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Ab Initio Investigation of Physicochemical, Thermodynamical and Spectroscopic Characteristics of Hydantoin Structures

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ABSTRACT*:* The derivatives of imidazolidine-2,4-dione (hydantoins) are promising candidates inthe new era of medicines on account of their wide spread use inthe treatment of high blood pressure, cancer pain and attentiondeficit hyperactivity disorder. All geometries of structures, charge distribution and important thermodynamical parameters were full optimized and obtained at the HF and DFT level of theory using the standard 3-21 and 6-31 basis set under Gaussian98 program. On the other side, inter molecular interaction in three position in dimers one to three by using these methods were investigated. On the basis ofthese calculations, a considerable model with noticing many electronic and energetic characteristics of these complexes dimer molecules of hydan to in were proposed**.**

KEYWORDS*:* Hydantion, Ab initio, Gaussian98, Entropy Energy, DFT Theory, Free Energy, HartreeFock.

I. INTRODUCTION

Since hydantoin or imidazolidine-2,4-dione was discovered by Bayer in 1861, a largeset of imidazolidine derivatives have been synthesizedshowing a wide range of biological activities like anticonvulsant, antischistosomal, tuberculostatic, etc.The first thioxo-hydantoin, the 2-thioxo-imidazolidin-4-one was prepared in 1890 by Klason [1-5].Hydantoins are biologically active molecules widely used in medicine as antiepileptic, antischistosomal, antiarythmic, antibacterial and tuberculostatic drugs [6-8]. It is also an effective medication for the treatment of metastatic prostate cancer. It is the parent compound of antiepileptic drug diphenylhydantoin[9].Hydantoin derivatives show biological activity against human parasites like trematodeos [10]. Besideits medical usage it is also used as herbicides and fungicides [11, 12]. In literature there are several studies investigating the crystal structure and hydrogen bondinginteraction of hydantoin [9, 10]. Also, experimental and theoretical vibrational analysis of hydantoinandits cobalt complexes have been reported in some studies [13–16]. Up to our knowledge there were no vibrational spectral study done by density functional computations. Also in the previous studies assignments ofthe fundamentals were based on isotopic frequencyshifts and earlier studies rather than TED calculations.Furthermore, there was no theoretical vibrational analysis on dimers of hydantoin.

Hydantoin, is of interest as the parent compound of theanti-epileptic drug diphenylhydantoin and as a supramolecularsynthon in its own right. Possessing equal numbers ofhydrogen-bond donor (two ring NH) groups and acceptor(two carbonyl O) atoms, it can form intricate networks, butwith a different presentation of these groups compared with the six-membered rings so often studied. Probably due to the difficulties with twinning described below, no structure ofhydantoin has appeared in the literature to date [18].

At present, electronic structure calculations play the role of the main predictive tool of chemistry and are rapidly becoming a feasible alternative to empirical methods in the discovery process. The resulting ability of modern chemists to generate increasingly large amounts of data calls for more attention to systematization of knowledge. In quantum chemistry, such systematization is facilitated by analysis of electronic wave functions. The above statement is from professor Cioslowskiabut the importance of the electronic wave function analysis. Modern approaches to analysis of electronic wave functions are the definitions of properties such as atomic charges, energies, valencies, bond orders,

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specialized orbitals, population analysis, frequencies and non- linear optic properties [19-22].Hydantoins have been found to have broad spectrum of activities in the field of medicine, industry and agriculture.

Until now, several research groups have documented the androgenic, antischistosomal and hypotensive actions of hydantoins[4–6].Some hydantoins have been used as effective drugs against parasitic disease such as schistosomiasiscaused by schistosomamansoni [2]. They are known as anticonvulsant,antimicrobial, anti-arrhythmic, anti-inflammatory andantitumor agents [1-5]. Hydantoins also possess tuberculostaticactivity [3] and cause hypnotic sedative effect in addition to antischistosomalaction. Some of its derivatives such as sodium benzylhydantoin have been reported to act as transporter for movingmolecules across cell membrane by coupling this process withenergetically favourable downhill movement of ions and protons [18].Guanidine and spiroiminodihydantoinsare known to mispair with adenine or guanine in consequence oftheir structural similarity to nitrogenous bases of DNA [4]. Thesefeatures of hydantoins can help in cancer control. Hydantoins like5-hydroxyhydantoin and 5-methyl-5-hydroxyhydantoin serveas blocking lesions for DNA polymerases[6]. Some hydantoinsare known to inhibit the P-glycoprotein efflux pump of mouseT-lymphoma cells, and act synergistically with anticancer drugdoxorubicin [5]. 5-(2-Phenyl-3_-indolal)-2-thiohydantoin haveshown inhibitory activity on several cancer lines organized into subpanels representing leukemia, melanoma, and cancer oflung, colon, kidney, ovary, breast, prostate and central nervoussystem by the National Cancer Institute anti-cancer drug screeningprogramme [6].Some hydantoins are known to interactwith DNA via intrinsic and extrinsic pathways; for example5-benzylidene-hydantoin is capable of either blocking EGFR tyrosinekinase activity or inducing genomic DNA damage. Researchstudy reveals that its derivatives might serve for the treatmentof lung cancer in patients irrepressible to classic tyrosine kinaseinhibitors [6].In agricultural field hydantoins have been reported as effectivepesticides and research is ongoing to improve their fungicidalaction [3-5]. Hydantoins have also registered their importanceas corrosion inhibitors. Dimethylol-5-methylhydantoin hasbeen tested to inhibit corrosion of carbon steel in raw waterby physisorption mode of adsorption [7]. Despite these broadrange applications, the understanding of the electrochemical oxidationmechanism of hydantoins is not clarified [23,24].

II. METHODS

All ab initio MO calculations were carried out using the GAUSSIAN 03 program package [20]. A lot of calculations have been performed on the cyclic hetroatomstructuresof hydantoinsand it has been cleared that the computational data are very sensitive to the level of employed theory. All structures of mono cycles and dimercomplexes were completely optimized at the level of HF/3-21 and B3LYP/6-31 using Gaussian 03 programs. In this study, vibrational frequencies of these compounds were also calculated by Hartree-Fock and Density Functional Theories at the same level. These harmonic frequencies could be used to characterize the stationary points of the potential energy surfaces as either minima or transition states [21].All calculations were carried out on a Pentium personal computer by means of GAUSSIAN03 program package. First, the structures compounds were drawn using Gauss View 03 [13]. To characterize the optimized geometries, the vibrational frequencies for all conformers have been calculated at B3LYP levels. The stationary structures, corresponding to the minimum of potential energy surface, were confirmed by ascertaining the fact that all ground states have only real frequencies.

III. RESULT AND DISCUSSION

Full geometry optimization was performed forboth monomer and dimmers of hydantoin usingtwo levels of theory: the HartreeFockTheory (HF)[20,21] and theDensity Function Theory (DFT) with the hybridfunctional B3LYP using in both case the6-31+G(d,p) basis set. The MP2 calculationswere performed in the frozen core approximation.Subsequently, the infrared frequencies (withoutany scale correction factor) and the infrared intensitieswerecalculated into the harmonic approximation.Also, from these vibrational calculationsthe zero point energies were evaluated for themonomer and for each H-complex.

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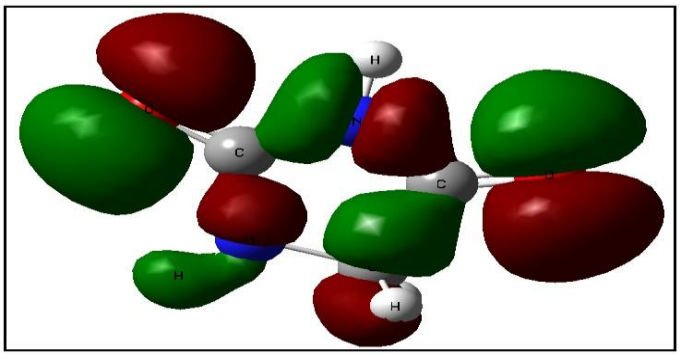

Figure-1. HOMOFrontier orbital of structure of Hydantoin in the gas phase

In this part, figures 1 and 2 related to HOMO and LUMO frontier orbitals of Hydantoin, indicates the situation of electroncloud concentration across the bondig atmosphere between the atoms by using HartreeFockmethod and level theorybasis set6-31+G(d,p) by Gaussian software.

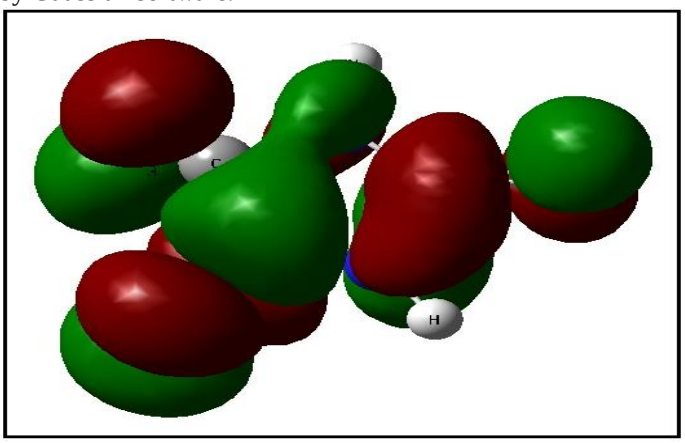

Figure-2. LUMOFrontier orbital of structure of Hydantoin in the gas phase

The structure of (imidazolidine-2,4-dione) hydantoin, C3H4-N2O2, has been studied from a twinned crystal. Ab initio molecular-orbital calculations yield more negative Lowdincharge on the former than the latter. Hydantoin molecules form two chains linked by N-H…O hydrogen bonds, from which inversion centres create a chain of rings.The two carbonyl bond lengths are nearly equal, even though one of them adjoins electron-donating NH groups to either side while the other is adjacent to only one.Many hydantoin derivatives carry polar substituents on the 5-position, which divert some or all of the hydrogen bonding away from the ring.

Table 1.Selected geometric parameters (A^0) in Hydantoin structure.

Bonding	Bonding Length (A^0)	Bonding	Angle (0)
C1-N1	1.38386	C1-N1-C3	113.21927
C1-N2	1.42519	C1-N2-C2	113.39013
C2-N2	1.39230	C2-C3-N1	102.42033
C2-C3	1.54231	C1-N1-O1	128.62366
C3-N1	1.46581	C2-N2-O2	127.29046
C1-O1	1.24237	C3-C2-O2	127.09936
C2-O2	1.24122		

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The results which have been noticed inTable-1 show bonding lengths and angles between atoms in Hydantoin rings. The most and least values in bonding lengths are related to (C3-N1) and (C2-O2) bonds respectively. On the other side, the angle of (C1-N1-O1) is 128.6 as the most value and (C2-C3-N1) is 102.4 as the least one.

Table 2.Hydrogen-bonding geometry (A0) in Dimer1-Hydantoin structure.

Dimer-1		**Dimer-2**		**Dimer-3**	
Hydrogen-Bonding	Bonding Length (A^0)	Bonding	Bonding Length (A^0)	Bonding	Bonding Length (A^0)
[1]6-O…[2]22-H	2.19355	[1]2O-H…[2]7-O	1.80663	[1]10-H…[2]17-O	2.17259
[1]11-H…[2]17-O	2.26000	[1]18-O…[2]11-H	2.33771	[1]6-O…[2]21-H	2.19546
[1]9-N…[2]22-H	3.49687	[1]19-N…[2]11-H	3.03087	[1]8-N…[2]21-H	4.26192

In the case of three states Dimer-1,Dimer-2 and Dimer-3, table-2 indicates inter molecular hydrogen bonding. In all of these structures N-H bond has the most value. This inter molecular (hydrogen bonding) considerably, could be efficient in the activities of hydantoin compound.

Table 3Thermodynamical values for the for the four hydantoin Structures studies in the gas phase.

Compound	**Thermal Free Energy (Hartree)**	**E (Thermal) KCal/Mol**	**CV Cal/MolKelvin**	**Entropy Cal/MolKelvin**	**Dipole Momentom (Debye)**
Hydantoin	-374.654564	53.997	20.582	75.562	3.1275
Dimer-1	-749.322236	110.093	44.863	112.251	2.0498
Dimer-2	-745.034033	118.119	41.867	110.117	4.6076
Dimer-3	-745.033675	118.069	42.024	109.885	1.7078

In this study, a substantial noticeable valuesof thermodynamical parameters including free energies, thermal capacity, entropy,dipole momentum of these four compounds hydantoin, Dimer 1 to 4 were calculated (see Tables 3).

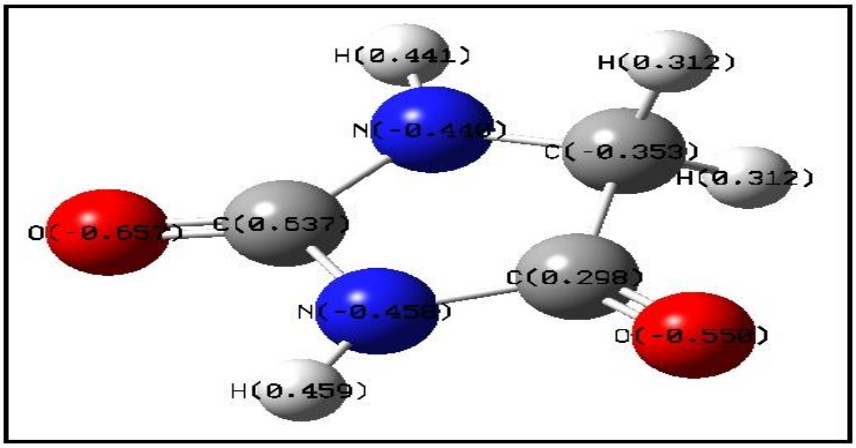

Figure-3. Structures and charge distribution of Hydantoin

Electron density as a noticable electronic parameter in these structures was investigated. As we see in figure-3 electronegative atoms including oxygens and nitrogens could move a considerable part of charge distribution toward themseleves. The maximum value of charge is belonged to one of oxygen (-0.65).

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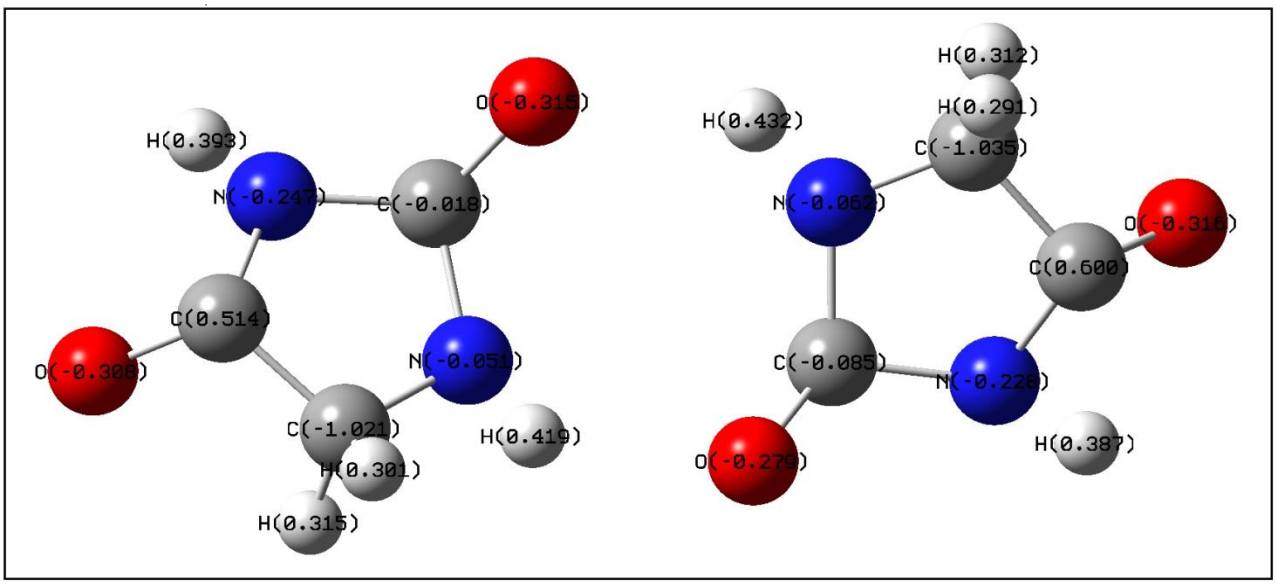

Figure-4. Structures and charge distribution of Hydantoin Dimer1

In figures 3-5, electronic state of all these structures have been investigated by applying Hartree-Fock method and level theory basis set 6-31+G(d,p) by utilizing Gaussian software. Distribution of charge in these compondes could be usefull and help to known better dimers1-3, on one hand, consideering the relation between electronic charge distribution and thermodynamical parameters and on the other hand, steric effects (see figures 3-5).

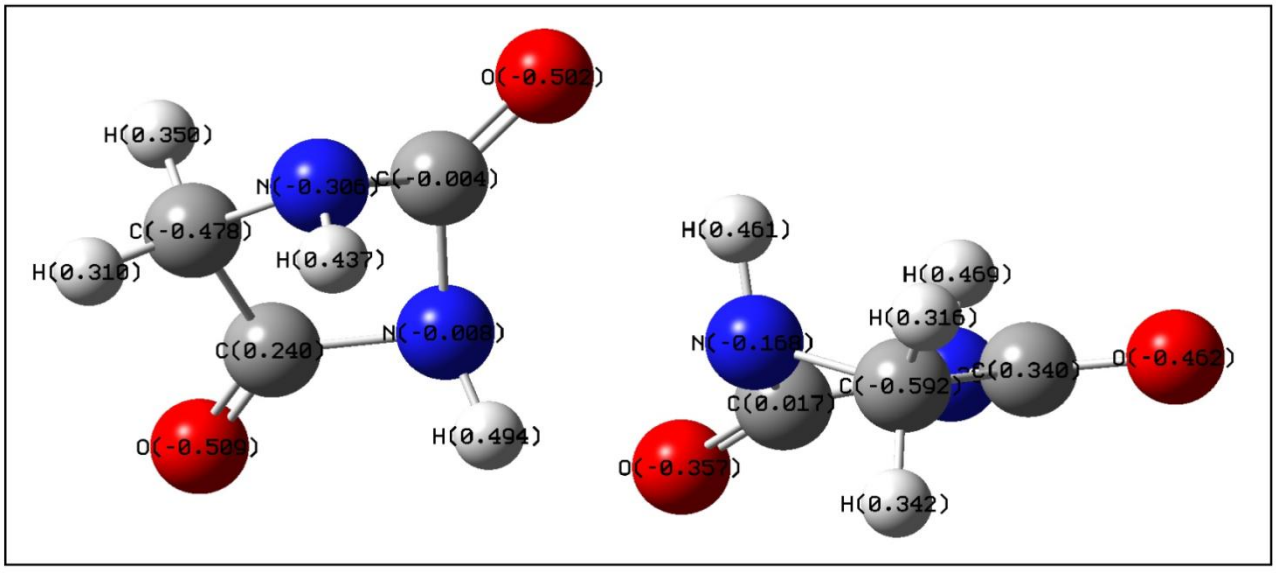

Figure-4. Structures and charge distribution of Hydantoin Dimer2

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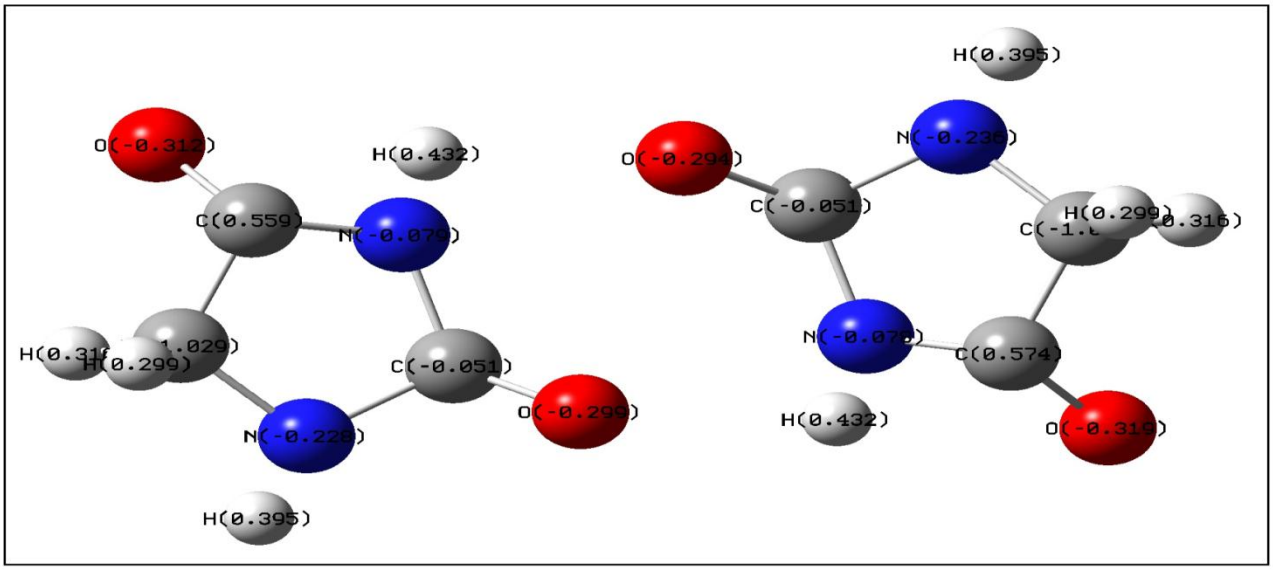

Figure-5. Structures and charge distribution of Hydantoin Dimer3

IV. CONCLUSION

Another important cyclic imide used as leading compound for the synthesis of drugs with anticonvulsiveand anti-parasite activities is the imidazolidine-2,4-dione or simply hydantoin.In this investigation, all geometryoptimization, electronic properties and also vital thermodynamic parametersincluding thermal free energy, entropy, diploe momentum and heat *capacity* (CV) was computed forboth monomer and dimmers of hydantoinutilizing some different levels of theories including Density Function Theory (DFT) with the hybridfunctional B3LYP and Hartree-Fock. In addition more, electronic distribution charge and vibrational frequencies of these four structures by applying Ab initio theory were considered.

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