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Geometrical Isomers of Dantrolene and Their Interactions with Calcium and Magnesium Cations

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Abstract

Geometrical isomers of dantrolene are considered within the constraints of density functional theory at the level of B3LYP/6-31++G(d,p). Dantrolene is a skeletal muscle relaxant which interferes with the release of calcium ion from the sarcoplasmic reticulum. On the other hand, some evidence exists that dantrolene is Mg^{2+}-dependent at least in certain species. Therefore, the present study not only considers the geometrical isomers of dantrolene but also focused on the interaction of isomers of dantrolene with Ca^{+2} and Mg^{+2} ions at the molecular level. All the systems of present interest have exothermic heat of formation values and favorable Gibbs free energy of formation values. They are electronically stable. In the case of composite from the *anti* isomer, Ca^{+2} or Mg^{+2} ion locates itself in the cavity/fjord formed in the composite of dantrolene whereas in the *syn* composite, Mg^{+2} prefers a location outside the cavity/fjord of the composite molecule. Various quantum chemical data have been collected and discussed including UV-VIS spectra.

1. Introduction

Dantrolene, is a hydantoin derivative (1-{[5-(p-nitro phenyl)furfurylidene]amino} hydantoin) and its synthesis and identification as skeletal muscle relaxant were reported by Snyder [1] and subsequently received further evaluation [2, 3]. It has a unique mechanism of spasmolytic action outside the central nervous system [4-6]. It relaxes skeletal muscles by acting directly on the muscle. The site of action of dantrolene within the muscle is not yet clearly understood. However, it is believed that it either directly or indirectly relaxes skeletal muscles by acting directly on the muscle. Dantrolene reduces skeletal muscle strength by interfering with excitation-contraction coupling in the muscle

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fiber. The normal contractile response involves release of activator calcium from its stores in the sarcoplasmic reticulum of the sarcomere. The calcium brings about the tension-generating interaction of actin with myosin. Dantrolene interferes with the release of calcium from the sarcoplasmic reticulum [5]. Thus the action of dantrolene involves neither central synapses nor the neuromuscular junctions, it is intercellular at the effector organ [4].

Dantrolene is a muscle relaxer that is used to treat muscle spasticity (stiffness and spasms) caused by conditions such as a spinal cord injury, stroke, cerebral palsy, or multiple sclerosis. Dantrolene is also used to treat or prevent muscle stiffness and spasms caused by malignant hyperthermia (a rapid rise in body temperature and severe muscle contractions) [7] that can occur during surgery with certain types of anesthesia [5,6]. In recent years dantrolene still attracts attention of many scientists and many publications exist in the literature. Grunau et al., have demonstrated that the use of dantrolene in the treatment of hyperpyrexia related to MDMA (3,4-methylenedioxymethamphetamine) is controversial [8]. The effects of dantrolene on arrhythmogenic triggers and contractile function in human atrial fibrillation (AF) and HF cardiomyocytes (CM) have been reported by Hartmann et al., [9]. The role of the disruption of intracellular calcium homeostasis on cell death, the pharmacologic and pharmaco-kinetic features of dantrolene, and the cytoprotective effects and potential application of dantrolene for the inhibition of cell damage in a wide variety of models of stress and disease have been investigated by Inan and Wei [10]. Dantrolene affects carbonic anhydrase enzyme activities that is reported by Gülçin et al., [11]. On the other hand, Choi et al., have provided some evidence that in skinned muscle fibers from rat that inhibition of sarcoplasmic reticulum Ca^{2+} release by dantrolene is Mg^{2+}-dependent [12,13].

Up to the best knowledge of the author, in the literature there exist no quantum chemical or density functional calculations directly involving dantrolene isomers and their interactions with calcium or magnesium cation, hence the lack of information in the literature has led the present research to be concentrated on the subject.

2. Method of Calculations

In the present study, all the initial structure optimizations of the structures leading to energy minima have been achieved by using MM2 method which is followed by semi empirical PM3 self consistent fields molecular orbital method [14-16]. 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) [17,18]. 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 [19]. The correlation term of B3LYP consists of the Vosko, Wilk, Nusair (VWN3) local correlation functional [20] and Lee, Yang, Parr (LYP) correlation correction functional [21]. 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 [22].

3. Results and Discussion

Dantrolene possesses two geometrical isomers (*anti* and *syn* isomers) about the >N=CHR bond which is flanked by an imide moiety (hydantoin) at one side and furfurylidene ring (R) on the other side. Figure 1 shows the optimized geometries of *anti* and *syn* isomers of dantrolene (in brevity indicated as *syn* and *anti*) as well as the direction of dipole moment vectors. The *anti* isomer is a coplanar structure whereas in the *syn* form the five-membered imide (hydantoin) ring is out of planarity with π-system of the N=C bond, thus with the rest of the molecule. Also note that in both of the isomers nitro phenyl and furfurylidene rings are coplanar with each other. The direction of dipole moment vector in each isomer is towards the nitro phenyl ring.

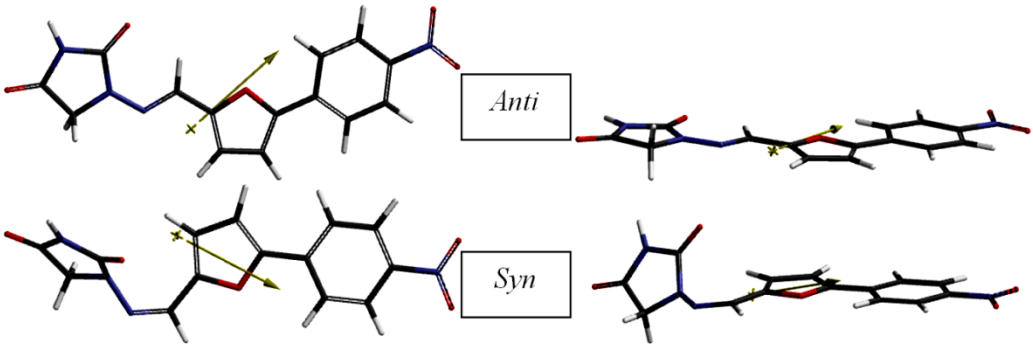

Figure 1. The optimized structures of *anti* and *syn* forms of dantrolene (top and side views).

Table 1 shows some thermo chemical values of the isomers considered. As seen in the table both of the isomers possess exothermic heat of formation and favorable Gibb's energy of formation values at the standard states. The same orders of H^o and G^o values (algebraically) are obtained as *anti* < *syn.* Whereas S^o values have the reverse order. Probably, not only the electronic effects but also steric effects should be responsible for the obtained orders. The *anti* isomer which has greater S^o value but more exothermic leads to more favorable G^o value compared to the *syn* isomer.

Table 1. Some thermo chemical values of dantrolene isomers.

Isomer	H^o	S^o (J/mol^o)	G^o
Anti	-2978238.331	520.21	-2978393.421
Syn	-2978212.653	513.46	-2978365.748

Energies in kJ/mol.

Table 2 lists some energies of the isomers considered, where E, ZPE and E_C stand for the total electronic energy, zero point vibrational energy and the corrected total electronic energy, respectively. As seen in the table all the isomers considered are electronically stable and the stability order (in vacuum) is that the *anti* isomer is more stable than the *syn.* The electronic stability order of the isomers is the same as their order of G^o values.

Table 2. Some energies of dantrolene isomers.

Isomer	E	ZPE	E_C
Anti	-2978871.68	617.63	-2978254.05
Syn	-2978846.74	618.88	-2978227.86

Energies in kJ/mol.

The aqueous energies of dantrolene isomers are shown in Table 3 and it seems that the *anti* isomer is more stable than the *syn* in water as it is in vacuum.

Table 3. Aqueous energies of dantrolene isomers.

Anti	*Syn*
-2978916.29	-2978891.33

Energies in kJ/mol.

The effect of isomerism on the chemical function descriptors (CFD) of the isomers are shown in Figure 2. Note that CFDs are attributes given to a molecule in order to characterize or anticipate its chemical behavior. In the figure different colors stand for different descriptors. Note that HBA and HBD mean hydrogen bond acceptors and donors, respectively. Both of the isomers have the same number of the same kind of CFDs. Therefore, differences in properties of them should arise from the minor differences in the gross and fine topology of the structures.

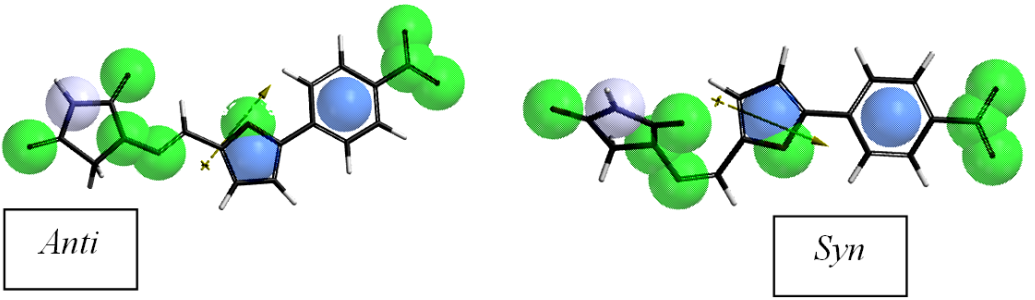

Figure 2. CFDs of the isomers considered (Green: HBA; Purplish: HBA, HBD and +ionizable; Bluish: Hydrophobe).

Some properties of dantrolene isomers are listed in Table 4. As seen in the table, the *anti* isomer possesses greater dipole moment and polarizability values as compared to the *syn* isomer. There, the polarizability is defined according to the bivariable formula [22].

$$\text{Polarizability} = 0.08*V - 13.0353*h + 0.979920*h^2 + 41.3791$$

where the independent variables, V and h are the Van der Waals volume and hardness, respectively. Hardness is defined as,

$$\text{Hardness} = -(\varepsilon_{HOMO} - \varepsilon_{LUMO})/2$$

where ε_{HOMO} and ε_{LUMO} are the molecular orbital energies of the highest occupied (HOMO) and the lowest unoccupied (LUMO) molecular orbital energies.

Polar surface area (PSA) is defined as the amount of molecular surface area arising from polar atoms (N,O) together with their attached hydrogen atoms. Molecules with PSA values greater than 140 Å² tend to be poor at permeating cell membranes whereas to penetrate the blood-brain barrier a PSA value of a molecule should be less than 90 Å² [23,24]. The data indicate that the *syn* isomer being more globular than the *anti* is comparatively more penetrating.

As for the Log P values, the calculations yield the same value. Note that hydrophilic drugs (having low octanol/water partition coefficients) are found primarily in aqueous regions.

Table 4. Some properties of dantrolene isomers.

	Dipole	Area (Å²)	Volume (Å³)	PSA (Å²)	Ovality	Log P	Polarizability
Anti	5.60	311.28	283.35	96.190	1.49	-2.06	63.61
Syn	3.53	306.70	283.05	95.923	1.47	-2.06	63.55

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

Figure 3 shows the electrostatic potential (ESP) charges on the atoms of dantrolene isomers. Note 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 [22].

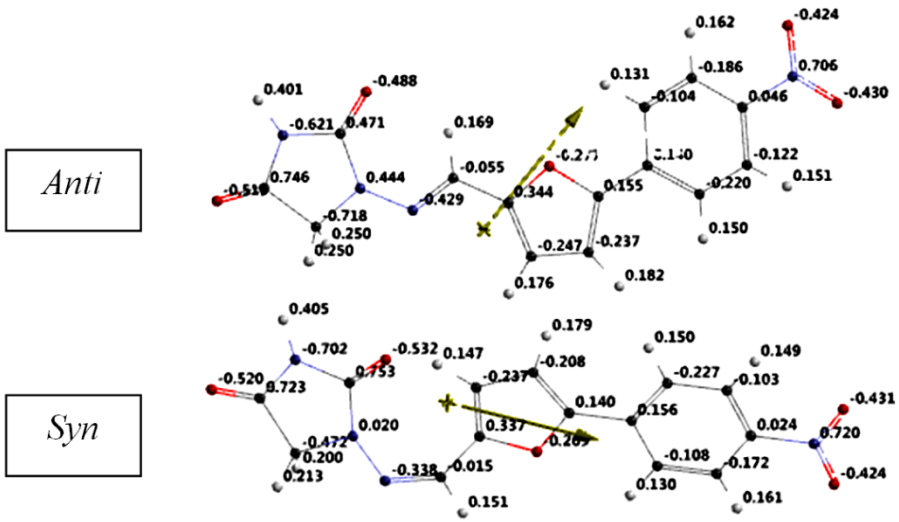

Figure 3. The ESP charges on the atoms of dantrolene isomers.

Figure 4 displays the electrostatic potential maps of dantrolene isomers considered. In the figure the red and blue colors stand for negative and positive potential regions, respectively. As seen in the figure, *anti/syn* isomerization mainly affects the imide moiety and the region of N=C bond. It is worth mentioning that in the *syn* isomer the imide moiety has a broken conjugation with the N=C bond (also see Figure 1).

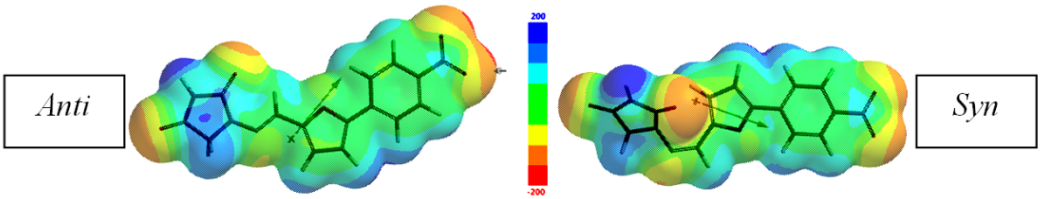

Figure 4. The electrostatic potential maps of dantrolene isomers.

The HOMO, LUMO energies and intermolecular orbital energy gap ($\Delta\varepsilon=\varepsilon_{LUMO}-\varepsilon_{HOMO}$) values of the species considered are shown in Table 5. The algebraic order of HOMO energies are *anti*< *syn,* whereas the LUMO energies follow the order of *syn*< *anti.* Consequently, the order of interfrontier molecular orbital energy gaps, Δε, becomes *syn* > *anti.* Since a better conjugation raises up the HOMO but lowers the LUMO energy levels [25] and the *anti* isomer has better conjugation as compared to the *syn* isomer (see Figure 1), the narrowing of the interfrontier molecular orbital energy gap (Δε) as going from the *syn* isomer to the *anti* isomer is quite expected.

Table 5. The HOMO, LUMO energies and Δε values of dantrolene isomers.

Isomer	HOMO	LUMO	Δε
Anti	-604.79	-300.44	304.35
Syn	-636.28	-314.49	321.79

Energies in kJ/mol.

Figure 5 displays some of the molecular orbital energy levels of dantrolene isomers considered. In the figure the smaller energy gap between the HOMO and NEXTHOMO of the *syn* isomer compared to the *anti* is especially noticeable.

Figure 6 is the local ionization potential maps of the isomers 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. As seen in the figure, imide ring in both of the isomers constitutes the electron poor region of the molecule whereas the imide carbonyl oxygens stand for relatively electron rich regions.

Figure 7 shows the LUMO maps of dantrolene isomers 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.

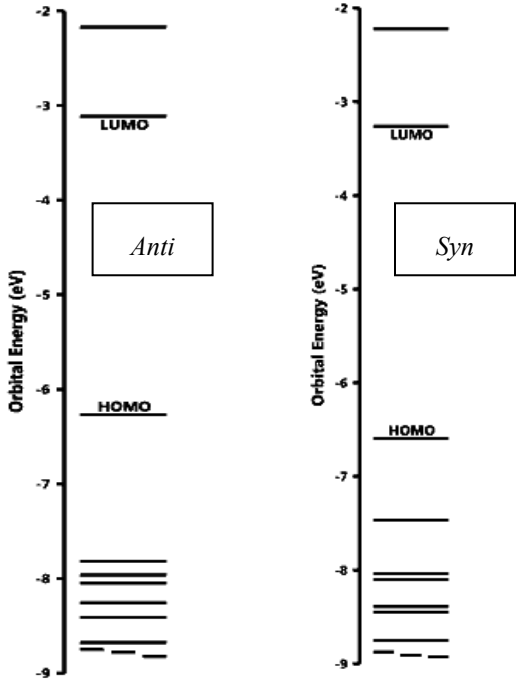

Figure 5. Some of the molecular orbital energy levels of dantrolene isomers considered.

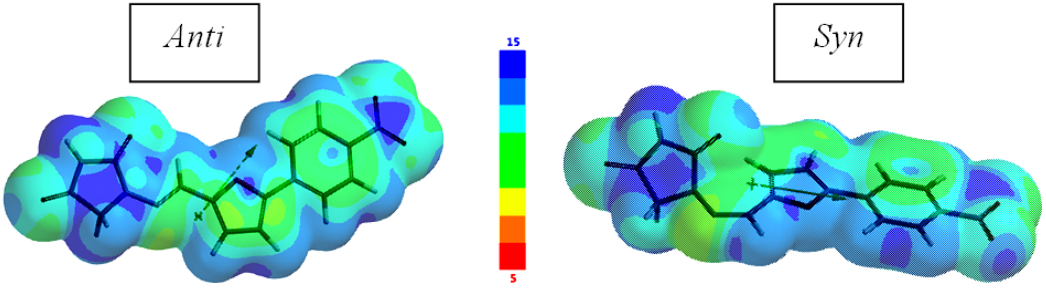

Figure 6. The local ionization maps of dantrolene isomers.

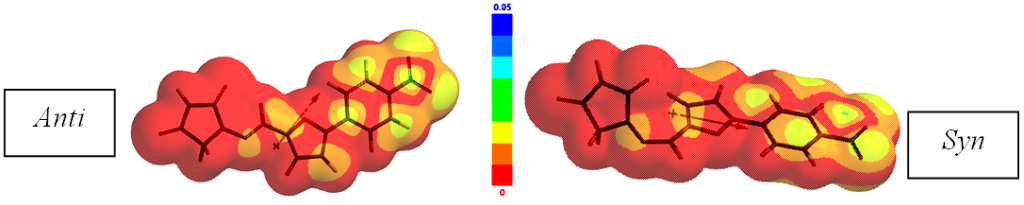

Figure 7. The LUMO maps of dantrolene isomers.

Interaction of dantrolene with calcium and magnesium cations

The ground state electronic configurations of Mg and Ca are $1s^2 2s^2 2p^6 3s^2$ and $1s^2 2s^2 2p^6 3s^2 3p^6 4s^2$, respectively [26]. In the +2 oxidation state both of them constitute closed shell systems.

Figures 8 and 9 show the optimized structures of Ca^{+2} and Mg^{+2} composites of *anti* and *syn* forms of dantrolene. In both of the cases of the cations considered, the nitro group is not coplanar with the phenyl ring (except *syn*+Mg^{+2} composite) in the composites. As seen in the figures the *anti* and *syn* forms constitute a cavity/fjord region where the calcium cation prefers to reside. Whereas the magnesium cation prefers the cavity/fjord region in the case of *anti* composite but its preference in the *syn* form is out of the cavity/fjord (see Figure 9).

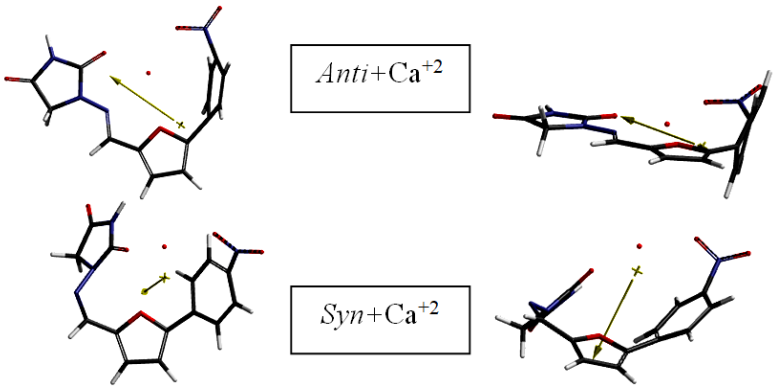

Figure 8. The optimized structures of dantrolene composites of *anti*+Ca^{+2} and *syn*+Ca^{+2} (two different views).

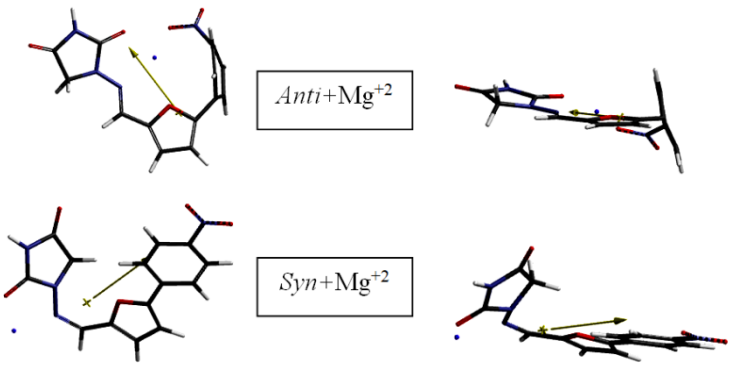

Figure 9. The optimized structures of dantrolene composites of *anti*+Mg^{+2} and *syn*+Mg^{+2} (two different views).

The outcome should arise from a complex interaction of charge-charge, charge-dipole and dipole-dipole types which determine the preferred site for the cations considered.

Table 6 shows some thermo chemical values of the Ca^{+2} and Mg^{+2} composites of dantrolene isomers considered. As seen in the table both of the isomers possess exothermic heat of formation and favorable Gibb's energy of formation values at the standard states. The same orders of Hº and Gº values (algebraically) are obtained in each group of composites as *anti*< *syn.* Whereas Sº values have *syn*<*anti* order in the case of Ca^{+2} composites, but the Mg^{+2} composites exhibit the order of *anti*< *syn*.

Table 6. Some thermo chemical values of dantrolene composites.

Isomer	Hº	Sº (J/molº)	Gº
Anti+Ca^{+2}	-4755994.735	539.83	-4756155.679
Syn+Ca^{+2}	-4755893.809	537.77	-4756054.151
Anti +Mg^{+2}	-3502163.771	531.32	-3502322.169
Syn +Mg^{+2}	-3502078.651	532.21	-3502237.338

Energies in kJ/mol.

Table 7 lists some energies of the composites considered. As seen in the table, all the composites considered are electronically stable and the stability order (in vacuum) is that in each case the composite from the *anti* isomer is more stable than the respective one from the *syn* isomer.

Table 7. Some energies of dantrolene composites.

Isomer	E	ZPE	E_C
Anti+Ca^{+2}	-4756618.70	621.50	-4755997.20
Syn+Ca^{+2}	-4756517.06	620.85	-4755896.21
Anti +Mg^{+2}	-3502801.01	623.89	-3502177.12
Syn +Mg^{+2}	-3502717.00	625.22	-3502091.78

Energies in kJ/mol.

Figure 10 displays the ESP charges on the atoms of dantrolene composites. As seen in the figure, either of the cations possesses a charge less than formal +2 which means some electron population has been transferred to the cation from the organic moiety. The magnitude of charge of the cation should be determined by the electron affinity of the cation in that part of the space nearby the organic moiety.

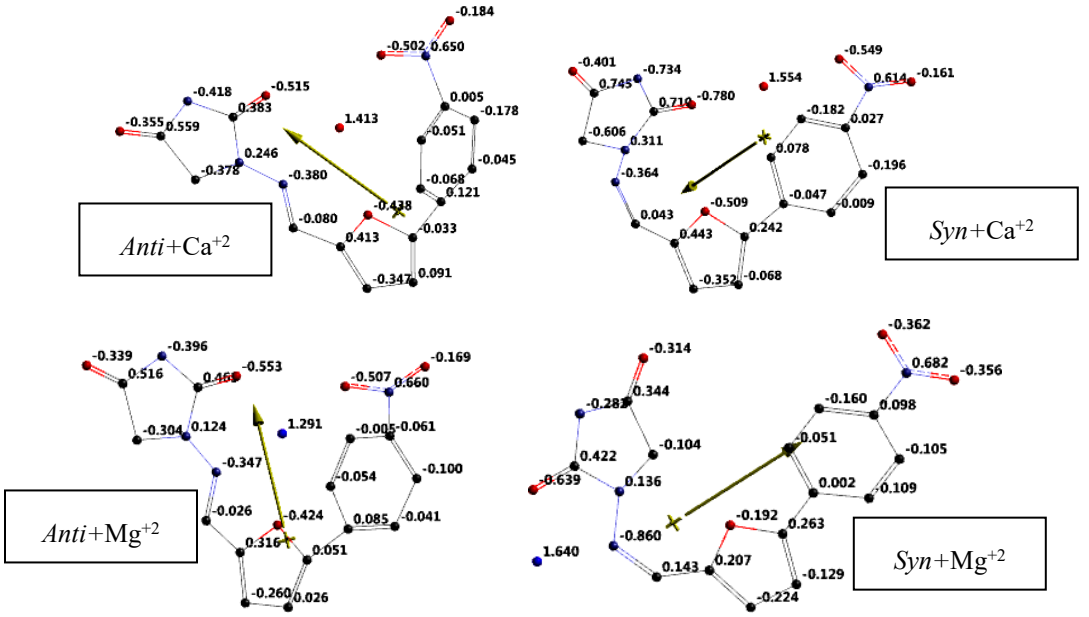

Figure 10. The ESP charges on the atoms of dantrolene composites (Hydrogens omitted).

Figure 11 shows the LUMO maps of dantrolene composites considered. It is worth remembering once again 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 (such as *Syn*+Mg^{+2} case) and the red colored region, associates with the minimum value.

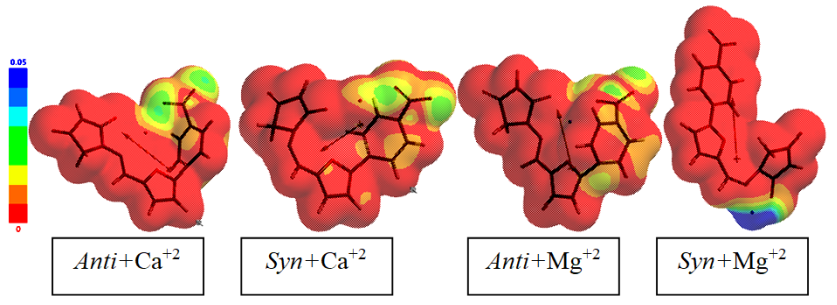

Figure 11. The LUMO maps of dantrolene composites considered.

The local ionization maps of all the composites considered are all blue in color. In such kind of maps, dark blue regions stand for electron poor, whereas green/greenish or light blue regions are relatively electron rich regions. So, in the present cases considered, the positive charge of a cation makes the whole system electron poor to be attacked by eletrophiles.

Figure 12 displays the calculated bond lengths of dantrolene and the composite systems considered. As seen from the figure some small perturbations occur going from one system to another system considered.

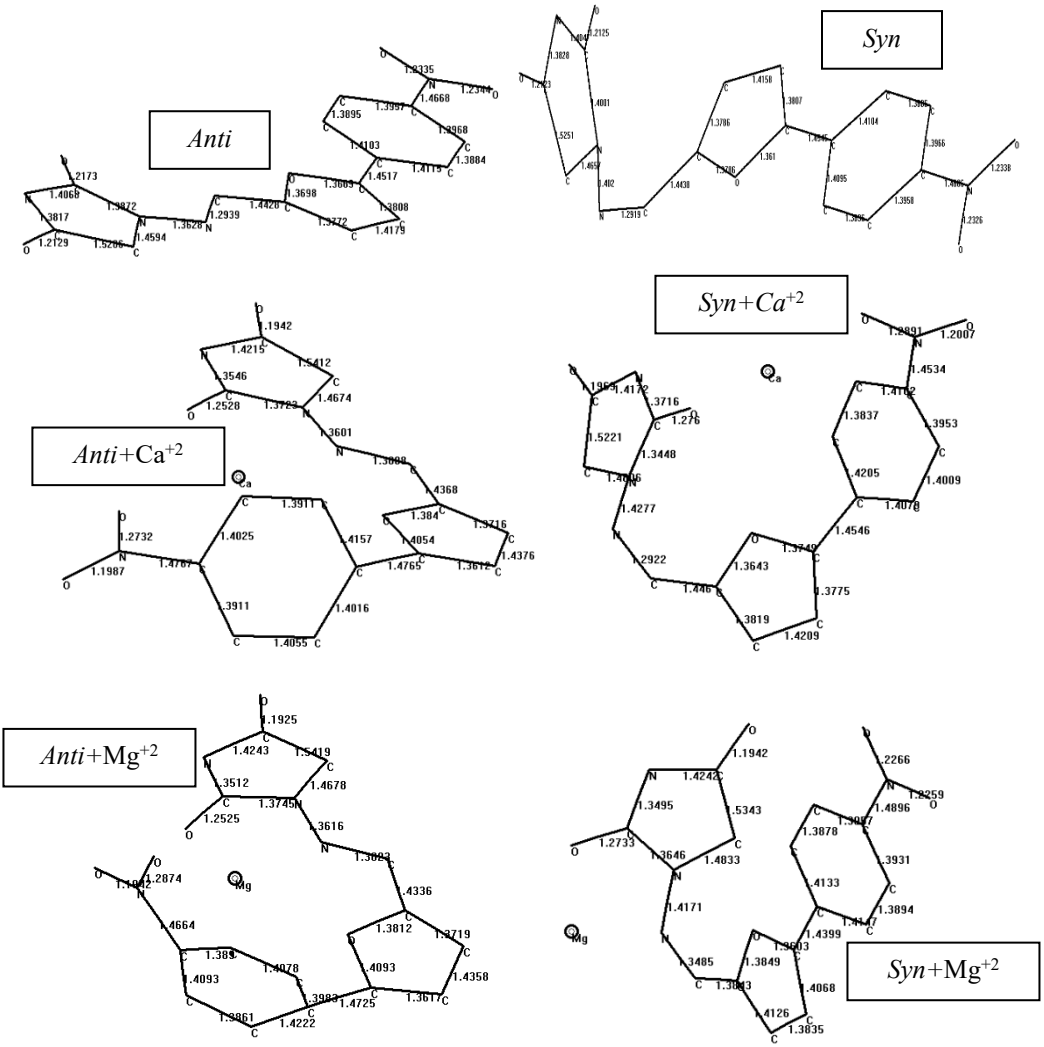

Figure 12. Calculated bond lengths of dantrolene and composite systems considered (Hydrogens omitted).

Table 8 shows the ESP charges on the Ca and Mg cations and the dipole moments of the composites considered. As seen in the table, either of the cations possesses a charge less than formal +2 indicating that certain interaction happens and some electron population has been transferred to the cation from the organic moiety. In that sense the cation in *anti*+Mg^{+2} composite seems that the cation in it had accepted more electron population than the cation in its *syn* analogue. A similar behavior exist in the case of calcium composites considered. The order of ionic charges is *Anti*+Mg^{+2} < *Anti*+Ca^{+2} < *Syn*+Ca^{+2} < *Syn*+Mg^{+2}. On the other hand, the order of dipole moments is *Anti*+$Ca^{+}2$ < *Anti*+Mg^{+2} < *Syn* < *Anti* < *Syn*+Ca^{+2} < *Syn*+Mg^{+2} which has to be dictated by the magnitudes and resultant directions of the bond dipoles (so the magnitudes of partial charges) in the presence or absence of the electrostatic field of the cations considered.

Table 8. The ESP charges on the Ca and Mg cations and the dipole moments of the composites considered.

	Anti	*Syn*	*Anti*+Ca^{+2}	*Syn*+Ca^{+2}	*Anti*+Mg^{+2}	*Syn*+Mg^{+2}
Charge on the inorganic cation	-	-	1.413	1.554	1.291	1.640
Dipole moment of the system	5.60	3.53	1.66	10.10	2.47	31.68

Dipole moments in debye units. Charges in esu units.

Figure 13 shows some of the calculated molecular orbital energy levels of the systems considered. The HOMO, LUMO energies and Δε values of dantrolene composites are shown in Table 9.

As seen in Figure 13 the perturbation caused by the presence of cations considerably lowers both the HOMO and LUMO energy levels compared to the unperturbed dantrolene isomers. Another point of worth mentioning is that the HOMO energy levels of the *anti* type composites are lower than the *syn* types but their LUMO energy levels are higher (see Table 9 also). As a result of these perturbations in the energies of the HOMO and LUMO levels, Δε values of the *syn* type composites are much lower than the respective values of the *anti* composites. Note that the reverse is true for the unperturbed *anti* and *syn* isomers (see Table 5).

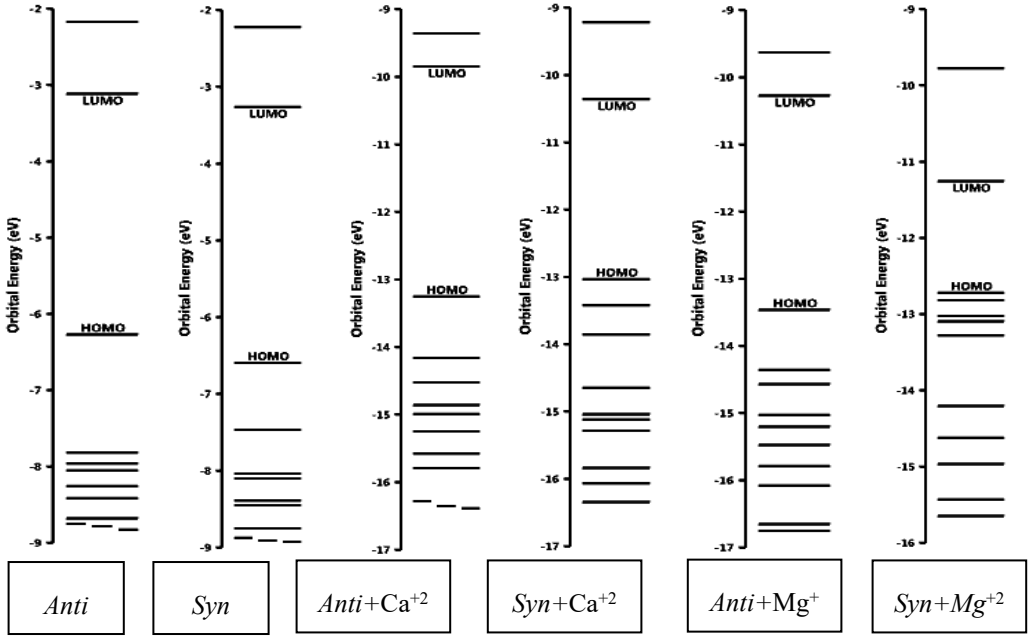

Figure 13. Some of the calculated molecular orbital energy levels of the systems considered.

Table 9. The HOMO, LUMO energies and Δε values of dantrolene composites.

Isomer	HOMO	LUMO	Δε
Anti+Ca^{+2}	-1278.55	-950.06	328.49
Syn+Ca^{+2}	-1257.44	-999.54	257.90
Anti+Mg^{+2}	-1298.81	-991.23	307.58
Syn+Mg^{+2}	-1227.22	-1085.90	141.32

Energies in kJ/mol.

Figure 14 shows the calculated (time dependent DFT type) UV-VIS spectra of the dantrolene isomers and the composites of dantrolene. The characteristic features of the spectra are that although unperturbed *anti* and *syn* dantrolenes absorb mainly in the UV but partly in the visible region, some bathochromic shifts occur in the cases of *Syn*+Ca^{+2}, *Anti*+Mg^{+2} and *Syn*+Mg^{+2}. The spectrum of the last one exhibits a considerable degree of bathochromic shift as expected from its Δε value (see Table 9).

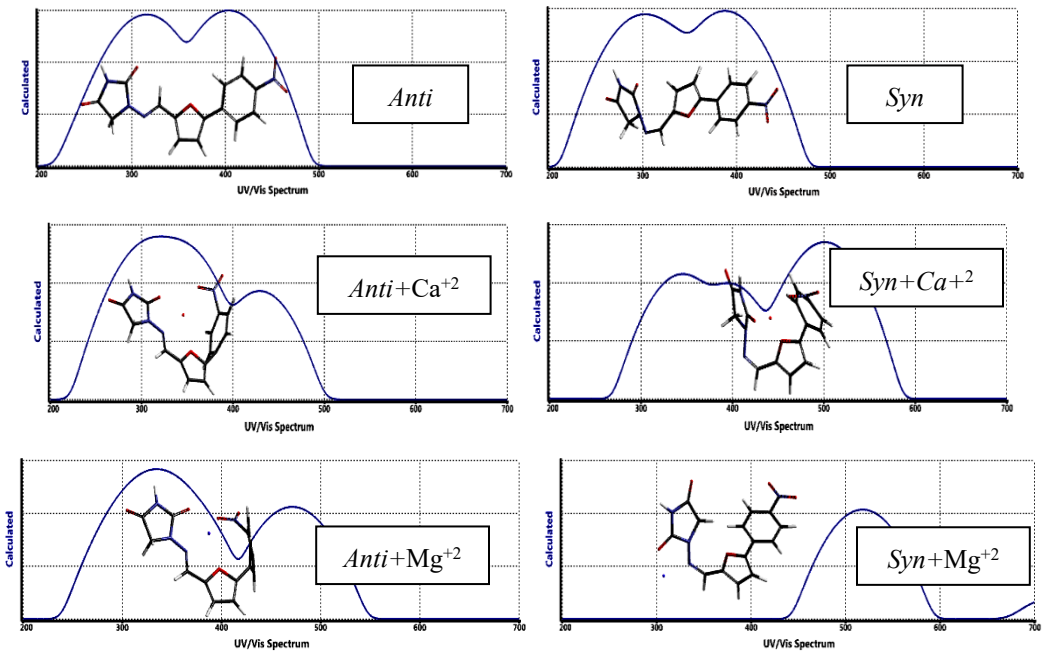

Figure 14. The calculated UV-VIS spectra of the composites of dantrolene.

4. Conclusion

The present DFT study at the level of B3LYP/6-31++G(d,p) indicates that in vacuum and aqueous conditions the dantrolene isomers have exothermic heat of formation values and favorable Gibbs free energy of formation values. The composites considered have also exothermic heat of formation values and their Gibbs free energy of formation values are favorable too. All the systems considered are electronically stable. In the case of composite from the *anti* isomer, Ca^{+2} or Mg^{+2} ion locates itself in the cavity/fjord formed in dantrolene moiety whereas in the *syn* composite, Mg^{+2} prefers a location outside the cavity/fjord of the molecule.

The perturbations caused by the cations affect many quantum chemical properties of the systems especially the molecular orbital energy levels. They lower both the HOMO and LUMO energy levels at unequal extends as compared to the unperturbed dantrolene isomers. The HOMO energy levels of the *anti* type composites are lower than the *syn* types but their LUMO energy levels are higher. The unperturbed *anti* and *syn* dantrolenes absorb mainly in the UV but partly in the visible region, however some bathochromic shifts occur in the cases of *Syn*+Ca^{+2}, *Anti*+Mg^{+2} and *Syn*+Mg^{+2}.

The present treatment at the molecular level reveals some similarities and differences not only between the geometrical isomers of dantrolene but also among the calcium and magnesium cation composites of them. Although, magnesium dependence of dantrolene is related to certain stage of its mechanism of action in biological systems, the factors considered in the present study, at least some of them, might be involving implicitly to dictate the magnesium dependence.

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