Theoretical Investigation of Solvation Effects on the Tautomerism of Maleic Hydrazide

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Abstract: A DFT study is used to calculate structural data of tautomers of maleic hydrazide (MH) in the gas phase and selected solvents such as benzene (non-polar solvent), tetrahydrofuran (polar aprotic solvent) and methanol (protic solvent), dimethyl sulfoxide (polar aprotic solvent) and water (protic solvent) using PCM model. All tautomers are optimized at the B3LYP/6-31++G(d,p). The results show that the tautomer MH₂ except in methanol is more stable than the other tautomers but in methanol MH₅ (Diol) is more stable. In addition, stability of the tautomers in deferent solvents shows interesting results. Variation of dipole moments and NBO charges on atoms in the solvents were studied.

Keywords: DFT study, NBO analysis, PCM model, Maleic hydrazide, Tautomerism

Introduction

Tautomerism interconversions¹⁻² have been investigated by chemists during last decades. Recently, study of tautomerism received renewed attention due to its importance on determination of compounds' properties and their area of applications. The importance of tautomerism is revealed more since in recent years the investigation about tautomerism has been the major topic in theoretical chemistry. For example, tautomerisms in keto-enol^{3,4}, imine-enamine^{5,6} and many other systems⁷ have been studied during past decades.

Tautomerisation and proton transfer of the keto-enol tautomer of heterocyclic systems with several basic centers, N, O and S atoms, are of great interest to medicinal and biochemical

applications. Also, understanding of the relative stabilities of heterocyclic tautomers and any subsequent conversions between tautomeric forms is very vital for both structural chemists and biologists^{8,9}. Along this line, relative stabilities of various tautomeric structures of five-, six- and seven-member heterocyclic rings were investigated using both theoretical and experimental tools¹⁰⁻¹⁴.

1,2-Dihydropyridazine-3,6-dione (Maleic hydrazide) uses as a plant-growth inhibitor¹⁵. The similarity between molecular structure of maleic hydrazide and that of pyrimidine bases suggests erroneous incorporation into nucleic acid as a possible mechanism of action¹⁶. Like nucleic acid bases, maleic hydrazide shows some tautomers^{17,18}.

The common studies of tautomerisation of carbonylic compounds such as hydantoin, uracil, thiouracil, 1, 2, 4-triazepines, oxazolidine and hydantoins, can anticipate that maleic hydrazide may exhibit five different tautomeric structures with different conformations. These tautomers have been covered extensively in the literature. However, this study employs density functional theory (DFT) on the investigation of those structures and to present a complete analysis of their relative stabilities in the gas phase and deferent solution. This work includes variation of dipole moments and NBO charges on atoms in the solvents and gas phase.

Experimental

All these calculations were carried out on a Pentium V personal computer by means of GAUSSIAN03 program package¹⁹ and for our computations. First, all compound's structures were drawn using Gauss View 03²⁰ and optimized in semi-empirical methods. To characterize all the optimized geometries the vibrational frequencies for all the conformers have been done at B₃LYP levels. The stationary structures are confirmed by ascertaining that all ground states have only real frequencies. The tautomers were also optimized in solvents according to the polarisable continuum method of Tomasi and co-workers, which exploits the generating polyhedra procedure²¹⁻²⁴ to build the cavity in the polarisable continuum medium, where the solute is accommodated. Atomic charges in all the structures were obtained using the Natural Population Analysis (NPA) method within the Natural Bond Orbital (NBO) approach²⁵⁻²⁷.

Results and Discussion

Gas phase

Structures and numbering of maleic hydrazide are depicted in Figure 1 and the results of energy comparisons of five tautomers in the gas phase and different solvents are given in Table 1. In the gas phase MH₂ forms are more stable than the other forms. The major difference between MH₂ and the other forms in gas phase was found for MH₁ with 40.60 kcal mol⁻¹. The order of stability of all the tautomers in the gas phase is MH₂ > MH₄ > MH₅ > MH₃ > MH₁.

Table 1. Total energies at B3LYP/6-31++G^{**} and relative stability in the gas phase and solvents

Tautomer	Gas (1.0)	Benzene (2.2)	THF (7.6)	Methanol (33)	DMSO (46.7)	Water (78.4)
MH ₁	414.7246325	414.7366826	414.7450211	414.7482222	414.7483539	414.7489765
MH ₂	414.7893364	414.8045766	414.8148037	414.8148037	414.8187938	414.8193252
MH ₃	414.7289362	414.7384611	414.7449898	414.7474751	414.7475604	414.7480266
MH ₄	414.7797625	414.7797629	414.8110299	414.8160292	414.8164571	414.8170376
MH ₅	414.7804313	414.79444	414.8036373	414.8703310	414.8071745	414.8079169

^aHartree, ^bRelative stabilities in kcal mol⁻¹

Figure 1. Tautomeric forms of maleic hydrazide and numbering of maleic hydrazide ring

This indicates that due to the N=N, MH₃ and MH₂ are less stable in the gas phase. Table 2 shows difference stability between all the tautomers.

Table 2. Energy^a difference between the tautomers of maleic hydrazide

Tautomer	Gas (1.0)	Benzene (2.2)	THF (7.6)	Methanol (33)	DMSO (46.7)	Water (78.4)
MH ₁	0.0647039	0.067894	0.0697826	0.1221088	0.0704399	0.0703487
MH ₂	00.000	00.000	00.000	0.0555273	00.000	00.000
MH ₃	0.0604002	0.0661155	0.0698139	0.1228559	0.0712334	0.0712986
MH ₄	0.0095739	0.0248137	0.0037738	0.0543018	0.0023367	0.0022876
MH ₅	0.0089051	0.0101366	0.0111664	00.000	0.0116193	0.0114083

^aHartree.

The calculated dipole moments for the maleic hydrazide are presented in Table 3. MH₄ tautomer has smaller dipole moments than the other forms and MH₃ tautomer with N=N bond has larger dipole moments. In MH₃ forms C₄ and C₅ atoms carry the most negative charge. It is noticeable that the differences between dipole moments of 1-H and 2-H forms are related to the double bond position.

Table 3. Calculated dipole moments of optimized tautomers of maleic hydrazide (Debye)

Tautomer	Gas (1.0)	Benzene (2.2)	THF (7.6)	Methanol (33)	DMSO (46.7)	Water (78.4)
MH ₁	3.7234	4.6765	5.4906	5.8379	5.8727	5.9094
MH ₂	3.3043	4.1845	4.9084	4.9084	5.2268	5.2518
MH ₃	4.7463	5.4312	5.9364	6.1246	6.1407	6.1566
MH ₄	1.0016	1.0043	2.5719	2.7664	2.7862	2.8084
MH ₅	1.6106	1.9427	2.2090	2.2925	2.3220	2.3101

The calculated values NBO charges using the natural population analysis (NPA) of optimized structures of maleic hydrazides tautomers in the gas phase and solvents are listed in Table 4. In MH₁ C5 atom carries the largest negative charge, in MH₂, MH₄ and MH₅ nitrogen atoms at position 1 or 2 carry the largest negative charge, in MH₃ carbon atoms at position 4 or 5 carry the largest negative charge and these positions will most effectively interact with electrophiles.

Table 4. Calculated NBO charges on ring atoms of maleic hydrazide

Atom		N1	N2	C3	C4	C5	C6
$\epsilon=$							
1.0	MH ₁	-0.195	-0.180	0.403	-0.239	-0.587	0.654
2.2		-0.223	-0.177	0.401	-0.217	-0.596	0.666
7.6		-0.248	-0.174	0.400	-0.197	-0.603	0.673
33		-0.259	-0.172	0.400	-0.187	-0.606	0.676
46.7		-0.260	-0.173	0.400	-0.186	-0.606	0.676
78.4	MH ₂	-0.261	-0.172	0.400	-0.186	-0.606	0.677
1.0		-0.422	-0.316	0.488	-0.251	-0.244	0.590
2.2		-0.419	-0.326	0.494	-0.248	-0.249	0.592
7.6		-0.415	-0.331	0.499	-0.245	-0.253	0.592
33		-0.415	-0.331	0.499	-0.245	-0.253	0.592
46.7	MH ₃	-0.414	-0.333	0.501	-0.243	-0.255	0.592
78.4		-0.413	-0.333	0.501	-0.243	-0.255	0.592
1.0		-0.160	-0.148	0.647	-0.550	-0.560	0.652
2.2		-0.170	-0.156	0.663	-0.554	-0.565	0.670
7.6		-0.175	-0.164	0.675	-0.558	-0.567	0.681
33	MH ₄	-0.178	-0.167	0.679	-0.559	-0.568	0.686
46.7		-0.178	-0.167	0.679	-0.559	-0.568	0.686
78.4		-0.178	-0.167	0.680	-0.559	-0.568	0.687
1.0		-0.469	-0.469	0.612	-0.247	-0.247	0.612
2.2		-0.468	-0.468	0.612	-0.247	-0.247	0.612
7.6	MH ₅	-0.430	-0.430	0.606	-0.249	-0.249	0.606
33		-0.426	-0.426	0.606	-0.249	-0.249	0.606
46.7		-0.426	-0.426	0.606	-0.250	-0.250	0.606
78.4		-0.425	-0.425	0.606	-0.250	-0.250	0.606
1.0		-0.309	-0.309	0.483	-0.251	-0.251	0.483
2.2	MH ₅	-0.332	-0.332	0.488	-0.251	-0.251	0.488
7.6		-0.349	-0.349	0.492	-0.250	-0.250	0.492
33		-0.355	-0.355	0.494	-0.250	-0.250	0.494
46.7		-0.356	-0.356	0.494	-0.250	-0.250	0.494
78.4		-0.356	-0.356	0.494	-0.250	-0.250	0.494

Solvent effects

Solvent effects are relevant in tautomers stability phenomena, since polarity differences among tautomers can induce significant changes in their relative energies in solution. PCM/B3LYP calculations were used to analyze the solvent effects on tautomerism of maleic hydrazides. It is important to stress that the PCM model does not consider the presence of explicit solvent molecules; hence specific solute–solvent interactions are not described and the calculated solutions effects arise only from mutual solute–solvent electrostatic polarization. The data presented in Table 1 show that polar solvents increase the stability of all maleic hydrazide tautomers in compare to gas phase. The difference between the total energies of maleic hydrazide and the other forms do not show a regular trend when changing from gas phase to most polar solvents (water).

The solvent interactions have pronounced effect on the order of stability of the tautomers in the gas phase. For example, in benzene with low dielectric constant, order of

stabilities of MH_5 more stable than MH_4 form and it can be due to strong interaction between benzene and aromatic ring in MH_5 tautomer, in THF, DMSO and water solvents as polar solvents MH_1 more stable than MH_3 and the order of stability of all the tautomers is $MH_2 > MH_4 > MH_5 > MH_1 > MH_3$, but in methanol MH_5 is more stable than the other tautomers, it is my be due to strong hydrogen bond interaction between methanol and hydroxyl group in MH_5 tautomer and after that MH_4 is more stable than the other tautomers. The solvent represented by a polarizable continuum is found shows significant effect on the dipole moments of the individual solute conformers. The dipole moments increases by changing the gas phase to the solution as well as by increasing the solvent polarity. The most significant variations being obtained in MH_3 form with 6.1566 D (Table 3). In addition, in gas phase and benzene MH_5 tautomers has higher dipole moment than MH_4 forms but in polar solvents (THF, methanol, DMSO and water), MH_4 tautomer has higher dipole moment than MH_5 form. We have examined the charge distribution of tautomers in the solvent as well as gas phase by using calculated NBO charges. The charge distribution in solvents with increase of polarity differently varies for any atoms.

Conclusion

The following points emerge from the present study:

1. In the gas phase MH_2 form was more stable than the other tautomers. In the solution the stability of some tautomers is deferent than gas phase and stability of tautomers were affected by deferent solvents. With increase of polarity total energy of all compounds were more negative.
2. The dipole moments of all compounds are affected by solvent. With increase of the polarity of solvents the dipole moments of all tautomers were increased.
3. The charges on all six positions were affected by solvents. In addition with increase of dielectric constant a variation was found.

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