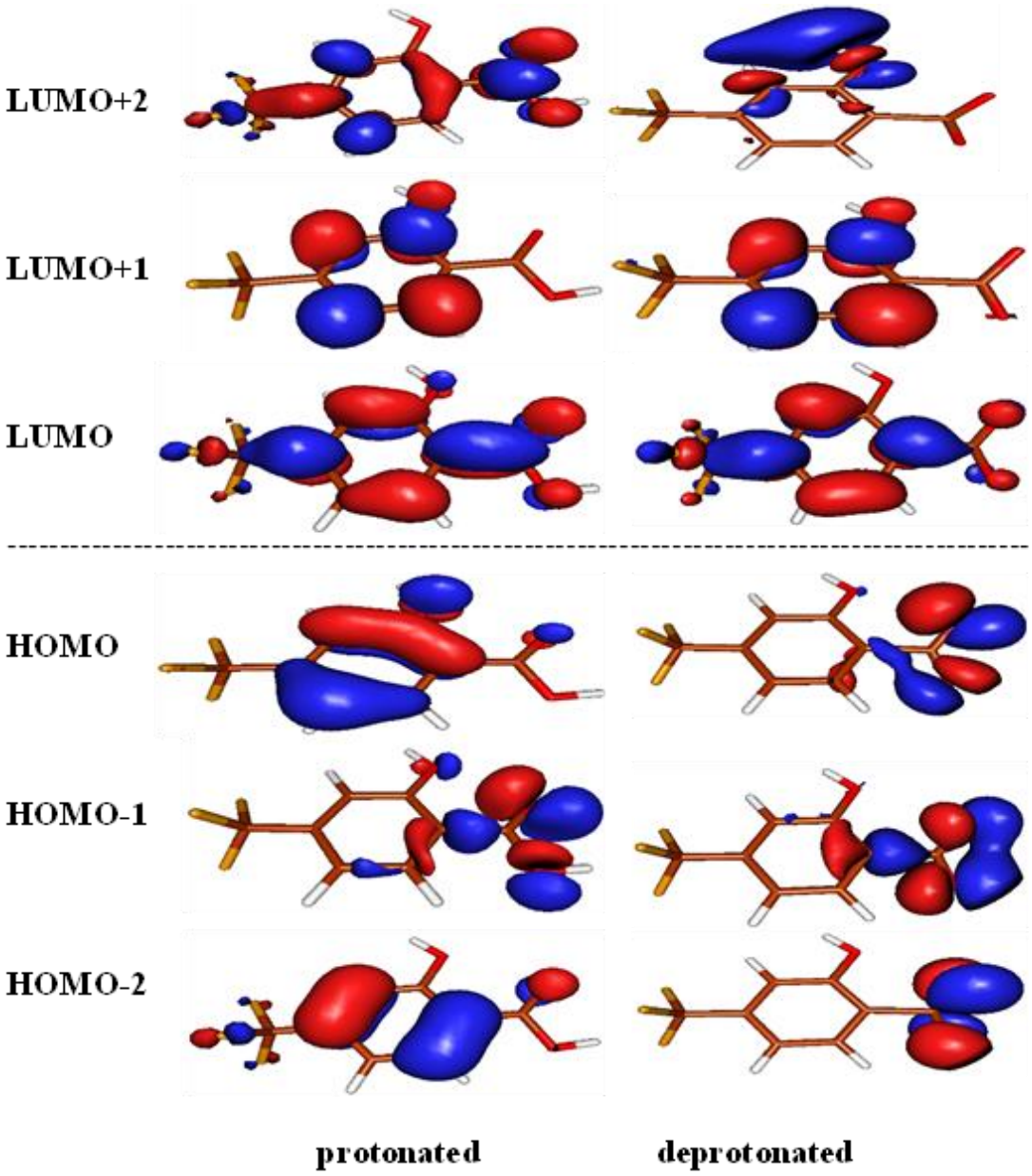

Figure 4. Molecular orbitals of the protonated (left) and deprotonated (right) species of the HTB.

Table 2. Mulliken atomic charges and spin densities (B3LYP/6-31G(d,p) level) for the atoms of triflusal and its metabolite Figure 1. For atomic labelling see Figure 3.

Triflusal Molecule				Active metabolite HTB Molecule				
numbering of atoms	atomic charge		Spin density of triplet state	numbering of atoms	atomic charge			spin density of triplet state
	singlet State	triplet State			singlet neutral state	singlet anion state	triplet anion state	
C_1	-0.097	-0.072	0.427	C_1	-0.109	-0.125	-0.089	0.295
C_2	-0.045	-0.075	0.497	C_2	-0.050	-0.057	-0.087	0.264
C_3	-0.113	-0.110	-0.195	C_3	-0.127	-0.150	-0.154	0.350
C_4	0.270	0.286	0.525	C_4	0.284	0.274	0.350	0.017
C_5	0.053	0.044	0.583	C_5	-0.006	0.010	-0.036	0.492
C_6	-0.118	-0.111	-0.152	C_6	-0.107	-0.121	-0.151	-0.002
H_7	0.122	0.132	-0.020	H_7	0.114	0.057	0.064	-0.015
H_8	0.129	0.133	0.005	H_8	0.125	0.073	0.062	-0.018
H_9	0.139	0.144	0.003	H_9	0.130	0.089	0.077	-0.003
C_{10}	0.797	0.795	-0.009	C_{10}	0.888	0.858	0.731	0.035
F_{11}	-0.257	-0.271	0.015	F_{11}	-0.288	-0.303	-0.309	0.018
F_{12}	-0.263	-0.266	0.002	F_{12}	-0.292	-0.306	-0.302	0.004
F_{13}	-0.264	-0.269	0.015	F_{13}	-0.294	-0.309	-0.307	0.005
O_{14}	-0.499	-0.480	0.072	O_{14}	-0.525	-0.552	0.579	0.390
C_{15}	0.587	0.605	0.010	C_{15}	0.517	0.444	0.518	0.012
O_{16}	-0.417	-0.402	0.020	O_{16}	-0.416	-0.507	-0.547	0.142
C_{17}	-0.411	-0.407	0.020	O_{17}	-0.530	-0.678	-0.569	0.019
H_{18}	0.150	0.152	0.002	H_{18}	0.337	0.302	0.329	-0.005
H_{19}	0.141	0.150	-0.001	H_{19}	0.347	-------	-------	-------
H_{20}	0.153	0.158	-0.001	-------	-------	-------	-------	-------
C_{21}	0.558	0.530	-0.016					
O_{22}	-0.463	-0.484	0.187					
O_{23}	-0.485	-0.513	0.014					
H_{24}	0.334	0.330	-0.002					

Spin densities upon the atoms of triflusal and its active metabolite HTB are shown in Table 1. The spin densities of the triplet state of the triflusal are localized mainly on the carbon atoms of aromatic system, C1, C2, C4, and C5 accounted to be 0.427, 0.497, 0.525, and 0.583, respectively. Whereas, the Mulliken atomic charge of singlet state of triflusal are localized on ester functional group and carboxylic acid moiety as well as with lesser extension of the trifluoromethyl moiety, with adjacent carbon atoms to these groups. Form other side, the spin densities of the triplet state of anion form of HTB are on the carbon atoms of aromatic system, C1, C2, C3, and C5 accounted to be 0.295, 0.264, 0.350, and 0.492 of electrons, in addition to this, the O14 (accounted 0.390) which a play an interesting role in an ionization process of this molecule during excitation to the triplet state which will be discussed later in this work.

ABSORPTION SPECTRA OF THE NEUTRAL AND THE DEPROTONATED SPECIES OF HTB.

TD-DFT methodology is applies herein in order to investigate the UV-visible spectrum of the active metabolite of HTB. In Figure 5, we display the computed UV-visible spectrum of both species of HTB. The results obtained show that the neutral (protonated) HTB has a capability to absorb UV-radiations especially in the region of 200 to 300 nm of the computed spectrum. The neutral form shows that the mainly peak at 198 nm with a good oscillator strength, with extended shoulder of two low peaks at 225 nm and 250 nm with low oscillator strengths. On the other hand, the deprotonated species shows a different pattern of UV-visible spectrum. Since it shows a peak at visible region above 400 nm and computed to be 425 nm with a low oscillator strength. The main peak is almost the same with the neutral form at around 200 nm with a good oscillator strength. This main peak followed by shoulder of three peaks at 225, 255 and 425 nm, all with low oscillator strengths. The results obtained herein are with the line of the experimental pervious works [28]. In addition, this difference is manifested as there is a difference in the MOs between the protonated and deprotonated forms of the active metabolite of the triflusal (HTB), see to the Figure 4.

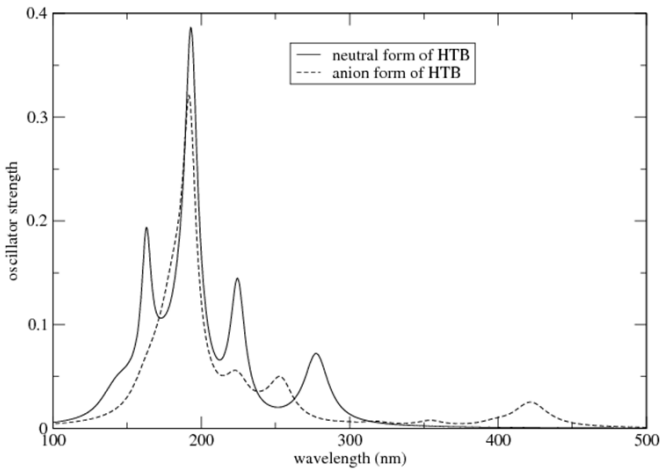

Figure 5. Computed absorption spectra in the 200-500 nm range of the protonated (solid) and deprotonated (dashed) forms of HTB, obtained at the TD-B3LYPL/6-31G(d, p) level.

EXCITATION OF THE DEPROTONATED SPECIES OF HTB.

Interestingly, during optimization of the triplet state of the deprotonated species of HTB, we noted that this species has a very interesting phenomenon in which the carboxylic acid moiety of the HTB has a capability to attractive the proton, that is forming a hydroxyl group of the HTB molecule attached to the carbon atom of the ring system, which is adjacent to that of the carbon atom connected to the carboxylic acid moiety. This can be manifested in such way that a good negative charge is localized on the carboxylic moiety of the origin optimized structure (singlet state) of the HTB, which is computed to be -0.741 e- and is reduced because of the acceptance of the proton which comes from the hydroxyl group and the deprotonated triplet state carboxylic moiety is neutralized, reduced and computed to be -0.269 e-, as shown in the Table 1. In other word, the starting point during optimization of the triplet state of the HTB molecule is deprotonated, and the final optimized species is in neutral (protonated) form, this process is going through what is named as a transition state. All these states have been explored in the Figure 6.

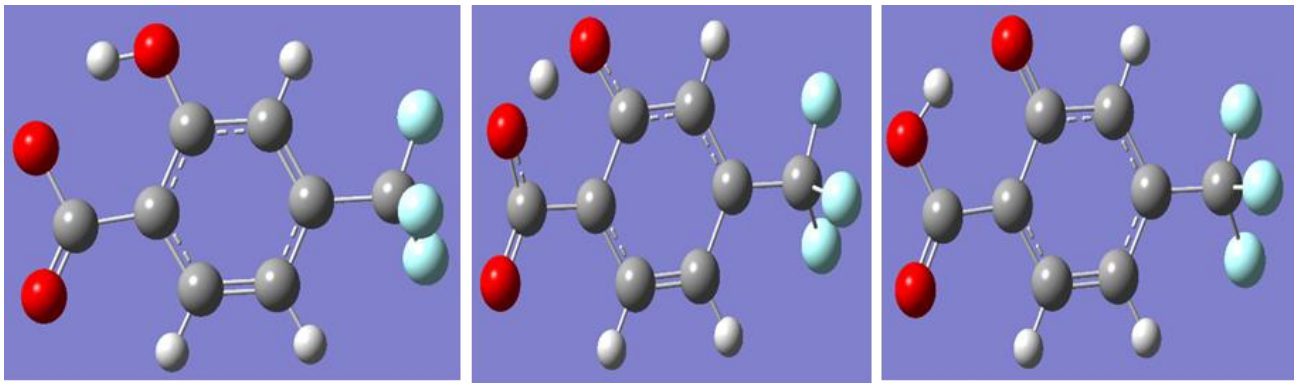

Figure 6. Triplet state optimization of the deprotonated (anion) form of the HTB. Starting molecule (left), transition state during optimization process (middle) and final optimized molecule (right).

CONCLUSION

Triflusal Chemically is nothing except a derivative of acetylsalicylic acid. In which a hydrogen atom that is in para-position to carboxylic moiety is replaced by a trifluoromethyl group. This chemical compound is metabolized or bio-transformed invivo under the effect of a deacetylation process into what is known HTB which is 2-hydroxyl-3-trifluoromethylbenzoic acid. One the most side effects of this drug is the cutaneous phototoxic/photoallergic side effect. It includes rash, itching and/or allergic reactions. We deeply investigate this drug by using a very excellent tool applicable to study such reactions that is DFT and TD-DFT.

The obtained results show that the triflusal in the form of its active metabolite HTB has a capability to absorb light mainly from the UV region and from visible region with a very low probability, as seen in UV-VIS spectrum shown above. The HOMOs of the deprotonated species of the HTB are localized on the carboxylic moiety of the molecule which different from the neutral form. This is manifested throughout the Mulliken charge distributions of various species. These findings show that the active HTB has a capability to induce phototoxicity and photoallergic reactions which in turn causes cutaneous phototoxicity side effects. The obtained findings put the basis to f the photodegradation mechanism of triflusal drug, indicating that the drug is a capable to react with macromolecules such as protein, lipid and nucleic acids. Further studies for various excitations of HTB and several considerations should be taken such as the presence of the trifluoromethyl moiety and its capability for photodegradation are required.

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