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Theoretical density functional study of gas-phase tautomerization and acidity of 5-methylhydantoin and its thio derivatives

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ABSTRACT

Tautomerization and acidities of various 5-methylhydantoins and their thio derivatives were predicted using Density Functional Theory (DFT). The functional used was B3LYP and the basis set for all atoms was 6-311+(d,p). Single point energy computations were performed at the 6-311+G(2df,2p) basis set. The relative stabilities of the different tautomers of the 2,4-dioxo, 2-thio-4-oxo, 4-thio-2-oxo and 2,4-dithio derivatives of the deprotonated 5-methylhydantoin have been studied. In all cases, the most stable deprotonated conformers are the oxo-thione, the dioxo or the dithio. As for the neutral and the protonated 5-methylhydantoin-thio derivatives, the tautomerization activation barriers are high enough as to conclude that the oxo-thione structures should be found in the gas phase. It was revealed that the ring-nitrogen atom at position 3 (N3) is more acidic than that at position 1 (N1), hence 5-methylhydantoin thio derivatives in the gas phase are an N3-acid. It has been found that the 2,4-dithio species is the most acidic compound among all the investigated compounds. The acidity values were found to be 343 (**2O4O**), 337 (**2S4O**), 336 (**2O4S**) and 332 kcal/mol (**2S4S**).

1. Introduction

Acidity and basicity of polyfunctional heterocyclic organic compounds are fundamental aspects in chemistry and central to the understanding of chemical reactivity [1-3]. Studies of acidities and basicities have received great attention from both experimental [4] and theoretical investigations [5-10]. Most of these studies have been carried out to predict the correct protonation and deprotonation sites and the possible role played by the protonation and deprotonation processes in decreasing the activation barrier for the 1,3-hydrogen transfer process. Of particular interest, the structural and reactivity changes caused by substitution of an oxygen atom by the bulkier and more polarizable sulfur atom is vital to the understanding of reasons of their different roles in biological activity.

Hydantoin and its thio derivatives are of significant medicinal and pharmaceutical interest, especially as anticonvulsants (e.g., norantoin, mephenytoin, nirvanol, and methetoin) [11-16]. Chemically, these compounds are polyfunctional heterocyclic organic compounds with the structure similar to imidazole with additional hydrogen atom at N3 and two oxygen/sulfur atoms at C2 and C4 positions, respectively. Recently, the gas phase tautomerization and protonation of four combinations of these species were reported [17,18]. These studies were performed by using DFT employing the B3LYP and BP86 levels of theory with the 6-311+(2df,2p)//6-311+(d,p) basis functions.

In continuation with our previous work on tautomeization [17] and protonation [18] of 5-methylhydantoin and its thio derivatives, the present paper is reporting a systematic theoretical study with the following two objectives. The first one is to study the gas-phase relative stabilities of tautomers and rotaomers, the energy barriers of 1,3-H migration from the most sable oxo-thione, dioxo and dithio forms to the most stable enolic structures, to investigate the enolioztion mechanism when the oxygen atom is substituted by a bulkier atom such as sulfur and to investigate the possible catalytic role of the deprotonation process of the different imidic groups on the tautomerization process. The second one is to determine the gas-phase acidity of the acidic centers of the neutral species and compare them with that of the radical ones at different basis sets. The molecules considered in this theoretical survey are 5-methyl-2,4-dioxo imidazolidine (**2O4O**), 5-methyl-2-oxo-4-thio imidazolidine (**2O4S**), 5-methyl-2-thio-4-oxo imidazole-idine (**2S4O**), and 5-methyl-2,4-dithio imidazolidine (**2S4S**) (Scheme 1).

2. Computational details

The geometries of the species under considerations were fully optimized with the aid of the Gaussian 09 set of programs [19], using the hybrid density functional theory (DFT) [20,21] at the B3LYP level [22-24] combined with the polarized triple split valence 6-311+G(d,p) basis functions. The relative B3LYP energies are often in excellent agreement with high-level ab initio results [18,25,26]. Harmonic vibrational frequencies were calculated at the same level of theory to identify the local minima and transition states (TS) and to estimate the corresponding ZPE. Final energies were obtained in single-point calculations carried out at the B3LYP/6-311+G(2df,2p) level. The corresponding relative energies were evaluated with inclusion of the corresponding ZPE corrections scaled by a factor of 0.9806 [27] and the thermal correction of energies.

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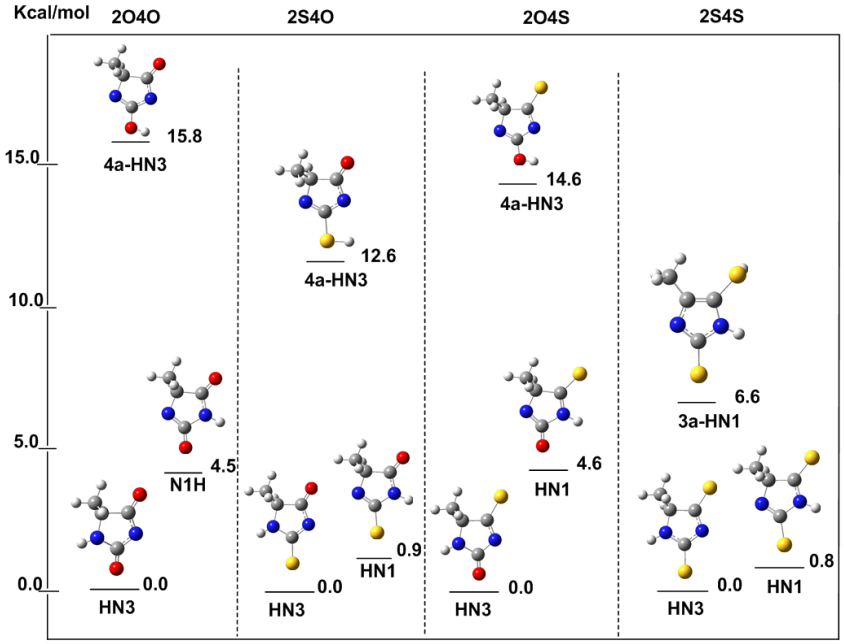


Figure 1. Relative stability of the most stable deprotonated forms of 5-methylhydantoin and its thio derivatives. All values are in kcal/mol.

Enthalpies were evaluated by considering the thermal corrections at 298.15 K. The gas phase-acidity was defined as the enthalpy of deprotonation (ΔH^{298}) for reaction (A) [7].

$$AH\ (g) \rightarrow A^{-}\ (g) + H^{+}\ (g) \qquad (A)$$

The enthalpy of deprotonation, ΔH^{298}, was computed using equations 1 and 2,

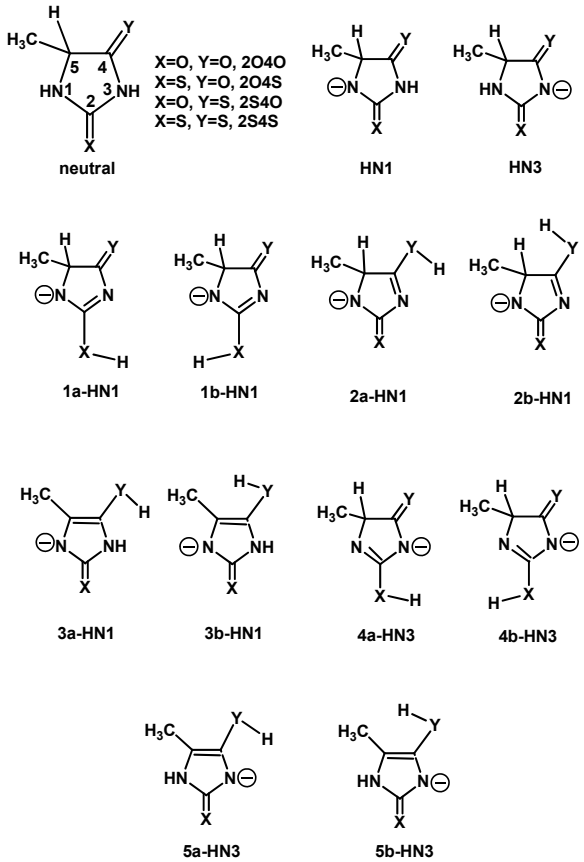
$$\Delta H^{298} = \Delta E^{298} + \Delta(pV) \qquad (1)$$

$$\Delta E^{298} = [E^{298}(A^{-}) + 3/2RT] - E^{298}(AH) \qquad (2)$$

where E^{298} stands for the total energies of the stable conformations of acids and their anions (including the thermal energy correction at T = 298.15 K). In equation 1, we substituted $\Delta(pV) = RT$ [one mole of gas is obtained in the reaction (A)]. Notice that there is an inverse relationship between the magnitude of the ΔH^{298} and the strength of the acid. The larger the value of the ΔH^{298}, the weaker is the acid [7].

3. Results and discussion

The structures of all different species that can be envisaged from deprotonation and tautomerization of the compounds under investigation are presented in Scheme 1. Thus, the first two structures in Scheme 1, **HN1** and **HN3**, correspond to the anions derived from the elimination of the imide protons N1-H and N3-H, respectively, while the remaining species are tautomers that produced by a 1,3-proton migration. All structures that are listed are minima on potential energy surface, PES. The full set of data (total energies, ZPE corrections, thermal corrections to energies (TCE) and thermal corrections to enthalpies (TCH)) for all tautomers in Scheme 1 are given in Table 1-4 of the Supporting Information. The relative energies of the two anions, **HN1** and **HN3**, which are derived from the deprotonation of 5-methylhydantoin and its thio derivatives and the first most stable enolic structures are shown in Figure 1. The relative energies and enthalpies of these and the remaining tautomers in Scheme 1 are reported in Table 5, together with information on the transition states connecting the most stable conformers in each case.



Scheme 1

Table 1. The total energies in atomic units at B3LYP/6-311+G(d,p) (E1) B3LYP/6-311+G(2df,2p)//6-311+G(d,p) (E2), zero-point energy (ZPE), thermal correction to energy (TCE), thermal correction to enthalpy (TCH) of the **2O4O** molecule. All values are in Hartree.

Species	E1	E2	ZPE	TCE	TCH
Neutral	-416.161560	-416.1855910	0.108153	0.115528	0.116472
HN1	-415.596786	-415.6197440	0.094269	0.101247	0.102191
HN3	-415.604876	-415.6279560	0.094840	0.101672	0.102616
1a-HN1	-415.579553	-415.6026830	0.094751	0.101640	0.102584
1b-HN1	-415.578788	-415.6019300	0.094791	0.101639	0.102583
2a-HN1	-415.556466	-415.5794640	0.093859	0.100855	0.101799
2b-HN1	-415.548904	-415.5725680	0.093335	0.100451	0.101395
3a-HN1	-415.548605	-415.5722840	0.092950	0.100492	0.101436
3b-HN1	-415.548605	-415.5722840	0.092952	0.100494	0.101438
4a-HN3	-415.579553	-415.6026840	0.094751	0.101639	0.102583
4b-HN3	-415.578788	-415.6019290	0.094790	0.101637	0.102581
5a-HN3	-415.561657	-415.5853950	0.093493	0.100979	0.101923
5b-HN3	-415.552378	-415.5767140	0.093145	0.100724	0.101668
TS3(HN1-3a-HN1)	-415.4833816	-415.5066209	0.088102	0.095452	0.096396
TS2(HN3-5a-HN3)	-415.4911592	-415.5145564	0.088568	0.095305	0.096249
TS3(HN3-HN1)	-415.4761668	-415.4986933	0.088738	0.095473	0.096417
TS1(HN1-1a-HN1)	-415.5286788	-415.5519821	0.089368	0.096093	0.097037
TS2(HN1-2a-HN1)	-415.5021294	-415.5256775	0.088621	0.095487	0.096431
TS1(HN3-4a-HN3)	-415.5259848	-415.5494008	0.089119	0.095905	0.096849

Table 2. The total energies in atomic units at B3LYP/6-311+G(d,p) (E1) B3LYP/6-311+G(2df,2p)//6-311+G(d,p) (E2), zero-point energy (ZPE), thermal correction to energy (TCE), thermal correction to enthalpy (TCH) of the **2S4O** molecule. All values are in Hartree.

Species	E1	E2	ZPE	TCE	TCH
Neutral	-739.115711	-739.1405330	0.105919	0.113616	0.114560
HN1	-738.567280	-738.5906630	0.092559	0.099902	0.100847
HN3	-738.568630	-738.5921120	0.092571	0.099870	0.100814
1a-HN1	-738.540920	-738.5650810	0.088736	0.096417	0.097362
1b-HN1	-738.540844	-738.5650570	0.088830	0.096437	0.097381
2a-HN1	-738.524820	-738.5480440	0.092085	0.099443	0.100387
2b-HN1	-738.516135	-738.5400770	0.091522	0.099020	0.099964
3a-HN1	-738.527882	-738.5523850	0.091282	0.099415	0.100359
3b-HN1	-738.527882	-738.5523850	0.091282	0.099415	0.100360
4a-HN3	-738.540920	-738.5650800	0.088733	0.096416	0.097361
4b-HN3	-738.540844	-738.5650570	0.088828	0.096436	0.097380
5a-HN3	-738.540340	-738.5647640	0.091755	0.099831	0.100776
5b-HN3	-738.530258	-738.5554920	0.090885	0.099413	0.100357
TS1(HN3-4a-HN3)	-738.503264	-738.5271504	0.085796	0.093020	0.093964
TS2(HN3-5a-HN3)	-738.455048	-738.4790078	0.086372	0.093603	0.094547
TS3(HN3-HN1)	-738.429890	-738.4528700	0.085855	0.093033	0.093977
TS4(HN1-1a-HN1)	-738.508102	-738.5318740	0.086092	0.093253	0.094197
TS5(HN1-2a-HN1)	-738.468998	-738.4928810	0.086879	0.094083	0.095027
TS6(HN1-3a-HN1)	-738.497638	-738.5211670	0.086966	0.094222	0.095167

Table 3. The total energies in atomic units at B3LYP/6-311+G(d,p) (E1) B3LYP/6-311+G(2df,2p)//6-311+G(d,p) (E2), zero-point energy (ZPE), thermal correction to energy (TCE), thermal correction to enthalpy (TCH) of the **2O4S** molecule. All values are in Hartree.

Species	E1	E2	ZPE	TCE	TCH
Neutral	-739.116632	-739.14118	0.105908	0.113659	0.114603
HN1	-738.563080	-738.58637	0.092365	0.099641	0.100585
HN3	-738.571030	-738.59434	0.092729	0.099982	0.100927
1a-HN1	-738.547970	-738.57128	0.092828	0.100061	0.101006
1b-HN1	-738.546550	-738.56984	0.092827	0.100042	0.100986
2a-HN1	-738.520230	-738.54435	0.087893	0.095661	0.096605
2b-HN1	-738.519030	-738.54371	0.087785	0.095610	0.096555
3a-HN1	-738.536200	-738.56278	0.088196	0.096198	0.097142
3b-HN1	-738.536200	-738.56278	0.088198	0.096198	0.097142
4a-HN3	-738.547970	-738.57128	0.092827	0.100060	0.101004
4b-HN3	-738.546550	-738.56984	0.092833	0.100047	0.100991
5a-HN3	-738.531590	-738.55775	0.087723	0.096006	0.096950
5b-HN3	-738.531590	-738.55775	0.087722	0.096006	0.096950
TS1(HN3-4a-HN3)	-738.489180	-738.51285	0.087067	0.094276	0.095220
TS2(HN3-5a-HN3)	-738.475280	-738.49936	0.085157	0.092605	0.093550
TS3(HN3-HN1)	-738.440200	-738.46296	0.086364	0.093462	0.094406
TS4(HN1-1a-HN1)	-738.494780	-738.51836	0.087459	0.094493	0.095437
TS5(HN1-2a-HN1)	-738.483310	-738.50714	0.085454	0.092705	0.093650
TS6(HN1-3a-HN1)	-738.513760	-738.53725	0.087958	0.095125	0.096070

3.1. Relative stabilities and catalytic effects of deprotonation process

As mentioned above, oxo- and thiohydantoin derivatives present different tautomers that can be generated through appropriate hydrogen shifts. Therefore, in order to rationalize their intrinsic reactivity, we must establish which tautomer is predominant in the gas phase. Recently, we have shown, in neutral [17] and protonated [18] molecules, that the dioxo tautomers in the case of 2,4-dioxohydantoin and the oxothione or the dithione tautomer in the case of thiohydantoin are the most stable. It was also found that the energy barriers connecting different neutral tautomers are very high. Therefore, the aforementioned tautomers, if the molecule is not excited, will be the only ones present in the gas phase.

Our first result, to be noted, deduced from the relative energy calculations listed in Table 5 and shown in Figure 1, is that in general, in all cases, the most stable deprotonated structure corresponds to the anion **HN3**, which produced by the direct elimination of the imide proton N3-H.

Table 4. The total energies in atomic units at B3LYP/6-311+G(d,p) (E1) B3LYP/6-311+G(2df,2p)//6-311+G(d,p) (E2), zero-point energy (ZPE), thermal correction to energy (TCE), thermal correction to enthalpy (TCH) of the **2S4S** molecule. All values are in Hartree.

Species	E1	E2	ZPE	TCE	TCH
Neutral	-1062.071259	-1062.096568	0.103742	0.111765	0.112709
HN1	-1061.531903	-1061.555677	0.090629	0.098273	0.099217
HN3	-1061.532566	-1061.556352	0.090253	0.098049	0.098993
1a-HN1	-1061.509142	-1061.533454	0.086779	0.094816	0.095760
1b-HN1	-1061.508605	-1061.532977	0.086891	0.094854	0.095798
2a-HN1	-1061.487869	-1061.512225	0.086167	0.094254	0.095198
2b-HN1	-1061.486115	-1061.511082	0.085957	0.094164	0.095108
3a-HN1	-1061.512344	-1061.539316	0.086580	0.095051	0.095996
3b-HN1	-1061.512344	-1061.539315	0.086580	0.095052	0.095996
4a-HN3	-1061.509142	-1061.533455	0.086779	0.094817	0.095761
4b-HN3	-1061.508605	-1061.532976	0.086891	0.094854	0.095798
5a-HN3	-1061.509724	-1061.536140	0.086579	0.095083	0.096027
5b-HN3	-1061.509724	-1061.536139	0.086582	0.095083	0.096027
TS1(HN3-4a-HN3)	-1061.466864	-1061.490962	0.083851	0.091416	0.092360
TS2(HN3-5a-HN3)	-1061.441384	-1061.465937	0.083376	0.091127	0.092071
TS3(HN3-HN1)	-1061.393450	-1061.416640	0.083356	0.090950	0.091894
TS4(HN1-1a-HN1)	-1061.474460	-1061.498560	0.084123	0.091620	0.092564
TS5(HN1-2a-HN1)	-1061.452251	-1061.477171	0.084003	0.092031	0.092975
TS6(HN1-3a-HN1)	-1061.452251	-1061.477171	0.084003	0.092031	0.092975

Table 5. Relative energies and enthalpies of the deprotonated tautomers and rotaomers of 5-methyldynatoin and its thio derivatives in gas phase. All values are given in kcal/mol.

Species	2O4O		2S4O		2O4S		2S4S	
	ΔE	ΔH	ΔE	ΔH	ΔE	ΔH	ΔE	ΔH
HN1	4.5	4.9	0.9	0.9	4.6	4.8	0.8	0.6
HN3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1a-HN1	15.8	15.8	12.5	14.8	14.6	14.5	10.2	12.4
1b-HN1	16.3	16.3	12.6	14.9	15.5	15.4	10.6	12.7
2a-HN1	29.3	29.9	27.1	27.4	25.7	28.7	22.8	25.4
2b-HN1	33.1	34.0	31.5	32.1	26.0	29.1	23.4	26.0
3a-HN1	33.1	34.2	23.9	24.7	14.7	17.5	6.6	8.9
3b-HN1	33.1	34.2	23.9	24.7	14.7	17.5	6.6	8.9
4a-HN3	15.8	15.8	12.5	14.8	14.6	14.5	10.2	12.4
4b-HN3	16.3	16.3	12.6	14.9	15.5	15.4	10.6	12.7
5a-HN3	25.5	26.3	16.6	17.2	17.4	20.5	8.6	10.9
5b-HN3	30.5	31.6	21.7	22.7	17.4	20.5	8.6	10.9
TS1(HN3-4a-HN3)	42.2	45.8	32.4	36.5	44.1	45.5	33.0	36.9
TS1(HN3-5a-HN3)	63.4	67.3	63.3	67.1	50.4	55.1	48.2	52.5
TS3(HN3-HN1)	73.5	77.3	79.0	83.2	74.5	78.4	79.1	83.3
TS4(HN1-1a-HN1)	40.9	44.3	29.7	33.7	41.1	44.3	28.3	36.7
TS5(HN1-2a-HN1)	56.6	60.4	55.2	58.7	45.8	50.2	41.1	46.0
TS6(HN1-3a-HN1)	68.2	72.4	37.6	41.0	29.9	32.8	28.1	35.2

In fact, isomer **HN3** was found largely more stable in the cases **2O4O** and **2O4S** than isomer **HN1** by about 4.5 and 4.6 kcal/mol,respectively. While this energy gap drops to 0.9 and 0.8kcal/mol,respectively, in the cases of **2S4O** and **2S4S**.

For **2O4O** compound, it was found that the relative stability trend of the most stable tautomers is as follow: **HN3 > HN1** > **1a-HN1** ≈ **4a-HN3** > **5a-HN3** > **2a-HN1** > **3a-HN1**. It was also found that the first less stable enolic structures **1a-HN1** and **4a-HN3** are almost degenerate, which is similar to the results obtained in the case of the neutral [17] and the protonated species [18]. Therefore, our tabulated results show that forms **1a-HN1** and **4a-HN3** are estimated to be 15.8 kcal/mol less stable than the global minimum isomer HN3 (Table 5). For **2S4O**, **2O4S** and **2S4S** species, our results suggest that the most stable deprotonated species corresponds to the **HN3** isomer (Table 5 and Figure 1). The relative stability trends of the most stable species are as follow:

2S4O: HN3 > HN1 > 1a-HN1 ≈ 4a-HN3 > 5a-HN3 > 3a-HN1 > 2a-HN1,

2O4S: HN3 > HN1 > 1a-HN1 ≈ 4a-HN3 > 3a-HN1 > 5a-HN3 > 2a-HN1, and

2S4S: HN3 > HN1 > 3a-HN1 > 5a-HN3 > 1a-HN1 ≈ 4a-HN3 > 2a-HN1,

For **2S4O** and **2O4S** compounds, the most stable enolic structures correspond to the **1a-HN1** and **4a-HN3** tautomers and they were found to be largely less stable by about 14.6 and 12.5 kcal/mol, respectively, than the global minimum, **HN3** isomer. The situation is completely different as far as the **2S4S** species is concerned. The first stable enolic structure corresponds to form **3a-HN1**, which can be produced starting from **HN1** isomer by a 1,-3 H migration from the C5H group to the adjacent C4=S group. Our calculated results indicate that the enolic structure **3a-HN1** was found to be largely stable by bout 2.0 and 3.6 kcal/mol, respectively, more stable than 5a-HN3 and 4a-HN3 forms, which can be produced by a suitable 1,3-H transfer starting from the global minimum, HN3 isomer.

In summary, the results reported for the **2O4O**, **2S4O** and **2O4S** species suggest that the 1,3-H migration can take place at the heteroatom attached to C2 of the HN3 and HN1 isomer, regardless of the heteroatom type and the deprotonation site. Whereas, in the case of **2S4S**, the 1,3-H migration is favored at the sulfur atom attached to C4 of the **HN1** isomer.

To study, which of the enolic structures can be observed in the gas phase, the transition states for 1,3-H migration have been calculated. Figure 2a-d shows schematic representation of the corresponding potential energy surface (PESs) of the tautomerization process of the species under investigation. The relative energies corresponding to the transition states, which connect the most stable deprotnated dioxo, dithio, and oxo/thio tautomers, **HN3**, with other species are listed in Table 5. As indicated above, tautomer **HN3** is the global minimum in all cases, but there are significant similarities regarding the relative stability of the remaining tautomers.

On going from the global minimum, **HN3** isomer, to the enolic forms, **4a-HN3** and **5a-HN3**, two possible enolization mechanisms, **TS1** and **TS2**, are proposed. The first mechanism (**TS1**) corresponds to the enolization of the oxo (or thione) groups attached to C2 by a 1,3-H shift from the adjacent N-H

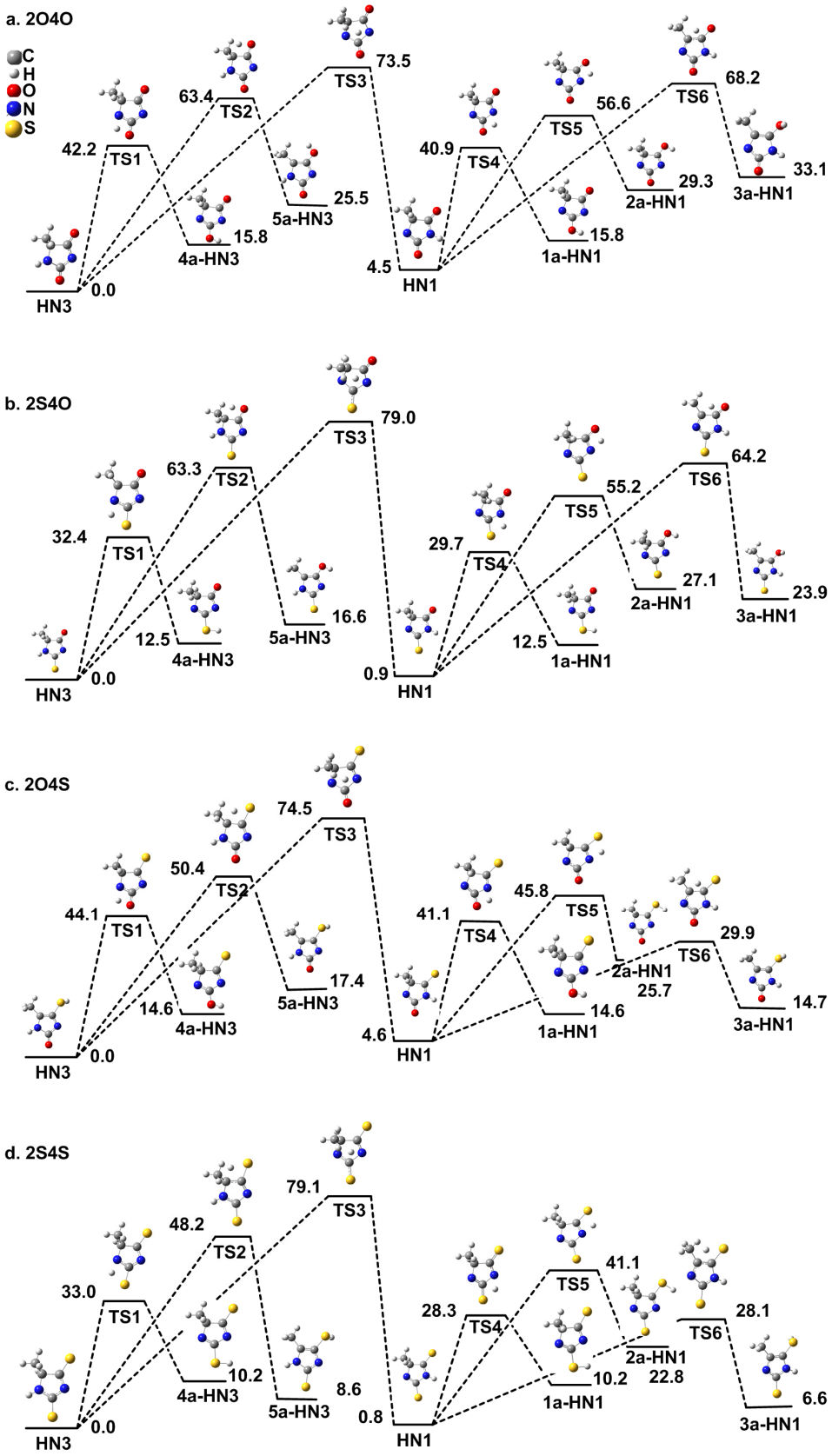


Figure 2. Energy profile of the unimolecular tautomerization processes of the deprotonated species (a) **2O4O**, (b) **2S4O**, (c) **2O4S** and (d) **2S4S**. All values are in kcal/mol

Table 6. Calculated 298 K deprotonation energies, ΔH^{298}, of the 5-methylhydantoin and its thio derivatives at B3LYP with 6-311G(d,p) and 6-311+G(2df,2p)//-311+G(d,p) [c]. All values are in kcal/mol.

Species	Method	Neutral		Radical	
		N1	N3	N1	N3
2O4O	B3LYP[a]	356	351	201	196
	B3LYP[b]	348	343	199	193
2S4O	B3LYP[a]	341	341	216	214
	B3LYP[b]	338	337	221	219
2O4S	B3LYP[a]	346	335	220	214
	B3LYP[b]	341	336	220	217
2S4S	B3LYP[a]	334	334	218	217
	B3LYP[b]	333	332	226	222

[a] B3LYP/6-311G(d,p).
[b] B3LYP/6-311+G(2df,2p)//6-311G(d,p).
[c] $\Delta H^{298} = \Delta E_{tot} + \Delta ZPVE + \Delta(H^{298}-H^0) + 6.2$ kJ; scaled ZPVE by 0.9806 empirical factor.

group to yield form **4a-HN3**, while the second mechanism (**TS2**) is accomplished by the enolization of the oxo (or thione) groups by a 1,3-H transfer from the adjacent CH group to yield species **5a-HN3**. Our results indicate that for all compounds the first mechanism (**TS1**) is thermodynamically favored than the second one (**TS2**). Also importantly, the first enolization process (**TS1**) is more favorable when the heteroatom attached to C2 group is sulfur than that of the oxygen atom. For example, for compounds **2S4O** and **2S4S** transition barrier is estimated to be 32.4 and 33.0 kcal/mol above the minimum. Similarly, for compounds, **2O4S** and **2O4O** tautomerization barriers (**TS1**) are found to be 44.1 and 42.2 kcal/mol, respectively, above the minimum. For compounds **2O4S** and **2S4S**, the tautomerization barriers (**TS2**) are estimated to be 50.4 and 48.2 kcal/mol, respectively, above the global minimum. Similarly, for compounds **2S4O** and **2O4O** transition barriers (**TS2**) lies 63.8 and 63.4 kcal/mol, respectively, above the global minimum. These results seem to be consistent with our previous studies [17,18], in the sense that the oxo (or thione) group attached to C2 should be more basic than that attached to C4. Additionally, sulfur seems to be more basic than oxygen. Also, the enoliztion process of sulfur atom is thermodynamically favored than the oxygen one.

The same conclusion can also be reached if we follow the formation of the enolic structures starting from the second most stable isomer, HN1. For example, for all compounds the formation of **1a-HN1** is thermodynamically more favored than **2a-HN1**. It is also worth mention that the formation of **1a-HN1** and **2a-HN3** can be produced by enoliztion of the oxo (or thione) groups attached to C2 and C4 by a 1,3-H shift from the N3-H. The enolization mechanism of the oxo (or thione) groups attached to C2 can be proceed either by a 1,3-H shift from the N3–H group to yield species 1a-HN1 or by a 1,3-H shift from the N1-H group to yield structure 4a-HN3. Although, our results indicate that the two tautomers are degenerate, the first mechanism is thermodynamically favored than the second one. Also importantly, these mechanisms are thermodynamically favored when the heteroatom attached to C2 is sulfur in all cases. These findings can be well explained as follow:,in compounds **2S4O** and **2S4S**, on going from **HN3** or **HN1** to either **4a-HN3** or **1a-HN1** a C=S and a N-H bonds are replaced by a C=N and a S-H bonds, respectively, while for compounds **2O4S** and **2O4O** one replaces a C=O and a N-H bonds by a C=N and a O-H bonds. However an S-H bond is weaker than a N-H linkage, a C=N bond is significantly stronger than a C=S one, so that the overall enolization process is more favorable for **2S4O** and **2S4S** than for compounds **2O4S** and **2O4O**. On the other hand, when these results are compared with those obtained for the neutral [17] and the protonated [18] species, in compound **2O4O** the activation barriers of the enolization process was found to be 12.7 and 7.9 kcal/mol lower than those obtained for the neutral[17] and protonated [18] species, respectively.

In summary, in what concerns the tautomer stability, the most important conclusion is that for **2S4O** and **2O4S** the most stable tautomer is the oxo-thione form. Similarly, for **2S2S** and **2O4O** compounds the dithione and the dioxo forms, respectively, are the most stable ones. On the other hand, as shown in Figure 2, the energy barriers connecting the different tautomers are very high, and therefore we can safely conclude that only the aforementioned tautomers will exist in the gas phase.

3.2. Gas-phase acidity

In Table 6 we have summarized the calculated acidities for the neutral 5-methylhydantoin and its thio derivatives. These values were obtained from DFT calculations using the B3LYP functional at 6-311G(d,p) and 6-311+G(2df,2p)//6-311+G(d,p) basis functions. For sake of comparison we included the acidity of the radical molecule at the same basis functions. The full set of data (total energies, ZPE corrections, TCE and TCH) for all species under investigation are given in Tables 7 and 8 of the Supporting Information. The analysis of the data listed in Table 6 indicates that the values obtained from the 6-311G(d,p) basis function are more than 8 kcal/mol higher than those obtained using 6-311+G(2fd,2p)//6-311+G(d,p) one. This suggests that diffuse functions are required to lower the computed deprotonation energies of anions [5,6,28].

As it is found in literature [29,30], data reported in Table 6 indicates that the most acidic site of 5-methylhydantoin and its thio derivatives is the N3-H group. It is noticed that, there is an inverse relationship between the magnitude of the ΔH^{298} and the strength of the acid. The larger the value of the ΔH^{298}, the weaker is the acid. For **2O4O** and **2O4S**, it is found that the acidity difference between N3 and N1 atoms is quite substantial and amounts to about 5.0 kcal/mol in favor of the former. Whereas, for **2S4O** and **2S4S** species, this acidity difference decreases to about 1.0 kcal/mol. The reason for this behavior is probably due to the high polarizability and size of the sulfur atom attached to C2 over the oxygen, which allows a delocalization of the negative charge at both atoms. Our results suggest that the gas phase acidity trend of the molecules under investigation is as follow: **2S4S** > **2S4O** > **2O4O** > **2O4O**, which agrees with those reported experimentally [29]. Experimental data [30] showed that 2-thiohydantoin (pka=8.5) is slightly stronger acid than hydantoin (pka = 9.0). From the results, we can deduce that both NH bonds are characterized by a weak acidity, which is sensibly lower than that of uracil and its thio derivatives (320-333 kcal/mol) [5,6] and higher than that of formamide (359 kcal/mol), *N*-methylformamide (~361 kcal/mol) or *N*-methylacetamide (362 kcal/mol) [31]. From the results obtained in this study, we can deduce that both NH bonds are characterized by a weak acidity, which is sensibly lower than that of uracil and its thio derivatives (320-333 kcal/mol) [5,6] and higher than that of formamide (359 kcal/mol), *N*-methylformamide (~361 kcal/mol) or *N*-methylacetamide (362 kcal/mol)[31].

In order to confirm our results concerning the acidity trend of the compounds under probe, an appropriate isodesmic reaction has been considered. Reactions 1 and 2 (Table 9) permit us to compare the relative stability of both HN1 and HN3 anions for the all the compounds.

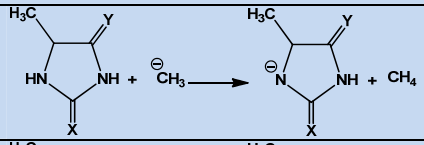
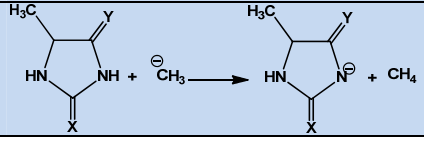
Table 7. B3LYP/6-311G(d,p) Optimized energies, E, zero-point energy, ZPE, thermal correction to energy, TCE, thermal correction to enthalpy, TCH, of the neutral and cationic Radicals of **2O4O**, **2S4O**, **2O4S** and **2S4S** molecules. All values are in hartree.

Species	E	ZPE	TCE	TCH
2O4O-neutral				
Neutral	-416.1503667	0.108394	0.115724	0.116669
N1	-415.5715871	0.094329	0.101299	0.102243
N3	-415.5799112	0.094942	0.101742	0.102686
2O4O-Radical				
Neutral	-415.8013220	0.105860	0.113224	0.114169
N1	-415.4713249	0.094462	0.1016	0.102544
N3	-415.4713250	0.093280	0.100747	0.101691
2S4O-neutral				
Neutral	-739.1077140	0.106177	0.113817	0.114761
N1	-738.5522520	0.092733	0.100062	0.101007
N3	-738.5524940	0.092668	0.099956	0.100900
2S4O-Radical				
Neutral	-738.7950590	0.105653	0.113406	0.114350
N1	-738.4399897	0.092255	0.099751	0.100695
N3	-738.4287180	0.092291	0.099961	0.100905
2O4S-neutral				
Neutral	-739.108544	0.106138	0.113845	0.114789
N1	-738.545945	0.092402	0.099697	0.100642
N3	-738.555045	0.092996	0.100209	0.101154
2O4S-radical				
Neutral	-738.7916610	0.105486	0.113239	0.114183
N1	-738.4306228	0.092319	0.099757	0.100702
N3	-738.4327490	0.092511	0.10008	0.101024
2S4S-neutral				
Neutral	-1062.065926	0.103997	0.111957	0.112901
N1	-1061.522989	0.090781	0.098411	0.099356
N3	-1061.522866	0.090482	0.098242	0.099186
2S4S-radical				
Neutral	-1061.758258	0.103163	0.111128	0.112072
N1	-1061.399692	0.090127	0.097925	0.098869
N3	-1061.392742	0.089747	0.097600	0.098544

Table 8. B3LYP/6-311+G(d,p) Optimized energies, E1, B3LYP/6-311+G(2df,2p)/6-311+G(d,p), single point energy, E2, zero-point energy, ZPE, thermal correction to energy, TCE, thermal correction to enthalpy, TCH, of the neutral and cationic radicals of **2O4O**, **2S4O**, **2O4S** and **2S4S** molecules. All values are in hartree.

Species	E1	E2	ZPE	TCE	TCH
2O4O-radical					
Neutral	-415.8066260	-415.8315030	0.105699	0.113085	0.114029
N1	-415.4821725	-415.5058033	0.094266	0.101435	0.102379
N3	-415.4610542	-415.4848640	0.093121	0.100618	0.101562
2S4O-radical					
Neutral	-738.8012690	-738.8278380	0.105454	0.113250	0.114195
N1	-738.4494504	-738.4614016	0.092133	0.099645	0.100589
N3	-738.4391405	-738.4639790	0.092315	0.099969	0.100913
2O4S-radical					
Neutral	-738.7975870	-738.8240070	0.105340	0.113118	0.114062
N1	-738.4386779	-738.4628818	0.092125	0.099597	0.100541
N3	-738.4430888	-738.4676920	0.092466	0.100049	0.100993
2S4S-radical					
Neutral	-1061.763577	-1061.790435	0.102948	0.110960	0.111904
N1	-1061.406195	-1061.419329	0.089998	0.097814	0.098758
N3	-1061.400349	-1061.425133	0.089574	0.097463	0.098407

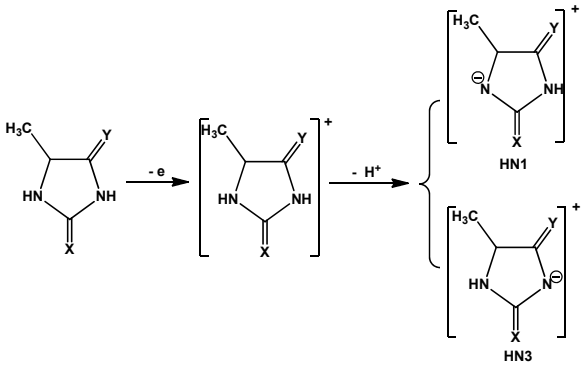
Table 9. Relative stability of both HN1 and HN3 anions by using an appropriate Isodesmic reaction

Species	Reaction	ΔE, kcal/mol			
		2O4O	**2S4O**	**2O4S**	**2S4S**
(1) HN1 -isomer		-67.6	-77.0	-74.2	-82.3
(2) HN3- isomer		-72.2	-77.9	-78.7	-83.1

The first conspicuous fact is that both reactions 1 and 2 are endothermic, which indicates that both **HN1** and **HN3** isomers are stabilized upon deprotonation. It was found that the stabilization energy is greater for the **HN3** isomer than the **HN1** isomer, indicating that the N3-H group is more acidic than the N1-H (Table 9). The results presented in chart 1 show that the deprotonated anions in the case of the **2S4S** compound are the most stable anions among all the species under probe. Therefore, the relative stability trend might be arranged as

follow: **2S4S** > **2O4S** > **22O** > **2O4O**, in agreement with our previous arrangement based on the deprotonation energies.

As it has been shown above, the most acidic site of the neutral 5-methylhydantoin and it thio derivatives is the N3-H group. Our results for the neutral radicals indicate that this is also the case in all cases. It is worth to mention that the radical cations have been obtained by ionization of the neutral molecules and then by deprotonation of the acidic sites in the ionized structures (Scheme 2). Our results show some significant changes, however, as far as the acidity of their radical cations is concerned. As should be expected, the 5-methylhydantoin and thiohydantoin radical cations are more acidic than the corresponding neutrals, but still in all of them the N3-H group remains as the most acidic site, although the gap with respect to the N1-H acidity is rather small for the particular case of 2S4S and 2S4O. It is found that the acidity values of the radical molecules are higher than those of the corresponding neutrals. Our tabulated results (Table 6) indicate that the acidity difference is ranging from 107 to 150 kcal/mol in favor of the radical cations.



Scheme 2

4. Conclusions

Similar to what was found previouly in protonation processes, the diketo, dithio, keto/thio and thio/keto isomers of the 5-methylhydantoin thio derivatives remain the most stable structures. It has been shown that, in all cases, **HN3** isomers were found to be more stable than the **HN1** ones. For **2O4O**, **2S4O** and **2O4S** compounds, the 1,3-H transfer is favored at the heteroatom attached to C2, regardless of its type. Whereas, for **2S4S** compound the 1,3-H transfer is favored at the sulfur atom attached to C4. The barriers for proton migration between different tautomers are rather large. Our results showed that the ring-nitrogen atom at position 3 (N3) is more acidic than that at position 1 (N1), hence the 5-methylhydantoin and its thio derivatives are an N3-acid. Among all the considered molecules, the **2S4S** molecule was found to be the most acidic one. It has been found that the two N-H bonds in the 5-methylhydantoin and its thio derivatives are characterized by a weak acidity.

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