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Conformational Studies of *Ortho*-and *Meta*- Isomers and Methyl, Dimethyl, and Chloro *Ortho*-Substituted Analogues of Dantrolene Using *Ab Initio* SCF-MO Procedures

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Abstract

The conformation of the nitro group of nitroaromatic compounds relative to the aromatic ring system is suggested to affect their metabolic activation and mutagenicity. We have recently showed the nitrophenylfuran skeletal muscle relaxant, dantrolene, to be a potent mutagen in *Salmonella*. Synthesis of *ortho*-substituted analogues of dantrolene was achieved in an effort to alter the conformation of the nitro group in a manner that will decrease the mutagenicity. Using *ab initio* techniques we investigated the minimum energy conformation of the nitro group of dantrolene (*p*-nitro) and its *o*-and *m*-nitro isomers as well as the nitro group conformation of dantrolene's *ortho*- mono- and di- substituted analogues. The most stable conformer for each isomer and analogue was found by optimizing the bond lengths and bond angles for each molecule and rotating about bonds of interest using the **STO-3G** basis set in the Gaussian-92 program at the Hartree-Fock level.

Introduction

The skeletal muscle relaxant Dantrolene belongs to a group of molecules known as nitrophenylfurans and has been shown to be hepatotoxic (Utili et al., 1977). Fifer et al. (1995) have synthesized and investigated the mutagenicities of a series of dantrolene analogues in an effort to develop a less mutagenic substitute for the drug. It has been theorized that the mutagenic activation of nitroaronmatic compounds via enzymatic nitroreduction can either be enhanced or inhibited by the orientation of the nitro group (parallel or perpendicular) relative to the aromatic ring. Work being done on nitropolycyclic aromatic hydrocarbons points to parallel (or co-planar) orientation of the nitro group relative to the aromatic ring as more responsible for the mutagenic behavior of compounds than the perpendicular (90 degrees offset from co-planar) orientation of the nitro group (Jung et al., 1991).

Our work with dantrolene and its analogues (Fig. 1 and 2) involves calculating the theoretically most stable (lowest energy) conformers of the drug and its derivatives and investigating the lowest energy conformation of the nitro group of each with respect to the aromatic ring. The low-energy conformers determined by our study may give some insight to the active conformation of the drug inside the body and help guide researchers to a less mutagenic substitute. For our conformational profile, we utilized the **Gaussian-92** package (Frish et al., 1992), a program that uses self-consistent field molecular orbital (SCF-MO) *ab initio* methods to generate useful information about the molecules under study, including total energy.

More specifically, we used the **STO-3G** basis set in the **Gaussian-92** program to determine the optimal bond lengths and angles for the molecules. The **STO-3G** basis set of functions was also used to determine the theoretically most stable, or lowest energy, conformer by altering specific torsion angles within the molecule.

The results of this study in conjunction with the mutagenicities of dantrolene and its derivatives provide more evidence to support the theory relating nitro group orientation in each compound and its subsequent mutagenicity. This research may aid in the development of an effective less toxic alternative for dantrolene.

Methods and Materials

Ab initio calculations on the molecules were performed using the Gaussian-92 program which was run on the IBM supercomputer cluster at Cornell University (Ithaca, NY) and several Silicon Graphics INDY 500 computers at UALR. Optimizations and rotations were first done at the **STO-3G** level of approximation, due to the size of the molecules under study (33 atoms or more). Larger basis sets of functions, such as **3-21G** and **6-31G**, which could render somewhat more accurate results will be used in future more rigorous conformational studies.

The Z-matrix (Hehre et al., 1986) was composed for

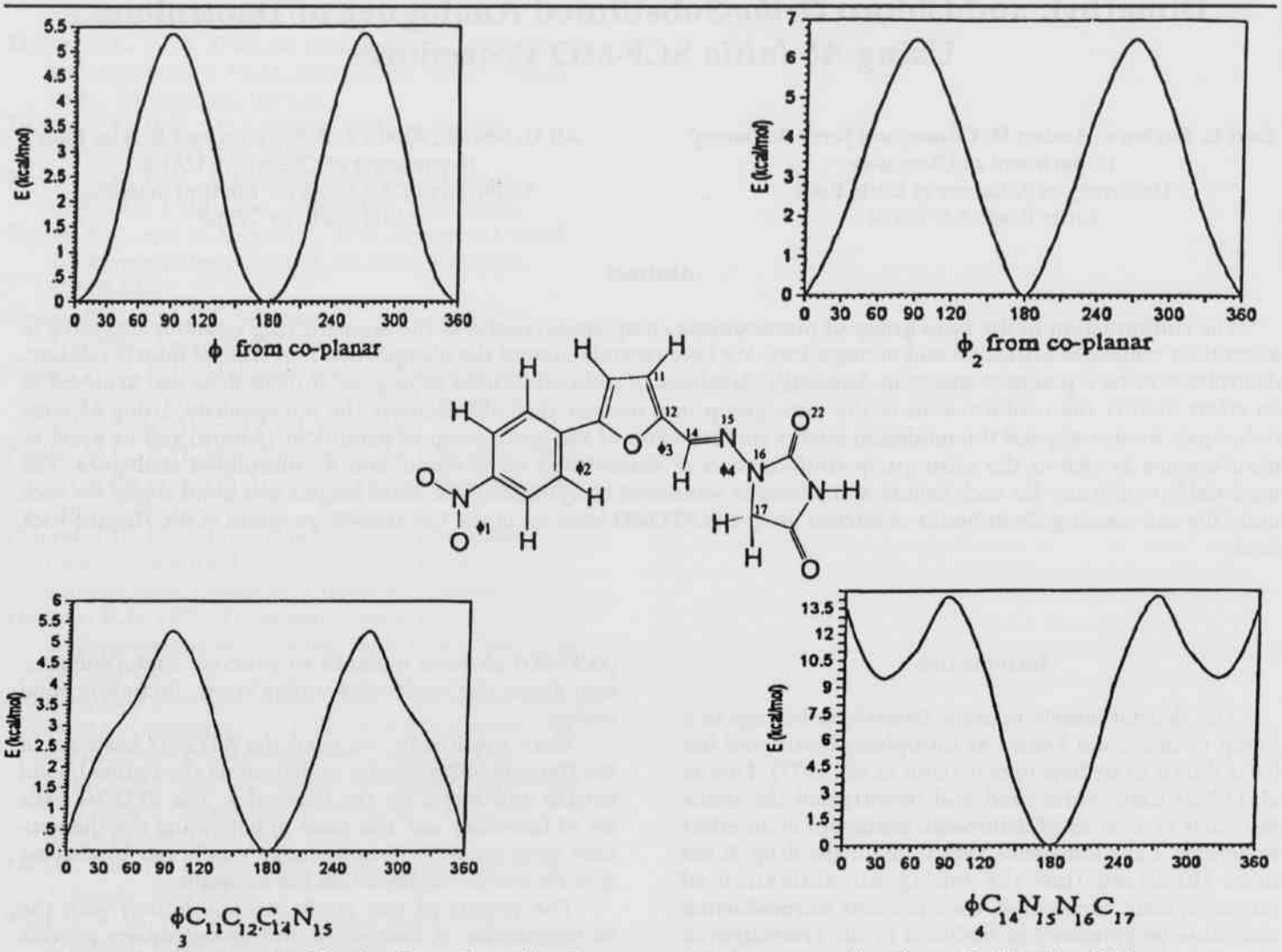


Fig. 1. Rotational energy profiles for dantrolene, showing energy barriers to rotation about ϕ1, ϕ2, ϕ3 and ϕ4.

each molecule of the study, in which the molecular geometry and connectivity for each was established with bond lengths, interatomic angles, and dihedral (or torsional) angles. The constructed Z-matrices were checked for flaws by using ChemDraft II software, which gives a visual image of the molecule defined by the matrix. These bond lengths and angles were then optimized by the program to provide a reliable starting geometry for rotations about bonds of interest.

The segments of dantrolene that were studied for rotational stability are labeled in Fig. 1. After the optimized geometries were found for each molecule, incremental 30 degree rotations about certain bonds were performed by changing pertinent dihedral angles within the molecule's Z-matrix. By monitoring the Roothan-Hartree-Fock energy calculated for each rotation, a lowest-energy conformation for the entire molecule could finally be determined.

The resulting lowest-energy conformer of dantrolene was used as a template for the starting conformation of its isomers and analogues. Some re-optimizations were necessary after the inclusion of new atoms and groups in the Z-matrix of the parent molecule in order to create a reliable starting computational matrix for the isomers and analogues to be studied. For each compound, only the nitro group was analyzed for rotational energies. Initial conformations of each of the studied molecules, along with the bonds about which rotational studies were performed, are listed in Figs. 3a - 3e.

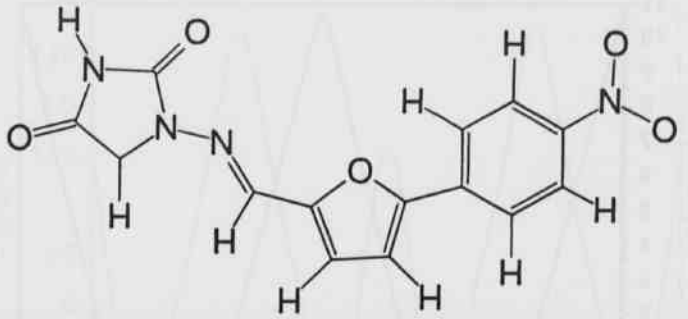
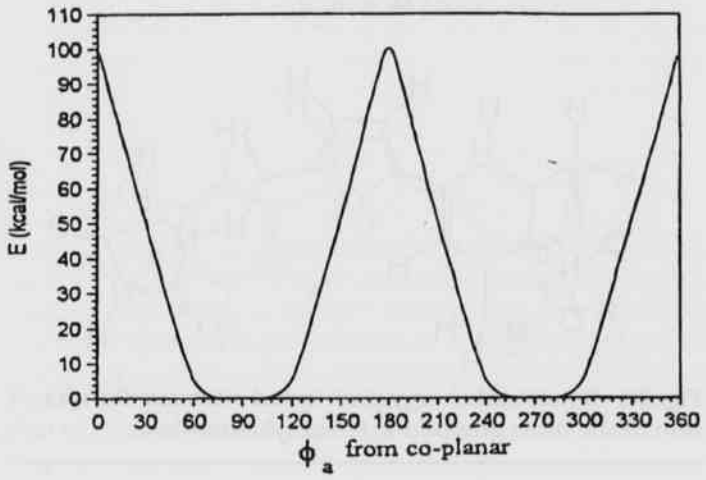


Fig. 2. The STO-3G calculated lowest energy conformer of dantrolene, with the nitro group co-planar to the rest of the molecule.



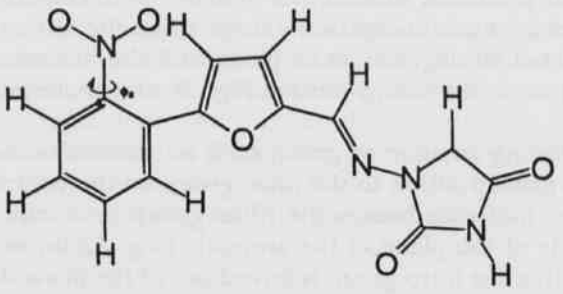
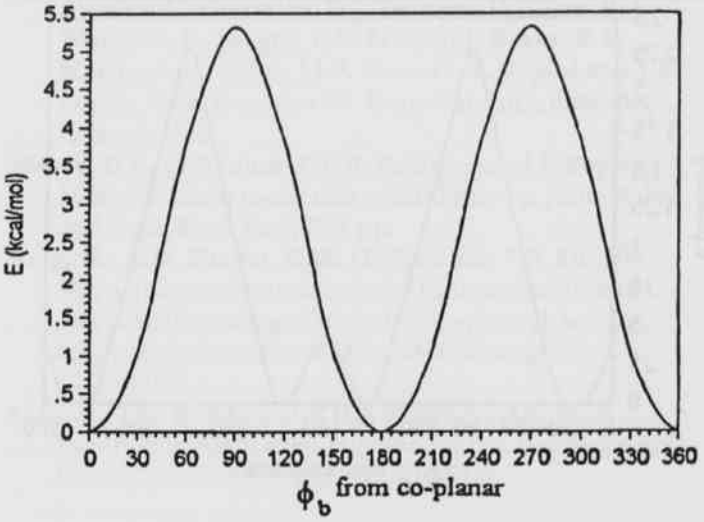


Fig. 3a.. Rotational energy profile and structure for rotation of the nitro group in 2-nitrodantrolene.



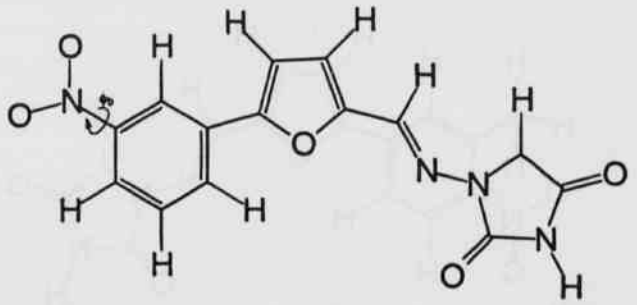


Fig. 3b. Rotational energy profile and structure for rotation of the nitro group in 3-nitrodantrolene.

Results and Discussion

For the parent dantrolene molecule, the plots of energy of the conformation vs. the dihedral angle between critical atoms, ϕ, is shown in Fig. 1. The plummeting energy at certain ϕ values indicates conformational stability at that dihedral angle. After analyzing the results of each rotation, a new, more stable conformer for dantrolene was found to be the one picture in Fig. 2. The nitro group orientation in dantrolene was found to be co-planar with the phenyl group, indicating that an entirely flat structure for dantrolene is energetically favored by the **STO-3G** basis set. A rotational barrier of slightly over 5 kcal/mol insures this conformation. Another interesting facet of the rotational profile of dantrolene is the strong (13.5 kcal/mol) tendency for the imidazolidine-2,4-dione (or hydantoin) ring to be rotated 180 degrees from its initial position. This may be a result of repulsion between the lone pair electrons of nitrogen #15 and oxygen #22 (see Fig. 1).

The calculated lowest-energy nitro group conformation for the 2-nitro and 3-nitro isomers of dantrolene can

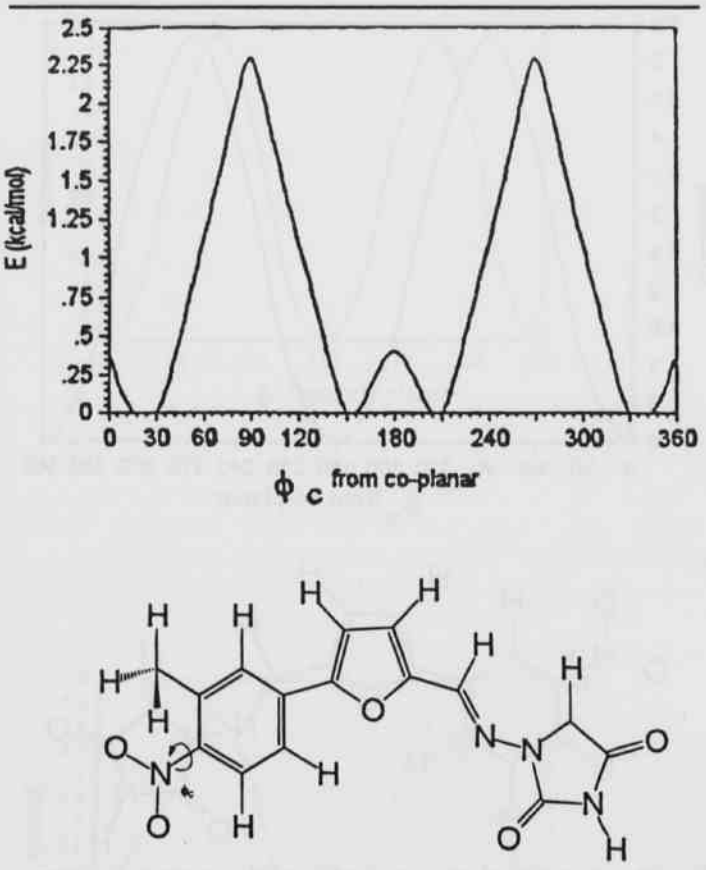


Fig. 3c. Rotational energy profile and structure for rotation of the nitro group in 3-methyldantrolene.

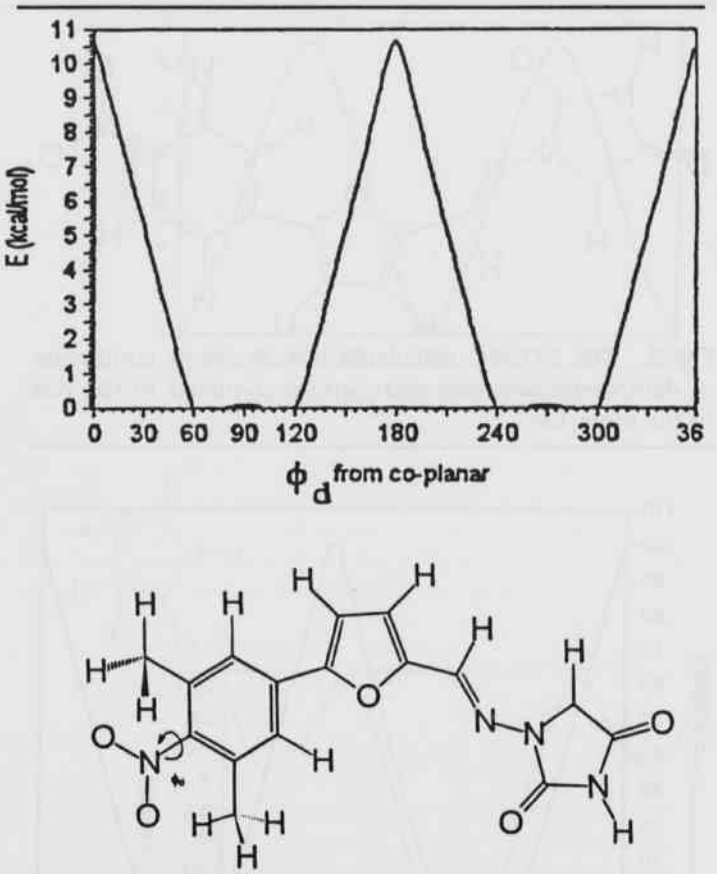


Fig. 3d. Rotational energy profile and structure for rotation of the nitro group in 3, 5-methyl dantrolene.

be surmised from the energy vs. ϕ plots in Figs 3a and 3b, respectively. The 2-nitro (*ortho*-nitro) isomer of dantrolene was found to be more stable with the nitro group perpendicular to the phenyl ring of the molecule, with a rotational energy barrier of 100 kcal/mol. This effect is probably due to steric crowding between the nitro group and the furan ring, which pushes the nitro group into a perpendicular position with respect to the rest of the molecule. The calculated stable conformation for 3-nitrodantrolene is shown in Fig. 3b.

The 3-nitro (*meta*-nitro) isomer of dantrolene was found to be most stable with the nitro group oriented parallel (co-planar) to the phenyl ring. Only a 5 kcal/mol energy barrier was found separating the co-planar and perpendicular orientations in 3-nitrodantrolene. Placement of the nitro group one carbon closer to the furan ring of dantrolene does not sterically crowd the structure enough to force a perpendicular conformation for the nitro group.

Interestingly, in the most stable conformations of the dantrolene analogues, 3-methyldantrolene, 3,5-dimethyldantrolene, and 3-chlorodantrolene, the nitro group is not as dramatically positioned at either planar or perpendicular positions. Instead, the 3-methyl and 3-chloro analogues are more energetically stable when the nitro group is rotated 30 degrees out of plane with the benzene ring as shown in the energy plots in Figs. 3c and 3e, respectively.

Placing an atom or group such as chlorine or methyl in an *ortho*- position to the nitro group on the dantrolene parent molecule causes the nitro group to orient itself outside of the plane of the aromatic ring. Again we propose that the nitro group is forced out of the plane due to steric crowding.

The addition of two methyl groups to the molecule in both *ortho*- positions produces a lowest energy value when the nitro group is oriented 60 degrees relative to the plane of the phenyl ring as shown in the energy plot in Fig 3d.

Conclusions

Our study reveals the lowest energy STO-3G confor-

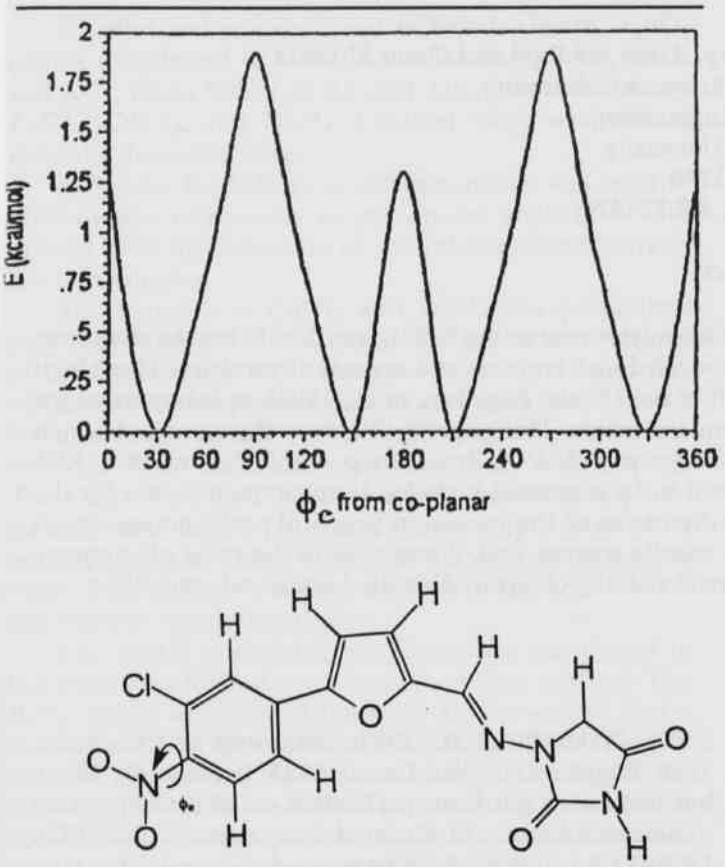


Fig. 3e. Rotational energy profile and structure for rotation of the nitro group in 3-chlorodantrolene.

mation for dantrolene and its derivatives. The nitro group in dantrolene was determined to be oriented co-planar to the phenyl ring, as was the nitro group in 3-nitrodantrolene. The nitro group in 2-nitrodantrolene was calculated to be prependicular to the phenyl ring. In 3-methyldantrolene and 3-chlorodantrolene, the nitro group was found to be 30 degrees from co-planar, and in 3,5-dimethyldantrolene it was found to be 60 degrees from co-planar (30 degrees from perpendicular).

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