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Clofibrate isomers, their corresponding acids and anions and interaction of the anions with zinc cation - A DFT treatise

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Abstract

Clofibrate is a lipid-lowering ester used for controlling the high cholesterol and triacylglyceride levels in the blood. In the present study, clofibrate isomers, their corresponding acids and carboxylate anions have been considered within the constraints of density functional theory at the level of B3LYP/6-31++G(d,p). Also, interactions of some of those species with the zinc(II) cation have been considered. Various quantum chemical data, including the UV-VIS spectra, have been collected and discussed. All the species considered possess favorable thermo chemical values and they are electronically stable. All the clofibrate isomers and the carboxylate anions of them strongly interact with the zinc cation affecting some properties of them.

1. Introduction

In the last couple of decades, the drug, known as clofibrate (Ethyl 2-(4-chlorophenoxy)-2-methylpropanoate, $C_{12}H_{15}ClO_3$), gained widespread attention as an effective and relatively nontoxic agent for lowering plasma levels of cholesterol and triglycerides in man [1-10]. Clofibrate (trade name Atromid-S) is a lipid-lowering agent used for controlling the high cholesterol and triacylglyceride levels in the blood. It belongs to the class of fibrates. It increases lipoprotein lipase activity to promote the conversion of VLDL to LDL, and hence reduce the level of VLDL. It can increase the level of HDL as well [11]. Clofibrate is rapidly and completely absorbed from intestine after oral administration and is hydrolyzed to clofibric acid during absorption and passage through the liver. Clofibric acid is a biologically active metabolite of the lipid-lowering drugs clofibrate, etofibrate and the ofibrate [12].

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Clofibrate is a fibric acid derivative. The lipid lowering activity of clofibrate is probably mediated by its interactions with the peroxisome-proliferator-activated receptor-alpha (PPARα), which regulates gene expression of enzymes involved in fatty acid oxidation. Clofibrate increases lipoprotein lipase levels which enhances clearance of triglyceride rich lipoproteins. Clofibrate was available for many years and frequently used in the therapy of hypertriglyceridemia (Fredrickson types IV and V hyperlipidemia) and hypercholesterolemia (Fredrickson types IIa and IIb). Use of clofibrate decreased with the availability of statins for therapy of hyperlipidemia and subsequently it was withdrawn from use in USA in 2002 [13].

Synthesis and biological evaluation of new clofibrate analogues were published by Perrone et al. [14]. Fibrates are known to exhibit their beneficial effects by activating peroxisome proliferator-activated receptor-α (PPARα) and used in the treatment of dyslipidemia and atherosclerosis and for the prevention of heart failure [14].

Comparison of hypocholesterolemic activity for cyclic analogs of clofibrate in normolipemic rats have been reported by Goldberg et al. [15]. Goldberg et al. reported the comparison of hypocholesterolemic activity for cyclic analogs of clofibrate in normolipemic rats [15].

Mechanism of clofibrate hepatotoxicity, mitochondrial damage and oxidative stress in hepatocytes were reported by Qu et al. [16]. Their findings suggest that one action of clofibrate might be to impair mitochondrial function, so stimulating formation of ROS, which eventually contribute to cell death.

Clofibrate has also been the subject of many medicinal and biological researches [17-21]. It has been reported that clofibrate induces alterations in zinc, iron and copper metabolism [22].

In the last few decades, zinc has proved to be one of the keys to good health. Many illnesses are due to zinc deficiency, such as anorexia, acne, depression, male infertility, common cold, allergies and schizophrenia [22,23]. Zinc cation is one of the metabolically imported ions involved in the structure of many enzymes [22,23]. It is used in numerous drugs as zinc acetate, zinc oxide, zinc permanganate, zinc stereate, etc., [23].

Up to the best knowledge of the author there are no quantum chemical researches in the literature on the clofibrate or/and its isomers, clofibric acid isomers and their carboxylate anions as well as the interaction of zinc cation with clofibrate isomers and the clofibric acid anions.

In the present study, firstly clofibrate and clofibric acid isomers as well as the carboxylate anions of the clofibric acid isomers have been considered within the restrictions of the density functional theory (DFT). Secondly, the interaction of clofibric acid anions with zinc cation has been considered again in the realm of (DFT).

2. Method of Calculations

In the present study, all the initial optimizations of the structures leading to energy minima have been achieved first by using MM2 method which is then followed by semi empirical PM3 self consistent fields molecular orbital method [24-26]. Afterwards, the structure optimizations have been achieved within the framework of Hartree-Fock and finally by using density functional theory (DFT) at the level of B3LYP/6-31++G(d,p) [27,28]. Note that the exchange term of B3LYP consists of hybrid Hartree-Fock and local spin density (LSD) exchange functions with Becke's gradient correlation to LSD exchange [29]. The correlation term of B3LYP consists of the Vosko, Wilk, Nusair (VWN3) local correlation functional [30] and Lee, Yang, Parr (LYP) correlation correction functional [31]. In the present study, the normal mode analysis for each structure yielded no imaginary frequencies for the 3*N*–6 vibrational degrees of freedom, where *N* is the number of atoms in the system. This search has indicated that the structure of each molecule considered corresponds to at least a local minimum on the potential energy surface. Furthermore, all the bond lengths have been thoroughly searched in order to find out whether any bond cleavage occurred or not during the geometry optimization process. All these computations were performed by using SPARTAN 06 [32].

3. Results and Discussion

Clofibric acid (also known as clofibrinic acid) is an obsolete plant growth regulator [33] and a highly water soluble metabolite of clofibrate [33]. Clofibrate increases the clearance of triglyceride-rich lipoproteins via an increase in the activity of lipoprotein lipase [34]. Upon absorption, the ester group is hydrolyzed and the anions are transported, mostly bound to albumin in plasma [34].

Zinc has the electronic configuration of $1s^2 2s^2 2p^6 3s^2 3p^6 3d^{10} 4s^2$ [35]. Figure 1 shows the optimized structures of the clofibrate isomers (where letters p, m and o stand for the *para*, *meta* and *ortho* isomers) and their composites with the zinc cation. The figure also shows the directions of the dipole moment vectors. In the cases of *para* and *meta* isomers

the vectors originate from the ester or the dimethyl moieties and the tip points of them, in each case, directs to the phenyl moiety. Whereas, the situation is different for the *ortho* isomer and the vector originates from somewhere around the chlorine substituent and points to the dimethyl substituent. In the zinc cation composites, the starting location for the vector is somewhere in the site where the cation is present and directs to the phenyl group. The outcome arises mainly from the charge distribution on the structures.

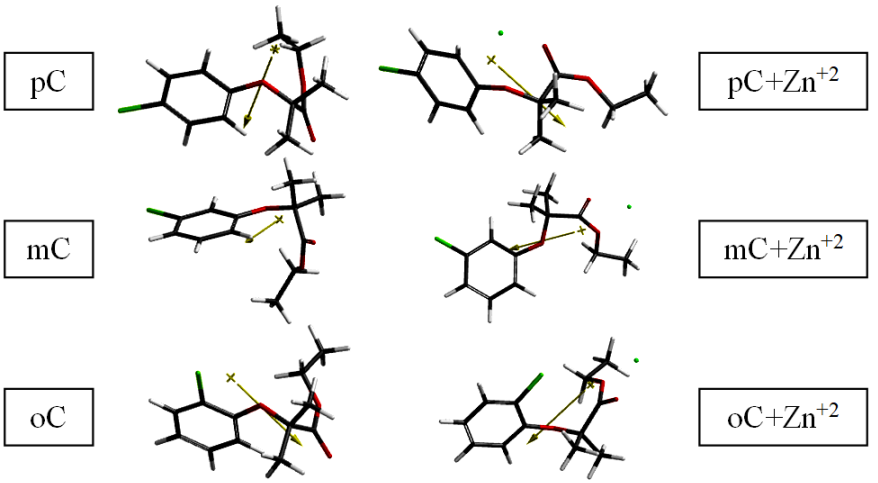

Figure 1. Optimized structures of the clofibrate isomers and their composites with the zinc cation.

Table 1 displays some thermo chemical properties of the species considered. All the species have exothermic heat of formations (H^o) and favorable free energy of formation (G^o) values at the standard states. As seen in the table, mC is the most exothermic and

Table 1. Some thermo chemical properties of the species considered.

Species	H^o	S^o (J/mol^o)	G^o
pC	-3024482.457	485.72	-3024627.281
mC	-3024483.665	486.15	-3024628.620
oC	-3024477.443	484.46	-3024621.873
$pC+Zn^{+2}$	-7694003.101	510.37	-7694155.276
$mC+Zn^{+2}$	-7693858.854	519.10	-7694013.603
$oC+Zn^{+2}$	-7693855.835	514.97	-7694009.376

Energies in kJ/mol.

most favorable isomer. Whereas for the composites, pC+Zn^{+2} becomes the most exothermic and most favorable one.

Some energies of the species considered are shown in Table 2, where E, ZPE and E_C stand for the total electronic energy, zero point vibrational energy and the corrected total electronic energy, respectively, electronic energy, respectively. As the data reveal, all of the structures are electronically stable. The algebraic order of E_C values is mC< pC< oC and for the composites pC+Zn^{+2} < mC+Zn^{+2}< oC+Zn^{+2}. Namely, mC and pC+Zn^{+2} are the most stable species of each class.

Table 2. Some energies of the species considered.

Species	E	ZPE	E_C
pC	-3025149.78	655.71	-3024494.07
mC	-3025151.89	656.68	-3024495.21
oC	-3025145.12	656.11	-3024489.01
pC+Zn^{+2}	-7694633.99	659.14	-7693974.85
mC+Zn^{+2}	-7694486.68	655.40	-7693831.28
oC+Zn^{+2}	-7694483.45	655.33	-7693828.12

Energies in kJ/mol.

Table 3 shows the aqueous energies of the clofibrate isomers which have the algebraic order of mC< pC< oC, means that isomer-mC is aquated better than the others. The ovality values for the pC, mC and oC are 1.40, 1.40, 1.39, respectively. Note that aqueous energies pC and mC are quite comparable in contrast to the respective energy of oC.

Table 3. Aqueous energies of the isomers.

oP	mC	oC
-3025165.67	-3025167.06	-3025159.73

Energies in kJ/mol.

Figure 2 displays the electrostatic potential (ESP) charges of the species considered. It is to be noted that the ESP charges are obtained by the program based on a numerical method that generates charges that reproduce the electrostatic potential field from the entire wavefunction [32]. As seen in the table in all the cases the charge on the cation is

less than the initial formal charge of +2 which means that some electron population has been transferred from clofibrate isomers to the zinc cation depending on the structure or conformational form. Also the distance between the cation and the negative charge centers should be implicitly influential. The order of positive charge on the cation is pC> oC>mC.

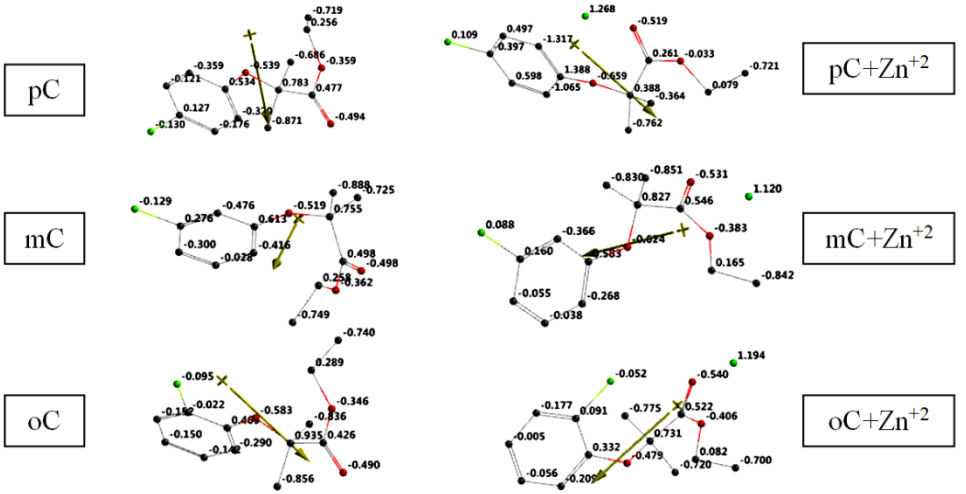

Figure 2. The ESP charges of the species considered (Hydrogens omitted).

Some properties of the species considered are shown in Table 4. As seen in the table, dipole moments are highly dispersed in contrast to the polarizability values. The order of dipole moments is oC+Zn^{+2} > mC+Zn^{+2} > pC+Zn^{+2} > pC > mC > oC. The order arises from the direction and magnitudes of bond dipoles in each structure which are dictated by the bond distances, angles and the local charges.

Table 4. Some properties of the species considered.

Species	Dipole (debye)	Polarizability	Log P
pC	4.03	59.75	1.19
mC	2.21	59.70	1.19
oC	2.01	59.70	1.19
pC+Zn^{+2}	8.49	60.89	-
mC+Zn^{+2}	11.20	61.63	-
oC+Zn^{+2}	12.09	61.54	-

Polarizabilities in 10^{-30} m^3 units.

Figure 3 displays the electrostatic potential maps of the parent isomers considered where negative potential regions coincides with red/reddish and positive ones with blue/bluish parts of the maps.

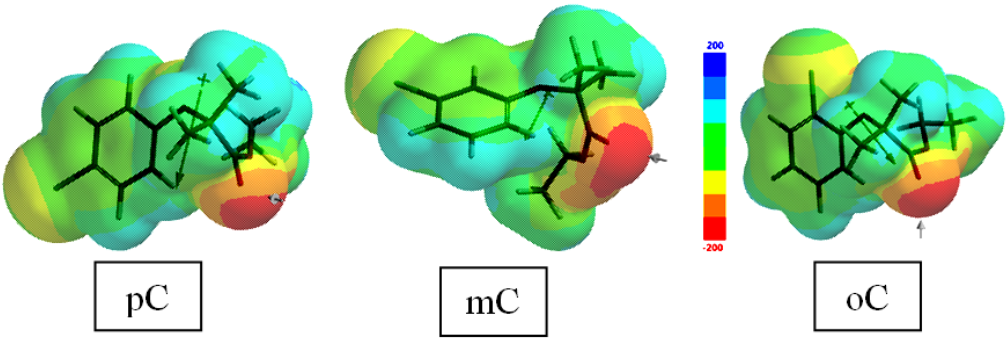

Figure 3. The electrostatic potential maps of the isomers considered.

Figure 4 shows the chemical function descriptors (CFDs) of the species considered. Note that CFDs are attributes given to a molecule in order to characterize or anticipate its chemical behavior. In the figure the blue and greens spheres on the molecules stand for hydrophobe and hydrogen bond acceptor regions, respectively.

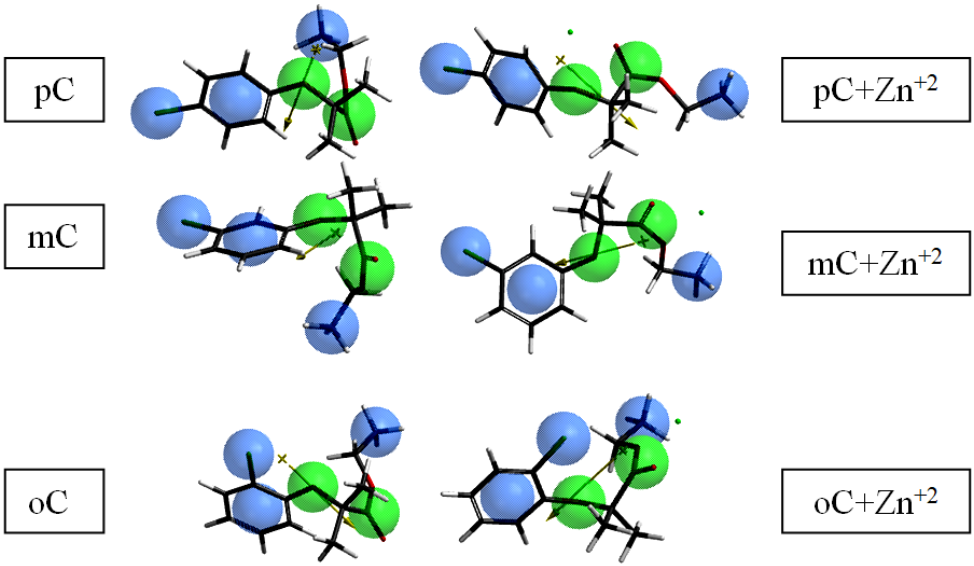

Figure 4. CFDs of the species considered.

Table 5 lists the HOMO, LUMO energies and the interfrontier molecular orbital energy gap values (Δε) values of the species considered. Note that it is defined as $\Delta\varepsilon=\varepsilon_{LUMO}-\varepsilon_{HOMO}$. The algebraic order of the HOMO energies is $pC+Zn^{+2} < oC+Zn^{+2} < mC+Zn^{+2} < mC < oC < pC$. The LUMO energies follow the order of $oC+Zn^{+2} < mC+Zn^{+2} < pC+Zn^{+2} < pC < mC < oC$. Thus, the presence of zinc cation not only substantially lowers the HOMO and LUMO energy levels of the parent isomers but also causes some ordinal changes in magnitudes. Consequently, Δε values exhibit the order of $mC+Zn^{+2} < oC+Zn^{+2} < pC+Zn^{+2} < pC < oC < mC$.

Table 5. The HOMO, LUMO energies and Δε values of the species considered.

Species	HOMO	LUMO	Δε
pC	-621.60	-89.77	531.83
mC	-642.14	-87.28	554.86
oC	-638.84	-87.05	551.79
$pC+Zn^{+2}$	-1367.29	-1085.19	282.10
$mC+Zn^{+2}$	-1252.94	-1206.90	46.04
$oC+Zn^{+2}$	-1291.14	-1233.91	57.23

Energies in kJ/mol.

Figure 5 displays the UV-VIS (time dependent DFT) spectra of the species

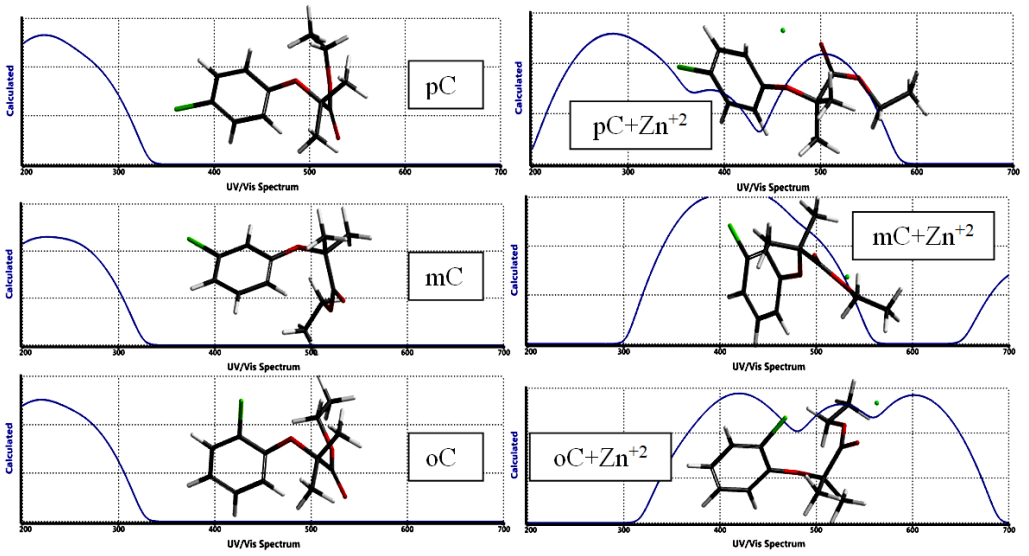

Figure 5. UV-VIS spectra of the species considered.

considered. As apparently seen in the figure, the presence of the zinc cation greatly affects the spectra of the parent isomers, causing tremendous bathochromic shift in each case.

Figure 6 shows the local ionization maps of the parent molecules considered where conventionally red/reddish regions (if any exists) on the density surface indicate areas from which electron removal is relatively easy, meaning that they are subject to electrophilic attack.

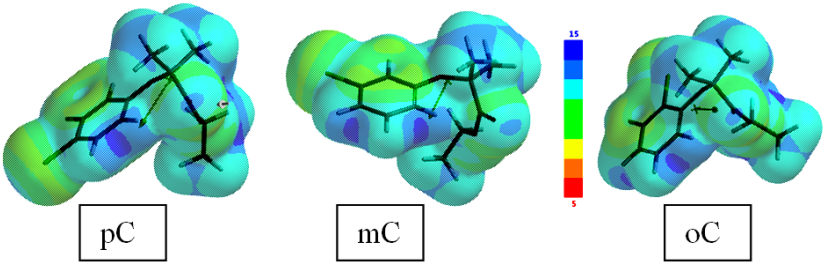

Figure 6. Local ionization potential maps of the isomers considered.

Figure 7 shows the LUMO maps of the species considered. Note that a LUMO map displays the absolute value of the LUMO on the electron density surface. The blue color (if any exists) stands for the maximum value of the LUMO and the red colored region, associates with the minimum value.

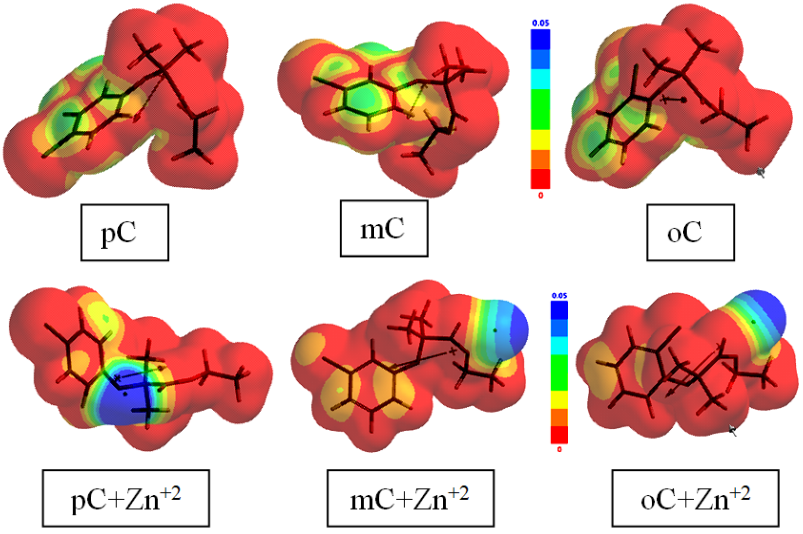

Figure 7. The LUMO maps of the isomers and the composites considered.

Clofibric acid isomers and their anions

Clofibric acid is a monocarboxylic acid. Upon absorption, the ester group of clofibrate is hydrolyzed forming clofibric acid [11,12,34]. Presently, clofibric acid isomers and their anions have been subjected to computational analysis. The abbreviations pCH, mCH and oCH stand respectively for the *para*, *meta* and *ortho* clofibric acids whereas their carboxylate anions are abbreviated as pC^A, mC^A and oC^A , respectively.

Figure 8 shows the optimized structures of the clofibric acids and their corresponding carboxylate anions considered. The figure also shows the direction of the dipole moment

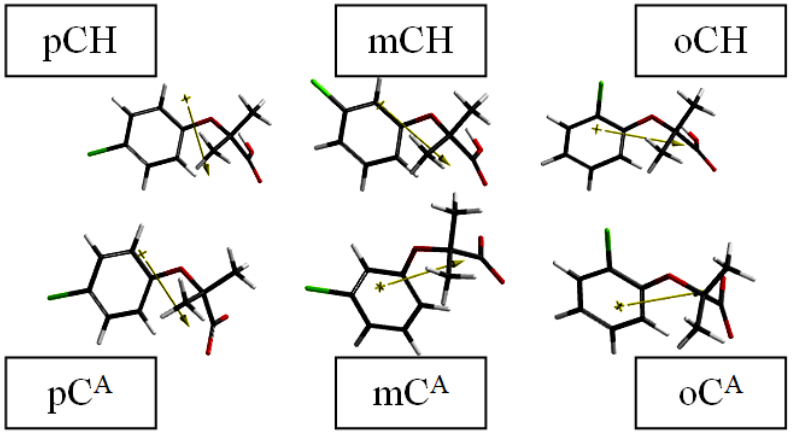

Figure 8. Optimized structures of the clofibric acids and their anions considered.

vectors. Their magnitudes are 3.51, 2.10, and 3.46 debye for the acids pCH, mCH and oCH, respectively. Whereas for the corresponding anions, they are 8.38, 7.31 and 8.01 debye, respectively. The variations should be due to the magnitudes of the local bond dipoles which are dictated by the bond lengths and local charges.

Some thermo chemical properties of the species considered are listed in Table 6. They all have the exothermic heat of formation and favorable G^o values at the standard states. In general the acids have more exothermic values than the corresponding anions and also they possess more favorable Gibbs free energy of formations. However among the acids and the anions, the *meta* isomers are the most exothermic and most favorable ones. Note that in the *meta* case the chlorine and the ether oxygen atom occupy positions such that in classical terms they are crossly conjugated.

Table 6. Some thermo chemical properties of the species considered.

Species	Hº	Sº (J/molº)	Gº
pCH	-2818234.911	443.91	-2818367.264
mCH	-2818236.198	444.63	-2818368.787
oCH	-2818228.452	441.77	-2818360.149
pC^A	-2816864.203	442.90	-2816996.240
mC^A	-2816865.725	443.11	-2816997.842
oC^A	-2816853.464	441.32	-2816985.056

Energies in kJ/mol.

Table 7 contains some energies of the clofibric acids and their anions considered. They are all electronically stable species. As expected the acids are more stable than the corresponding anions. Again the *meta* isomers are more stable than the others in each set of structures.

Table 7. Some energies of the clofibric acids and their anions considered.

Species	E	ZPE	E_C
pCH	-2818750.95	508.52	-2818242.43
mCH	-2818752.20	508.40	-2818243.80
oCH	-2818744.73	508.94	-2818235.79
pC^A	-2817343.64	472.12	-2816871.52
mC^A	-2817345.94	472.98	-2816872.96
oC^A	-2817333.26	472.60	-2816860.66

Energies in kJ/mol.

Table 8 list the aqueous energies of the clofibric acids and their anions considered. As seen in the table, in each set of structures *meta* isomer is better aquated than the others.

Table 8. Aqueous energies of the clofibric acids and their anions considered.

pCH	mCH	oCH	pC^A	mC^A	oC^A
-2818770.88	-2818771.62	-2818764.64	-2817593.97	-2817596.25	-2817590.62

Energies in kJ/mol.

Some properties of the clofibric acids and their anions considered are listed in Table 9. Although, the calculated log P values for the parent isomers are the same, the *meta* isomer has the lowest dipole moment value and the polarizability. The order of dipole moments is mCH< oCH< pCH. The same order holds for the anions considered.

Table 9. Some properties of the clofibric acids and their anions considered.

Species	Dipole (debye)	Polarizability	Log P
pCH	3.51	56.60	0.59
mCH	2.10	56.54	0.59
oCH	3.46	56.56	0.59
pC^A	8.38	56.76	-
mC^A	7.31	56.75	-
oC^A	8.01	56.79	-

Polarizabilities in 10^{-30} m^3 units.

The HOMO, LUMO energies and Δε values of the clofibric acids and their anions considered are shown in Table 10. As expected, the anions push up the HOMO energy levels in each case substantially as compared to the parent cases. The order of HOMO energies is oCH < mCH < pCH < mC^A < pC^A < oC^A. Whereas for the LUMO energies the order becomes oCH < mCH < pCH < oC^A < pC^A < mC^A. Consequently, Δε values follow the order of mCH > oCH > pCH > mC^A > pC^A > oC^A.

Table 10. The HOMO, LUMO energies and Δε values of the clofibric acids and their anions considered.

Species	HOMO	LUMO	Δε
pCH	-661.36	-113.13	548.23
mCH	-683.93	-110.03	573.90
oCH	-688.57	-115.09	573.48
pC^A	-199.36	213.23	412.59
mC^A	-199.43	214.37	413.80
oC^A	-196.05	200.07	396.12

Energies in kJ/mol.

Figure 9 is the calculated (time dependent DFT) spectrums of the *para* clofibric acid and its carboxylate anion. All the other acids and anions considered possess a similar spectra all confined to UV region.

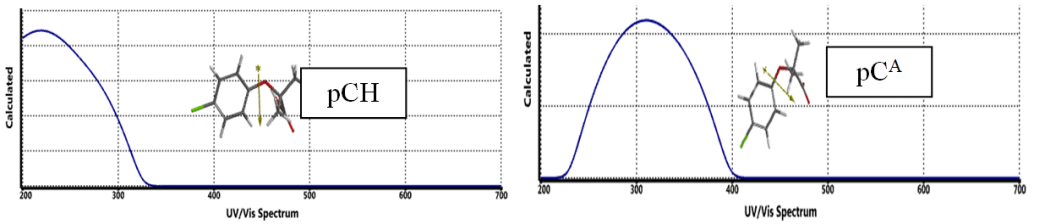

Figure 9. The calculated UV-VIS spectrum of pCH and pC^{A}.

Interaction of clofibric acid anions with the zinc cation

In the present section, composites of clofibric acid anions (derived from the *para*, *meta* and *ortho* isomers of clofibric acid) with the Zn^{+2} are considered. Note that the overall charge of the composites is +1. In this case the interactions between the components are not simply dipole-dipole type but also charge-charge or/and charge-dipole types. The composites have been labeled as shown in Figure 10, where letter-Z stands for the zinc cation. The rest of the notation in each case is the same as the ones used before.

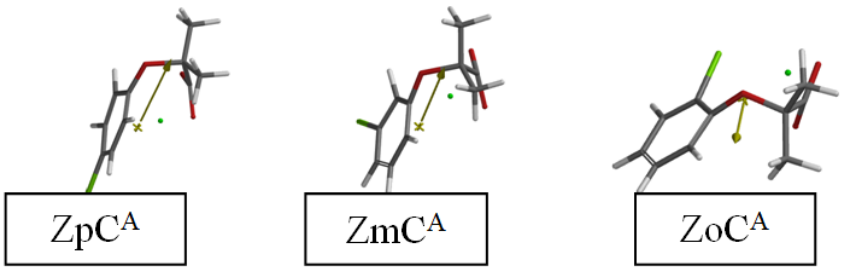

Figure 10. Optimized structures of the composites of clofibric acid anions with zinc cation.

Table 11 shows some thermo chemical properties of the anion composites considered.

Table 11. Some thermo chemical properties of the anion composites considered.

Species	H^o	S^o (J/mol^o)	G^o
ZpC^A	-7487152.602	461.04	-7487290.075
ZmC^A	-7487154.729	461.81	-7487292.412
ZoC^A	-7487138.897	462.99	-7487276.947

Energies in kJ/mol.

Some energies of the anion composites considered are shown in Table 12.

Table 12. Some energies of the anion composites considered.

Species	E	ZPE	E_C
ZpC^A	-7487599.91	480.43	-7487119.48
ZmC^A	-7487602.23	480.83	-7487121.40
ZoC^A	-7487586.33	480.46	-7487105.87

Energies in kJ/mol.

The HOMO, LUMO energies and Δε values of the anion composites considered are displayed in Table 13.

Table 13. The HOMO, LUMO energies and Δε values of the anion composites considered.

Species	HOMO	LUMO	Δε
ZpC^A	-1094.29	-756.05	338.24
ZmC^A	-1089.12	-750.38	338.74
ZoC^A	-1032.28	-772.08	260.20

Energies in kJ/mol.

Figure 11 displays the calculated (time dependent DFT) UV-VIS spectra of the composites of clofibric acid anions with zinc cation. As compared to Figure 9, one observes that the interactions between the clofibric acid anions and the zinc cation are so great to produce very considerable degree of bathochromic shifts, especially in the case

of ZoC^A. Note that it possesses the narrowest interfrontier molecular orbital gap among the series (see Table 13). The rest, namely ZpC^A and ZmC^A have comparable Δε values and thus their spectrums are alike. The composite, ZoC^A also differs from the others by having a fourth absorption maximum in the visible region. In this composite, the substituents of the organic moiety should exert their inductive and mesomeric effects in such a way that extended conjugation occurs, leading to a likely narrowing of the intermolecular orbital energy gap. Thus, it possesses the smallest Δε value. As for the intensities, of course they are mainly dictated by the transition moments for the molecular orbitals involve in the transitions during the electronic excitations.

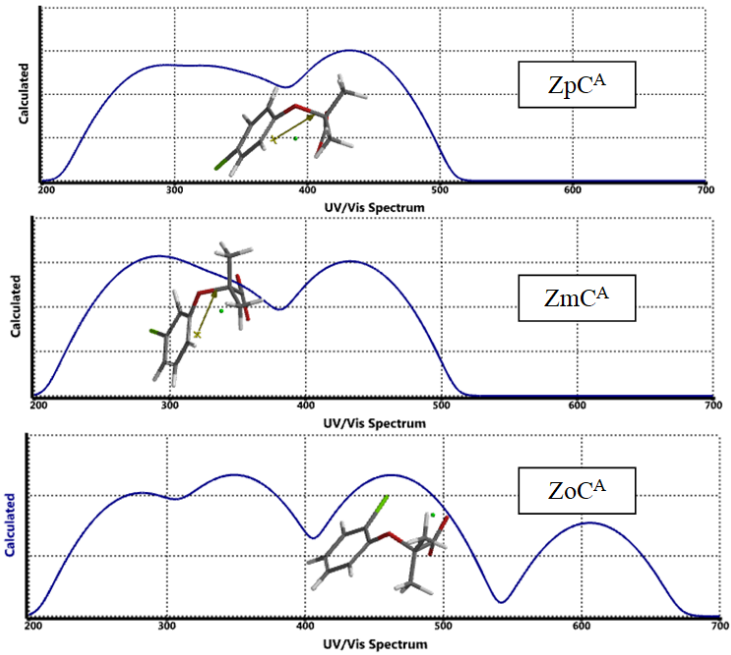

Figure 11. The calculated UV-VIS spectra of the composites of clofibric acid anions with zinc cation.

4. Conclusion

In the present computational study, within the constraints of DFT treatment at the level of B3LYP/6-31++G(d,p), isomers of clofibrate, their corresponding clofibric acids and their anions are considered. Additionally, the composites of isomers of clofibrate and anions derived from clofibric acids with the zinc cation have been considered. The data reveal that all the structures considered possess thermo chemically favorable values and

they are electronically stable. Interaction with the zinc cation causes great perturbation on various properties of the structures considered. In the aqueous media zinc cation is most probably in the aquated form, hence the interaction of the species with the core cation should be highly depended on the relative polarizabilities of the competing nucleophiles.

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