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Effect of perturbations on dantrolene - A DFT treatise

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Abstract

Dantrolene and an isomer of dantrolene which is obtained by a pair of centric perturbations (carbon to nitrogen replacement in N-N=CH moiety) 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.

Both of the isomeric structures of present interest have exothermic heat of formation values and favorable Gibbs free energy of formation values. They are electronically stable as well. The perturbation results in a more exothermic and more favorable isomer than dantrolene. It is also electronically more stable than the parent structure. Various quantum chemical data have been collected and discussed including IR and UV-VIS spectra.

1. Introduction

Dantrolene was originally synthesized by Snyder and his co-workers in 1967 [1]. It was found to have skeletal muscle relaxant properties after intravenous administration in animals.

Chemically, dantrolene is a hydantoin derivative (1-{[5-(p-nitro phenyl)furfurylidene] amino}hydantoin) and identification of it as skeletal muscle relaxant were also reported by Snyder [1]. Dantrolene subsequently received further evaluation [2,3]. Dantrolene was initially used as a muscle relaxant in the long term treatment of skeletal muscle spasticity [4].

Dantrolene is highly lipophilic and therefore poorly soluble in water. This property

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created problems for its clinical introduction until the 1980s. Its widespread applicability had to await a suitable intravenous preparation [5].

It has been found that dantrolene has a unique mechanism of spasmolytic action outside the central nervous system [6-7] and it was established that it relaxes skeletal muscles by acting directly on the muscle. Although, the site of action of dantrolene within the muscle has not been yet clearly understood, 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 fiber. It is known that dantrolene interferes with the release of calcium from the sarcoplasmic reticulum [7]. Note that the normal contractile response involves release of activator calcium from its stores in the sarcoplasmic reticulum of the sarcomere and the calcium triggers the tension-generating interaction of actin with myosin. Thus the action of dantrolene involves neither central synapses nor the neuromuscular junctions, it is intercellular at the effector organ [6].

Dantrolene is a muscle relaxer and for a long period of time it is used to treat muscle spasticity (stiffness and spasms) caused by conditions such as a spinal cord injury, stroke, cerebral palsy, or multiple sclerosis. Beside those cases, dantrolene is also used to treat or prevent muscle stiffness and spasms caused by malignant hyperthermia which is a rapid rise in body temperature and severe muscle contractions [8] that can occur during surgery with certain types of anesthesia [6,7]. It was reported by Grunau et al., that the use of dantrolene in the treatment of hyperpyrexia related to MDMA (3,4-methylenedioxy-methamphetamine) is controversial [9]. Hartmann et al., have reported the effects of dantrolene on arhythmogenic triggers and contractile function in human atrial fibrillation and cardiomyocytes [10]. The effect of dantrolene on intracellular calcium homeostasis on cell death, the pharmacologic and pharmaco-kinetic features of dantrolene have been investigated. The cytoprotective effects and potential application of dantrolene for the inhibition of cell damage in certain models of stress and disease also have been investigated [11]. It was reported that dantrolene affects carbonic anhydrase enzyme activities [12]. 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 [13,14]. Molecular aspects implicated in dantrolene selectivity with respect to ryanodine receptor isoforms has been investigated by Gaburjakova and Gaburjakova [15].

Although, dantrolene is a drug for the treatment of malignant hyperthermia, has

recently been evaluated for prospective use as a neuroprotective agent for the treatment of neurodegenerative syndromes including Alzheimer's disease [16].

Up to the best knowledge of the author, in the literature there existed no quantum chemical or density functional calculations directly involving dantrolene isomers until a recent publication by Türker [17]. Therefore, in the present study an isomer of dantrolene has been constructed via certain centric perturbations and subjected to density functional (DFT) treatment and the results obtained are compared with the respective data of dantrolene.

2. Method of Calculation

In the present study, all the initial structure optimizations of the isomers considered leading to energy minima have been achieved by using MM2 method which is followed by semi empirical PM3 self consistent fields molecular orbital method [18-20]. 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) [21,22]. 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 [23]. The correlation term of B3LYP consists of the Vosko, Wilk, Nusair (VWN3) local correlation functional [24] and Lee, Yang, Parr (LYP) correlation correction functional [25]. In the present study, the normal mode analysis for each structure yielded no imaginary frequencies for the $3N–6$ 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 [26].

3. Results and Discussion

The present study deals with dantrolene and an isomer of dantrolene obtained by a pair of centric perturbations, namely carbon to nitrogen replacement in N-N=CH moiety. More explicitly it involves conversion of >N-N=CH- moiety to >N-CH=N- moiety. Centric perturbations arise from electronegativity differences and/or bonding variations at

the location of the atom replacement(s). Presently, those isomers constructed are labeled as isomer-A (dantrolene, parent) and isomer-B (product, perturbed structure).

Figure 1 shows the optimized structures (top and side views) and the direction of the dipole moment vectors of the isomers considered. As seen in the figure, the hydantoin and p-nitrophenylfurfurylidene moieties are planar and thus both molecules are totally planar, too.

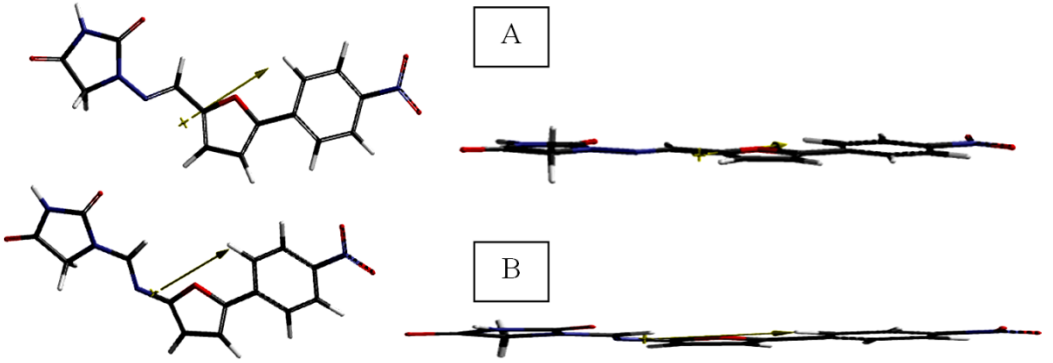


Figure 1. Optimized structures of the isomers considered (top and side views).

Table 1 displays the dipole moment components, their magnitudes and the magnitudes of total dipole moment values of the isomers considered. The bond dipoles constituting the dipole moment components yield the resultant dipole moment vectors such that the magnitudes of the resultants are B>A. Note that the bond dipoles are functions of atomic charges and the respective bond lengths. As seen in the table, the striking effect of perturbations is a directional change in the case of Z-component.

Table 1. The dipole moment components and the magnitudes of total dipole moment values of the isomers considered.

Isomers	X	Y	Z	Total
A	3.577208	4.304216	0.009288	5.596676
B	4.155026	4.007529	-2.199712	6.177642

In debye units.

Figure 2 shows the calculated bond lengths of optimized structures of the isomers considered. The data excerpted from the figure is that the bond lengths at the region of perturbations are quite comparable, except C-C bond of dantrolene which turns into N-C

bond in structure-B. The bond length variation is 1.44 Å to 1.36 Å. Also some rotations happen about the single bonds accompanying the perturbational changes to generate isomer-B.

Figure 3 displays the ESP charges on the atoms of dantrolene isomers considered. 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 [26]. The data in the figure reveal that the ESP charges considerably vary while the perturbation happens. It is quite expectable for the atom replacements, however the changes at the far distances are due to conjugation effects. In the case of dantrolene, N-N bond does not permit any electron delocalization between the two 5-membered ring systems and π-systems therein, so they are isolated in terms of the classical approach.

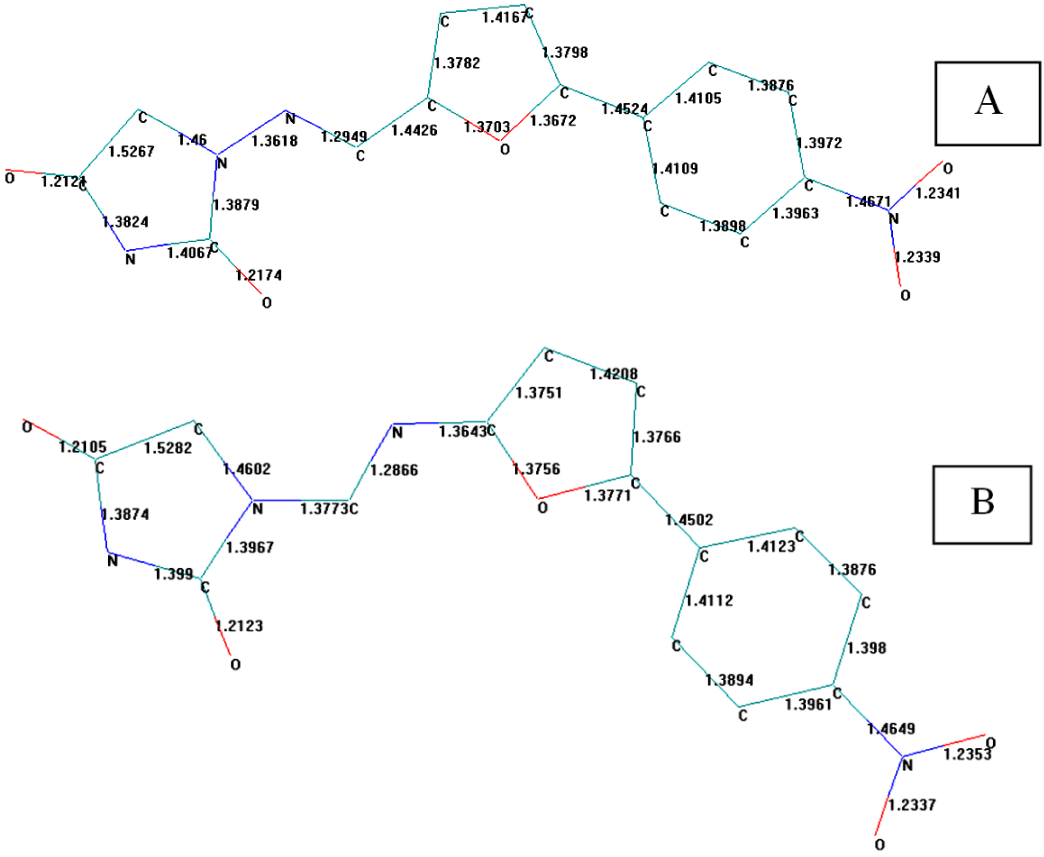


Figure 2. The calculated bond lengths (Å) of optimized structures of the isomers considered (hydrogens omitted).

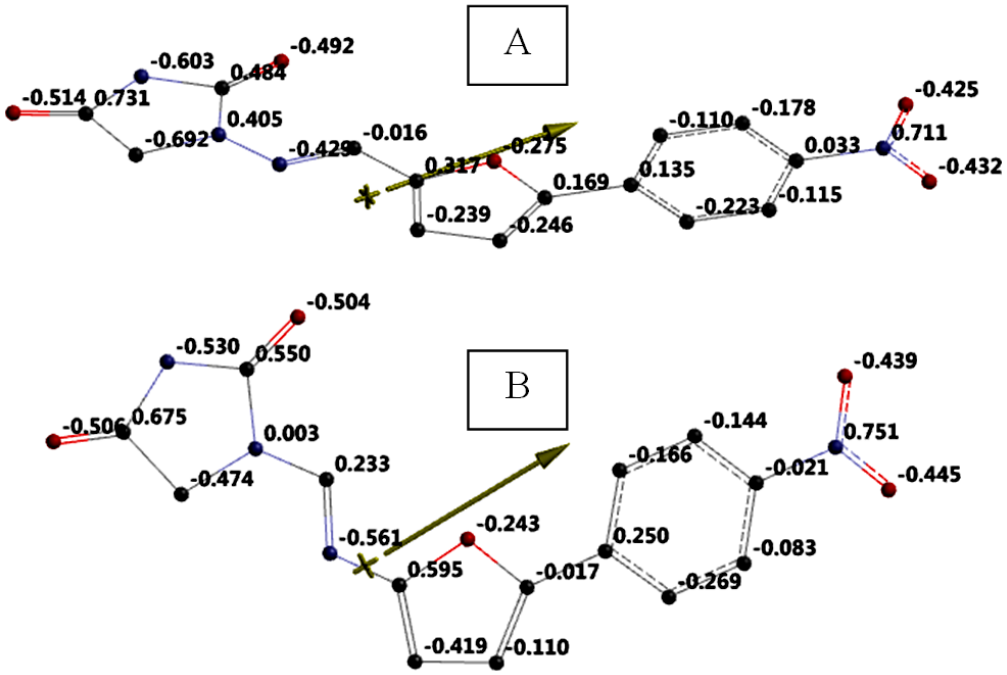
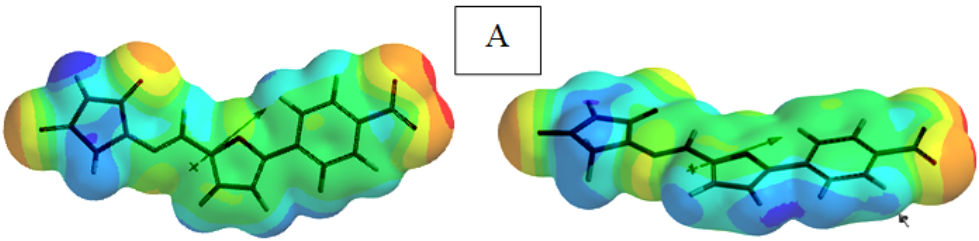


Figure 3. The ESP charges on the atoms of dantrolene isomers considered.

Figure 4 stands for the electrostatic potential maps of dantrolene isomers considered (top and side views). It is noteworthy that an electrostatic potential map is a graph that shows the value of electrostatic potential on an electron density isosurface.

Figure 5 shows the calculated IR spectra of the isomers considered. The N-H stretching in both of the isomers A and B happens at 3635 cm^{-1} and 3640 cm^{-1}, respectively. The C=O stretchings occur at 1850-1800 cm^{-1}. The C=N stretching of dantrolene occurs at 1648 cm^{-1} coupled with some bending vibrations of aromatic moiety. In isomer-B it happens at 1689 cm^{-1}. Note that stretching frequencies are some function of bond constant and the reduced mass [27].



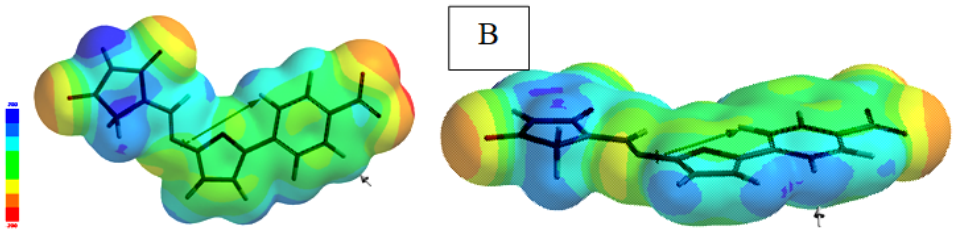


Figure 4. The electrostatic potential maps of dantrolene isomers considered (top and side views).

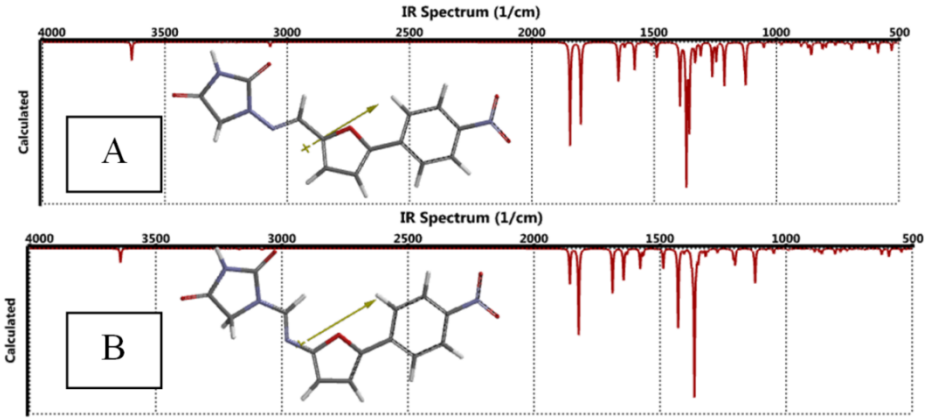


Figure 5. Calculated IR spectra of the isomers considered.

Table 2 shows some thermo chemical properties of the isomeric species considered. Both of the isomers have exothermic heat of formations (Hº) and favorable free energy of formation (Gº) values at the standard states. However, isomer-B is more exothermic and more favorable than isomer-A.

Table 2. Some thermo chemical properties of the isomers considered.

Isomers	Hº	Sº (J/molº)	Gº	Cv (J/molº)
A	-2978238.384	520.23	-2978393.500	221.28
B	-2978337.786	516.89	-2978491.904	221.22

Energies in kJ/mol.

Some energies of the isomeric species considered are tabulated in Table 3 where E, ZPE and E_C stand for the total electronic energy, zero point vibrational energy and the corrected total electronic energy, respectively. Whereas E_{aq} and E_{Sol} are aqueous energy

and solvation energy, respectively. As seen in the table, both of the isomers considered are electronically stable and the stability order (in vacuum) is that the isomer-B is more stable than isomer-A. The electronic stability order of the isomers is the same as their order of G^o values. Note that in isomer-A, at the region of perturbation, there exist two nitrogen atoms side by side, and beside some other factors, nitrogen-nitrogen lone-pair repulsions (α-effect [28]) causes increase of the energy.

Table 3. Some energies of the isomers considered.

Isomers	E	ZPE	E_C	E_{aq}	E_{Sol}
A	-2978916.19	617.48	-2978298.71	-2978916.19	-44.595
B	-2978972.90	619.68	-2978353.22	-2978972.90	-39.632

Energies in kJ/mol. Solvation Energy by SM5.4/A model.

Table 4 displays some calculated properties of these isomeric structures considered. In the table 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. The polarizability is defined according to the multivariable formula which is a function of Van der Waals volume and hardness [26]. Hardness is defined as,

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

Table 4. Some properties of the isomers considered.

Isomers	Area (Å²)	Volume (Å³)	PSA (Å²)	Ovality	Log P	Polarizability
A	311.29	283.36	96.194	1.49	-0.54	63.61
B	312.02	283.73	93.703	1.49	0.42	63.66

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

As seen in the table, most of the calculated properties of the isomers considered are comparable with each other except PSA values and the log P values. Note that isomer-A has a negative log P value in contrast to isomer-B. It is worth mentioning that a negative value for log P means the compound has a higher affinity for the aqueous phase (it is more hydrophilic); when log P = 0 the compound is equally partitioned between the lipid and aqueous phases; a positive value for log P denotes a higher concentration in the lipid phase (i.e., the compound is more lipophilic). Thus, the single centric perturbation applied on dantrolene should completely change its partitioning character and isomer-B becomes more likely to be lipophilic. Note that dantrolene itself has been reported as

lipophilic compound [5] and in practice its salts are used. Therefore, in the light of log P results isomer-B is expected to be more lipophilic than dantrolene.

The chemical function descriptors (CFD) of the isomers are shown in Figure 6 where HBA and HBD stand for hydrogen bond acceptor and donor, respectively. Note that CFDs are attributes given to a molecule in order to characterize or anticipate its chemical behavior.

Both of the isomers possess the same HBD and HBA counts, namely 1 and 9, respectively. The MW is 314.257 amu. So both of them fulfill the criteria of Lipinsky rule [29-31] and isomer-B, like dantrolene should be in general an orally active drug. Note that the rule of 5 (Lipinsky rule) states that poor absorption is more likely to occur when there are more than (i) 5 hydrogen-bond donors, (ii) 10 hydrogen-bond acceptors, (iii) a molecular weight greater than 500, and (iv) a calculated Log P greater than 5.

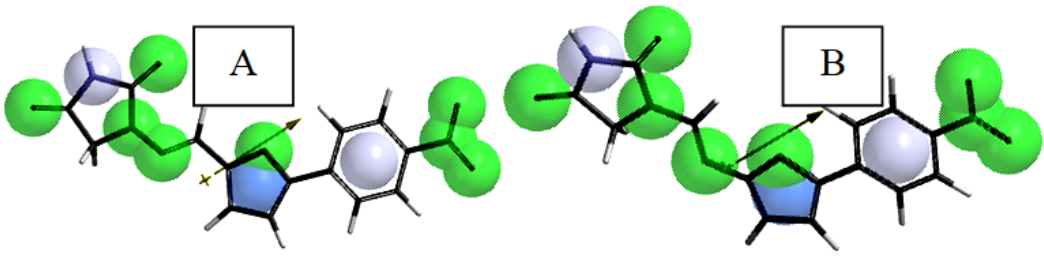


Figure 6. The chemical function descriptors (CFD) of the isomers (Green: HBA; Purplish: HBA, HBD and +Ionizable; Pale grey: Hydrophobe, Aromatic; Bluish: Hydrophobe).

Figure 7 displays some of the molecular orbital energy levels of the isomers considered. The HOMO, LUMO energies and Δε values of the isomers considered are shown in Table 5. Evaluation of the data present in the Figure and Table 5 reveals that these two isomers in terms of molecular orbital energies do not differ much from each other.

Figure 8 shows the calculated UV-VIS spectra (time-dependent DFT, TDDFT) of the isomers considered. There, the effect of the perturbation is apparent. The only difference is presence of a shoulder in the case of isomer-B. Some shift of λ_{max} values also accompany the perturbation such that peaks of isomer-A at 316.40 nm and 403.72 nm are replaced by peaks at 284.22 nm (shoulder), 322.72 nm and 409.92 nm in the case of isomer-B.

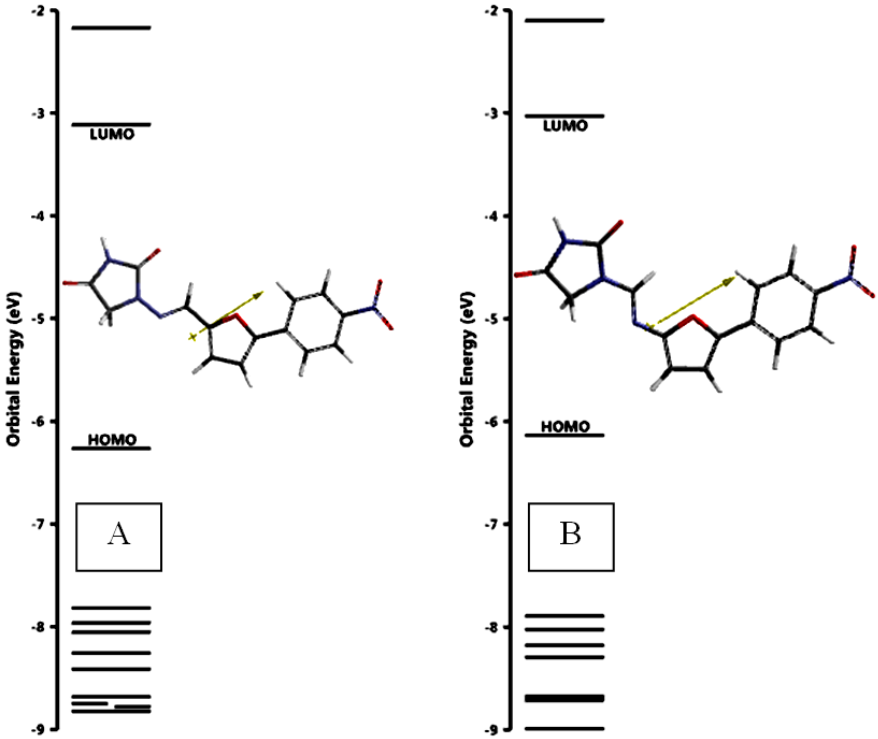


Figure 7. Some of the molecular orbital energy levels of the isomers considered.

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

Isomers	HOMO	LUMO	Δε
A	-604.53	-300.45	304.08
B	-592.01	-292.46	299.55

Energies in kJ/mol.

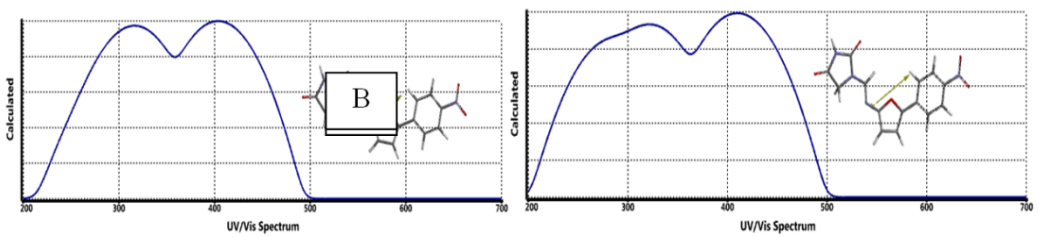


Figure 8. Calculated UV-VIS spectra of the isomers considered.

Figure 9 shows the local ionization potential maps of the isomeric 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. Note that a local ionization potential map is a graph of the value of the local ionization potential on an isodensity surface corresponding to a van der Waals surface.

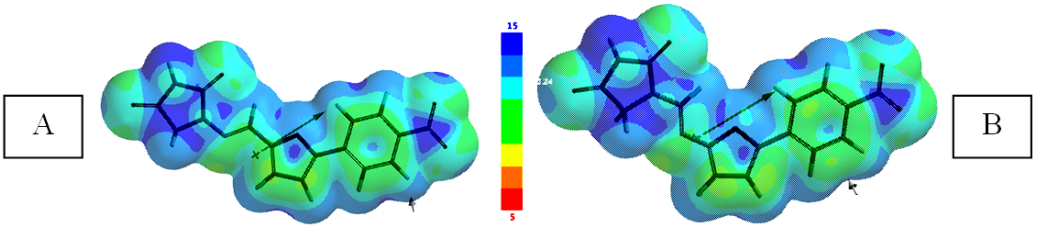


Figure 9. The local ionization potential maps of the isomers considered.

Figure 10 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.

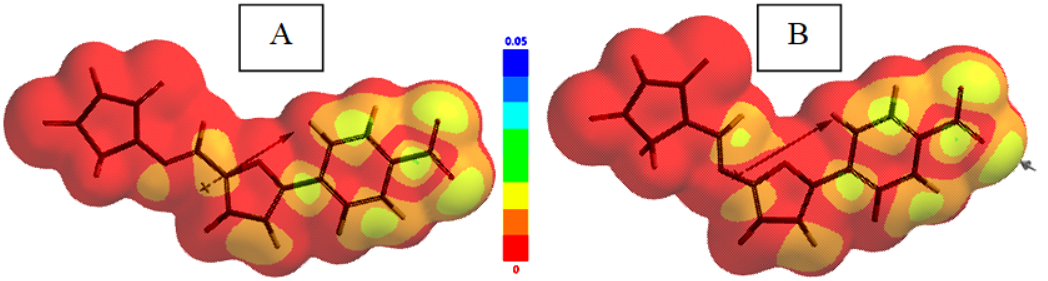


Figure 10. The LUMO maps of the isomers considered.

4. Conclusion

In the present computational study, within the restrictions of DFT study at the level of B3LYP/6-31++G(d,p), the perturbational effects arising from doubly bound nitrogen to carbon and doubly bound carbon to nitrogen replacements at N-N=CH moiety of dantrolene have been considered.

The results indicate that in the vacuum conditions, both of the isomers, are

characterized with exothermic heat of formation and favorable Gibbs free energy of formation values and they are electronically stable.

Evaluation of the data harvested has revealed that the perturbed structure does not have any striking differences compared to dantrolene. Both of the isomers fulfill the required criteria of Lipinsky rules for being an orally active drug. Hence, the perturbed isomer is worth trying for biological tests. Medicinally it might exhibit dantrolene-like behavior.

References

[1] Snyder, H.R., Davis, C.S., Bicker ton, R.K., & Holliday, R.P. (1967). 1-[5-Arylfurfurylidene)amino]hydantoins. A new class of muscle relaxants. *J. Med. Chem*., *10*, 807-810. https://doi.org/10.1021/jm00317a011

[2] Chyatte, S.B., Birdsong, J.H., & Bergman, B.A. (1971). The effects of dantrolene sodium on spasticity and motor performance in hemiplegia. *Southern Med. J*., *64*(2), 180-185. https://doi.org/10.1097/00007611-197102000-00011

[3] Chyatte, S.B., & Birdsong, J.H. (1971). The use of dantrolene sodium in disorders of the central nervous system. *South. Med. J., 64*(7), 830-834. PMID: 4933014. https://doi.org/10.1097/00007611-197107000-00011

[4] Dykes, M.H. (1975). Evaluation of a muscle relaxant: dantrolene sodium (Dantrium). *Journal of the American Medical Association, 231*, 862-4. https://doi.org/10.1001/jama.1975.03240200058032

[5] Krause, T., Gerbershagen, M.U., Fiege, M., Weißhorn, R., & Wappler, F. (2004). Dantrolene – A review of its pharmacology, therapeutic use and new developments. *Anaesthesia, 59*, 364-373. https://doi.org/10.1111/j.1365-2044.2004.03658.x

[6] Miller, R.D. (1984). Skeletal muscle relaxants. In B.G. Katzung (Ed.), *Basic and clinical pharmacology* (pp. 268-275). Los Altos, California: Lange Medical Pub.

[7] Britt, B.A. (1984). Dantrolene. *Can. Anaesth. Soc. J.*, *31*, 61-75. https://doi.org/10.1007/BF03011484

[8] Kolb, M.E., Horne, M.L., & Martz, R. (1982). Dantrolene in human malignant hyperthermia. *Anesthesiology*, *56*(4), 254-262. PMID: 7039419. https://doi.org/10.1097/00000542-198204000-00005

[9] Grunau, B., Wiens, M., & Brubacher, J. (2010). Dantrolene in the treatment of MDMA related hyperpyrexia: A systematic review. *Canadian Journal of Emergency Medicine*, *12*(5), 435-442. https://doi.org/10.1017/S1481803500012598

[10] Hartmann, N., Pabel, S., Herting, J., Schatter, F., Renner, A., Gummert, J., Schotola, H., Danner, B.C., Maier, L.S., Frey, N., Hasenfuss, G., Fischer, T.H., & Sossalla, S. (2017). Antiarrhythmic effects of dantrolene in human diseased cardiomyocytes. *Heart Rhythm*, *14*(3), 412-419. https://doi.org/10.1016/j.hrthm.2016.09.014

[11] Inan, S., & Wei, H. (2010). The cytoprotective effects of dantrolene: a ryanodine receptor antagonist. *Anesth. Analg*., *111*(6), 1400-1410. https://doi.org/10.1213/ANE.0b013e3181f7181c

[12] Gülçin, İ., Beydemir, Ş., & Büyükokuroğlu, M.E. (2004). *In vitro* and *in vivo* effects of dantrolene on carbonic anhydrase enzyme activities. *Biological and Pharmaceutical Bulletin, 27*(5), 613-616. https://doi.org/10.1248/bpb.27.613

[13] Choi, R.H., Koenig, X., & Launikonis, B.S. (2017). Dantrolene requires Mg2+ to arrest malignant hyperthermia. *Proc. Natl. Acad. Sci. USA*. *114*(18), 4811-4815. https://doi.org/10.1073/pnas.1619835114

[14] Cannon, S.C. (2017). Mind the magnesium, in dantrolene suppression of malignant hyperthermia. *Biological Sciences*, *114*(18), 4576-4578. https://doi.org/10.1073/pnas.1704103114

[15] Gaburjakova, J., & Gaburjakova, M. (2023). Molecular aspects implicated in dantrolene selectivity with respect to ryanodine receptor isoforms. *Mol. Sci., 24*, 5409-22. https://doi.org/10.3390/ijms24065409

[16] Bolognino, I ., Giangregorio, N., Tonazzi, A., Martínez, A.L., Altomare, C.D., Loza, M.I., Sablone, S., Cellamare, S., & Catto, M. (2021). Synthesis and biological evaluation of dantrolene-like hydrazide and hydrazone analogues as multitarget agents for neurodegenerative diseases. *Chem Med Chem.*, *16* (18), 2807-2816. https://doi.org/10.1002/cmdc.202100209

[17] Türker, L. (2024). Geometrical isomers of dantrolene and their interactions with calcium and magnesium cations. *Earthline Journal of Chemical Sciences 11*(1), 1-18. https://doi.org/10.34198/ejcs.11124.001018

[18] Stewart, J.J.P. (1989). Optimization of parameters for semi empirical methods I. *J. Comput. Chem*., *10*, 209-220. https://doi.org/10.1002/jcc.540100208

[19] Stewart, J.J.P. (1989). Optimization of parameters for semi empirical methods II. *J. Comput. Chem*., *10*, 221-264. https://doi.org/10.1002/jcc.540100209

[20] Leach, A.R. (1997). *Molecular modeling*. Essex: Longman.

[21] Kohn, W., & Sham, L.J. (1965). Self-consistent equations including exchange and correlation effects. *Phys. Rev*., *140*, 1133-1138. https://doi.org/10.1103/PhysRev.140.A1133

[22] Parr, R.G., & Yang, W. (1989). *Density functional theory of atoms and molecules*. London: Oxford University Press.

[23] Becke, A.D. (1988). Density-functional exchange-energy approximation with correct asymptotic behavior. *Phys. Rev. A*, *38*, 3098-3100. https://doi.org/10.1103/PhysRevA.38.3098

[24] Vosko, S.H., Wilk, L., & Nusair, M. (1980). Accurate spin-dependent electron liquid correlation energies for local spin density calculations: a critical analysis. *Can. J. Phys.*, *58*, 1200-1211. https://doi.org/10.1139/p80-159

[25] Lee, C., Yang, W., & Parr, R.G. (1988). Development of the Colle-Salvetti correlation energy formula into a functional of the electron density. *Phys. Rev. B*, *37*, 785-789. https://doi.org/10.1103/PhysRevB.37.785

[26] SPARTAN 06 (2006). Wavefunction Inc. Irvine CA, USA.

[27] Ferguson, L.N. (1969). *The modern structural theory of organic chemistry*. New Delhi: Prentice-Hall.

[28] Fleming, I. (1976). *Frontier orbitals and organic reactions*. London: Wiley.

[29] Lipinski, C.A., Lombardo, F., Dominy, B.W, & Feeney, P.J. (2012). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Delivery Rev., 64*, 4-17. https://doi.org/10.1016/j.addr.2012.09.019

[30] Lipinski, C.A. (2004). Lead- and drug-like compounds: the rule-of-five revolution. *Drug Discovery Today, 1*, 337-341. https://doi.org/10.1016/j.ddtec.2004.11.007

[31] Lipinski, C.A. (2016). Rule of five in 2015 and beyond: Target and ligand structural limitations, ligand chemistry structure and drug discovery project decisions. *Advanced Drug Delivery Reviews, 101*, 34-41. https://doi.org/10.1016/j.addr.2016.04.029