



## Quantum chemical studies on tautomerism of barbituric acid in gas phase and in solution

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### Summary

*Ab initio* and density functional theory (DFT) methods were used to study the tautomers of barbituric acid in the gas phase and in a polar medium. In the gas phase, the tautomers were optimized at the HF/6-31G\*, MP2/6-31G\* and B3LYP/6-31G\*, B3PW91/6-31G\* levels of theory. The self-consistent reaction field theory (SCRF) at the HF/6-31G\* level of theory has been used to optimize the tautomers in a polar medium. The relative stability of the tautomers was compared in the gaseous and polar mediums. The ability of maximum hardness principle to predict the stable tautomer has been studied. The  $^{13}\text{C}$ -NMR chemical shift for carbon atoms in the tautomers was calculated and the results are discussed.

### Introduction

For the last two decades nitrogen and oxygen containing heterocyclic compounds have been attractive in biology due to their pharmaceutical action, mainly attributable to their ability to make the hydrogen bonds. Among them, derivatives of barbituric acid are perhaps the most widely used pyrimidines in medicine [1]. The possibility of tautomerism in pyrimidine derivatives has been the subject of interest for long time. Most of the pyrimidine derivatives exhibit the keto form rather than the enol configuration [2]. Enols have been widely suggested as reactive intermediates in a wide variety of organic and biological reactions [3, 4]. Thioketones are generally unstable in solution and they readily tautomerize to the corresponding thioenols provided that they have  $\alpha$ -enolizable hydrogen atom [5]. The structural interest of barbituric acid is attributed to its behaviour as a carboxylic acid comparable in strength with formic acid. This activity is apparently associated with the combination of the active methylene group and the potential imino group. Barbituric acid (B.A) is an interesting molecule, in the sense that it can exhibit two kinds of

tautomers through transfer of either imino hydrogen or methylene hydrogen to keto oxygen. So, B.A. can be considered as a model system in which methylene group is attached in fifth position and imine groups are present in first and third position of the ring (Figure 1). The triketo form of B.A in the solid state and in aqueous solutions is well established [6], and it also exists in the same form in non-polar solvents [7]. Rita Kakkar et al. [7] have studied the tautomerism and electronic structure properties of B.A. employing semiempirical molecular orbital methods.

Previous studies [7–9] on tautomerization of similar compounds show that the semi-empirical methods are inadequate for predicting the order of stabilities, physical and chemical properties of the tautomers (or conformers), which are much dependent on the theoretical models used. The electron correlation and dispersion energy terms are very important and should be included in the theory to predict the relative stability of the molecules very accurately [10, 11]. Density functional theory (DFT) has become popular, since correlation is included from the beginning and it provides highly accurate results for many molecular properties. The inclusion of gradient corrected approximation (GGA) terms into the exchange-correlation functional ( $E_{\text{XC}}$ ) significantly improves the descrip-

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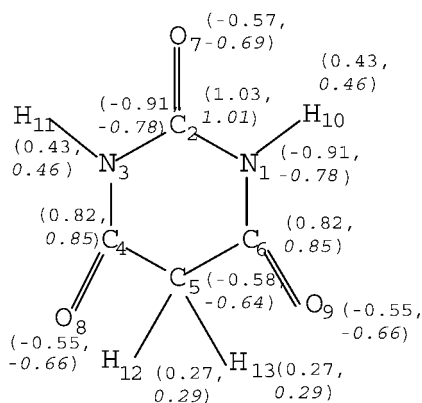


Figure 1. The geometrical arrangements and labeling of atoms of the triketo form of barbituric acid. Values given in parenthesis are individual atomic charges calculated from Mulliken and *NBO* population analysis schemes.

tion of hydrogen bonding over the local density approximation (LDA) and at the same time the situation is different for applications to complexes stabilized by the dispersion interactions [12–15]. Even though the exact  $E_{XC}$  contains dispersion term, the available LDA and GGA functionals do not have the correlation between different dipolar density functions [16]. Recently, a new functional have been included in the DFT to incorporate the dispersion term [12–15]. DFT methods are routinely used to study the molecular structure and interaction of molecules. Limited DFT studies have been performed for the hydrogen-bonded complexes [17–19]. Salahub and co-workers [20] have reported the DFT studies for water dimer, water-formaldehyde complex and it has been concluded that the LDA results are unreliable for the complexes.

A detailed analysis of the structural and energetic changes caused by the migration of hydrogen atom would enable us to understand the different properties of the tautomers. Most of the tautomers were not studied by experiment due to their low concentration and stability. Quantum chemical calculations are the best tools to study the relative stability of such tautomers. In addition to the relative stability, computational studies permit a direct analysis of physical and chemical properties of the molecules. Heterocyclic tautomeric equilibria are highly sensitive to environmental effects such as solvent polarity [21, 22]. Interactions between solute and solvent molecules are responsible for various physical, chemical properties and reactivity of solute. Knowledge of the changes in tautomerisation energy in an aqueous environment can give an idea about the role of solvent effect in molecular properties

such as bio-chemical processes. In the present study, solvent effect is studied by using self-consistent reaction field theory (SCRF). Each tautomer has different rotomers. The rotamer in which the migrating hydrogen atom is directed towards the atom from which it originated is more stable than the others, it concludes that after enolization there is no rotation about the C–O single bond. The purpose of this investigation is, to study the structure and relative stability of eleven tautomeric forms of the B.A. using *ab initio* and DFT methods. Moreover for the past few years, we have been working on isomer stability using chemical hardness values [23, 24]. The tautomeric form of B.A. is a good candidate to study chemical hardness, chemical potential and the maximum hardness principle. In addition to the above,  $^{13}\text{C}$ -NMR chemical shift studies have also been carried out for all the tautomers, which helps to study the different environments for carbon atoms in the tautomers.

### Computational details

The *ab initio* and density functional theory methods were used to optimize the geometry of tautomers of the B.A. All the calculations have been performed with the Gaussian 94W programme [25]. The restricted Hartree-Fock (RHF), Møller-Plesset perturbation theory (MP2) [26] of *ab initio* method and Becke's three parameter exact exchange functional (B3) [27] combined with gradient corrected correlation functional of Lee- Yang- Parr (LYP) [28] and Perdew and Wang's 1991 (PW91) [29] of DFT method were employed to optimize the tautomers by using the 6-31G\* basis set. The harmonic vibrational frequencies were calculated using the analytical second derivatives at the HF/6-31G\* level of theory. SCRF calculations have also been performed to optimize the tautomers at HF/6-31G\* level of theory. Tomasi et al.'s [30] self-consistent isodensity polarizable continuum model (SCI-PCM) has been used to evaluate the free energies of hydration. The chemical hardness ( $\eta$ ) and chemical potential ( $\mu$ ) have been calculated using the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energies determined by the HF/6-31G\* and MP2/6-31G\* levels of theory. The chemical hardness and chemical potential can be expressed with an orbital basis as

$$\eta = \frac{I - A}{2}, \quad \mu = -\frac{I + A}{2},$$

where  $I = -E_{\text{HOMO}}$  and  $A = -E_{\text{LUMO}}$ :  $I$  and  $A$  are the ionization potential and electron affinity of a molecule. NMR shielding tensors for carbon atoms in tautomers of B.A. have been calculated by using Gauge-independent atomic orbital (GIAO) method [31, 32].

## Experiment

$^{13}\text{C}$ -NMR spectra were recorded for the triketo form of barbituric acid on a Varian AMX-400 instrument in  $\text{D}_2\text{O}$  solvent in the range of 0 to 200 ppm using tetramethylsilane (TMS) as an internal standard.

## Results and discussion

The tautomers of the B.A. were optimized at HF, MP2, B3LYP and B3PW91 levels of theory using the 6-31G\* basis set and the optimized tautomers are presented in Figure 2. The structural parameters of the triketo form of B.A. are presented in Table 1 along with the crystal structure values of barbituric acid dihydrate [6]. Post Hartree-Fock and DFT methods are well known for the accurate prediction of vibrational frequencies [33–35]. The frequencies determined by the Hartree-Fock method is also very reasonable and suitable scaling factor is to be used to compare the experimental frequencies [36–38]. Since we are interested only to locate the transition state of the tautomers, the harmonic vibrational frequencies have been calculated using analytical second derivative at HF/6-31G\* level of theory. The calculated values indicate that the optimized tautomers are at stationary points, corresponding to local minima in the potential energy surface without an imaginary frequency. The bond lengths and bond angles calculated by MP2/6-31G\*, B3LYP/6-31G\* and B3PW91/6-31G\* levels of theory are found to be the similar. The optimized structural parameters of the triketo form in a polar medium are also presented in Table 1. The difference in structural parameters between the free barbituric acid and in polar medium at HF/6-31G\* level of theory is found to be very small. The noticeable difference in structural parameters between the experiment and theory is due to the fact that in crystalline state, there exist crystal forces and inter-molecular hydrogen bonding. A similar discrepancy was also observed in the previous studies on tautomers of 2-thiouracil [39]. The atomic charges of each atom of B.A. have been calculated by

using Mulliken and natural bond orbital (NBO) population analysis schemes at HF/6-31G\* level of theory and are presented in Figure 1. It is observed that the charge separation between the C2 and O7 carbonyl group is higher than those on the other two carbonyl groups. The nitrogen atoms N1 and N3 have equal negative charges, oxygen atoms O8 and O9 have also equal negative charges, and the carbon atoms C4 and C6 have equal positive charges, which indicate that the structure of B.A. has two fold symmetry. However, the experimental results do not favor the two fold symmetrical structure. The inertia defect ( $\Delta I$ ) calculated from the rotational constants show that the tautomers have planar structure (Table 2).

The relative energies of the tautomeric forms calculated at various levels of theory are presented in Table 2. The relative stability of the different tautomeric forms is of fundamental importance for the prediction of the probability of spontaneous mutations in bio-mechanisms. The Semi-empirical method, MNDO has predicted that the trihydroxy form is the most stable form [7], which is in disagreement with all the experimental results [6, 40]. The other two methods AM1 and PM3 favor the stability orders as  $1 > 2 > 3 > 4 > 8 > 5 > 11 > 9 > 10$  and  $1 > 2 > 3 > 4 > 11 > 8 > 5 > 9 > 10$ , respectively. In the present study, *ab initio* and DFT methods predict that, among the eleven tautomeric forms, the triketo form (1) is found to be the most stable form and is followed by mono hydroxy forms, 2,4-diketo 6-hydroxy (2,3), 4,6-diketo 2-hydroxy (4) forms. The trihydroxy form (11) is the next stable form and one of the 4,6 dihydroxy forms (7) is the least stable form. Figure 3 illustrates that the order of stability is decreasing as  $1 > 2 > 3 > 4 > 11 > 8 > 5 > 10 > 6 > 9 > 7$  in all the considered levels of theory. The MP2/6-31G\* level of theory, the 2-keto 4,6 dihydroxy form (6) is slightly lower in energy (0.25 kcal/mol) when compared with 4-keto 2,6-dihydroxy form (10). The order of stability obtained by the PM3 method coincides well with the higher level of *ab initio* and DFT methods. It has been reported that the role of electron correlation energy and zero point vibrational effects did not have significant effect on relative stabilities of tautomers [41]. Moreover, some of our recent studies indicate that the DFT methods are capable of producing results comparable to the high cost *ab initio* and experimental results [24, 42]. Since the relative energies of the tautomers are more than 12 kcal/mol in all the levels of theory, the omission of electron correlation and dispersion en-

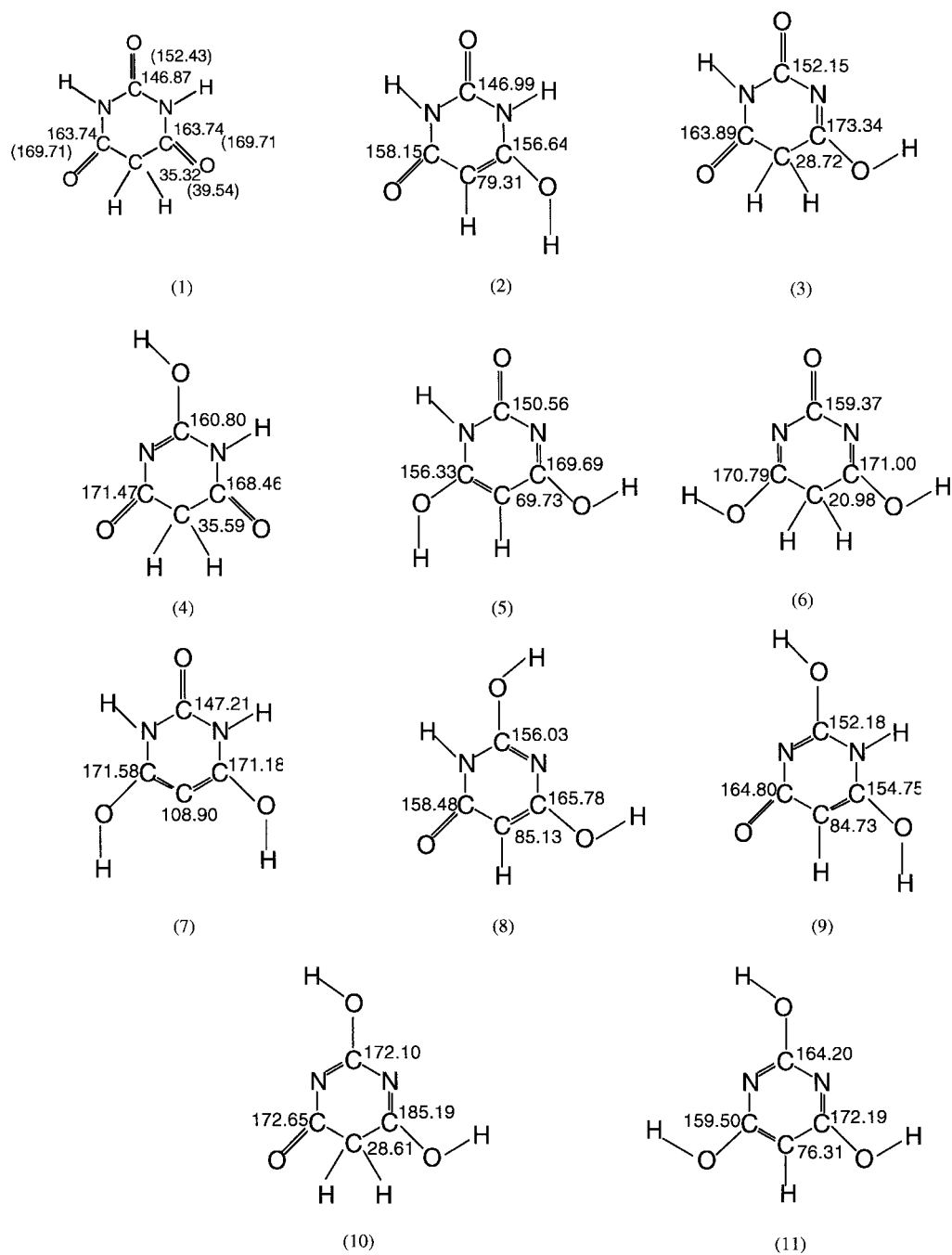


Figure 2. Schematic representations of various barbituric acid tautomers along with the  $^{13}\text{C}$ -NMR chemical shift data. Values given in parenthesis are experimental values.

Table 1. Geometrical parameters (bond length in Å, bond angle in degrees) of the triketo form of barbituric acid in gaseous and polar mediums.

Parameters <sup>a</sup>	HF	MP2	B3LYP	B3PW91	Expt. <sup>b</sup>	SCRF - HF	RMSD
R(N1-C2)	1.376	1.391	1.393	1.389	1.378	1.372	0.009
R(C2-N3)	1.376	1.391	1.393	1.389	1.356	1.372	0.014
R(N3-C4)	1.375	1.389	1.390	1.386	1.388	1.370	0.008
R(C6-N1)	1.375	1.389	1.390	1.386	1.367	1.370	0.010
R(C4-C5)	1.510	1.512	1.519	1.514	1.503	1.506	0.006
R(C5-C6)	1.510	1.512	1.519	1.514	1.501	1.506	0.006
R(N1-H10)	0.999	1.017	1.014	1.014	–	1.001	0.008
R(N3-H11)	0.999	1.017	1.014	1.014	–	1.001	0.008
R(C2=O7)	1.188	1.219	1.213	1.211	1.217	1.195	0.013
R(C4=O8)	1.188	1.222	1.213	1.212	1.211	1.194	0.012
R(C6=O9)	1.188	1.222	1.213	1.212	1.219	1.194	0.014
R(C5-H12)	1.083	1.095	1.096	1.096	–	1.083	0.007
R(C5-H13)	1.083	1.095	1.096	1.096	–	1.083	0.007
θ(N3C2N1)	115.2	114.2	114.6	114.6	118.0	116.0	1.405
θ(C4N3C2)	127.7	128.2	128.1	128.1	125.5	127.1	1.038
θ(C5C4N3)	116.1	115.7	115.6	115.5	117.4	116.5	0.723
θ(C6C5C4)	117.2	118.0	118.0	118.1	115.8	116.9	0.897
θ(H10N1C2)	115.4	115.2	115.2	115.1	–	115.7	0.238
θ(H11N3C2)	115.4	115.2	115.2	115.1	–	115.7	0.238
θ(O7C2N1)	121.4	122.9	122.7	122.7	119.3	122.0	1.362
θ(O8C4N3)	122.4	121.4	121.4	121.4	118.7	121.3	1.246
θ(O9C6N1)	122.4	121.4	121.4	121.4	119.6	121.3	0.907
θ(H12/13C5C4)	108.2	108.2	108.2	108.2		108.2	–

<sup>a</sup>For numbering of atoms see Figure 1.

<sup>b</sup>values are taken from [6].

ergies in HF and DFT methods did not affect the order of stability.

Since the Huckel's rule for aromaticity  $[(4n + 2) = \text{number of } \pi\text{-electrons: for aromaticity } n \text{ should be integer}]$  is not satisfied for B.A., the complete enol form (11) is less stable than the keto form (1). In general the keto form has higher stability than the corresponding enol form, which is associated with the much stronger double bond of  $\text{C=O}$  compared with the strength of  $\text{C=C}$  and  $\text{C=N}$  bonds. Among the 2,4-diketo 6-hydroxy forms (2 and 3), the stability of form 2 over 3 reveals that the migration of a methylene hydrogen is preferred. The relative instability of 4 over 3 indicates that the migration of the imine hydrogen to oxygen leads to lesser stability. The dipole moments of rotational tautomers indicate that the less stable tautomer has higher dipole moment and it is possible to gain stability in a polar medium [43]. The tautomers of B.A. were optimized at SCRF-HF/6-31G\* level of theory to study the effect of a polar medium on the relative stability. The relative energies of tautomers in the polar

medium are presented in Table 2, and it is found that except for the trihydroxy form, the relative energies of all the other forms decrease from their respective values in the gas phase, which indicates that the tautomers with partially enolized forms can be stabilized in aqueous medium. It is interesting to note that in the gas phase partially enolized forms have higher dipole moments compared with the triketo and trihydroxy forms of all the considered levels of theory (Table 2). Except for the dihydroxy forms the order of stability is same as in gas phase. The partially enolized tautomers, which have higher dipole moment in gas phase can be stabilized in polar environment. In aqueous phase the following stability order is arrived for tautomers of B.A.;  $1 > 2 > 3 > 4 > 8 > 5 > 11 > 9 > 10 > 6 > 7$ .

The chemical hardness ( $\eta$ ) and chemical potential ( $\mu$ ) are important tools to study the stability of a molecule or to study the relative stabilities of different conformers of a molecule. The chemical hardness received much attention after the invention of Pearson's maximum hardness principle (MHP), which states that

Table 2. Total energies  $E$  (in Hartree), relative energies  $\Delta E$  (in kcal/mol), dipole moment  $\mu_m$  (in debye) and inertia defect  $\Delta I^*$  (in amu  $\text{\AA}^2$ ) in the gas phase and in solution.

Level of theory / Parameters	Triketone (1) <sup>a</sup>	2,4-diketone 6-hyd (2)	4,6-diketone 6-hyd (3)	4,6-diketone 2-hyd (4)	2-keto 4,6-dihyd (5)	2-keto 4,6-dihyd (6)	4-keto 2,6-dihyd (7)	4-keto 2,6-dihyd (8)	4-keto 2,6-dihyd (9)	Trihyd (10)	Trihyd (11)
<b>HF/6-31G*</b>											
-E(480+)	7.36053	7.33443	7.33175	7.32475	7.31108	7.30001	7.24942	7.31803	7.29711	7.30286	7.31977
$\Delta E$	0.00	16.38	18.06	22.45	31.03	37.97	69.72	26.67	39.79	36.19	25.58
$\mu_m$	0.293	4.786	3.759	3.718	6.345	5.470	1.599	5.737	6.050	4.118	1.645
$\Delta I$	-2.90	-0.06	-2.76	-2.81	-0.03	-3.17	-0.03	-0.20	-0.06	-3.24	-0.03
<b>MP2/6-31G*</b>											
-E(480+)	8.69756	8.67161	8.67010	8.66181	8.64969	8.64063	8.59548	8.65712	8.63688	8.64024	8.65871
$\Delta E$	0.00	16.28	17.23	22.43	30.04	35.72	64.05	25.37	38.07	35.97	24.38
$\mu_m$	0.322	4.911	3.864	3.732	6.518	5.658	1.751	5.836	6.187	4.138	1.655
$\Delta I$	-2.92	-0.24	-3.81	-3.31	-1.04	-3.06	-0.01	-7.29	-0.20	-3.02	-0.02
<b>B3LYP/6-31G*</b>											
-E(489+)	1.05998	1.03723	1.03358	1.02584	1.01602	1.00369	0.96162	1.02316	1.00216	1.00560	1.02362
$\Delta E$	0.00	14.31	16.57	21.46	27.61	35.33	61.74	23.09	36.27	34.13	22.84
$\mu_m$	0.043	4.500	3.250	3.543	5.860	4.887	1.589	5.292	5.674	3.751	1.527
$\Delta I$	-2.89	-0.53	-2.83	-3.33	-0.06	-3.36	-0.10	-0.17	-0.18	-2.88	-0.13
<b>B3PW91/6-31G*</b>											
-E(480+)	9.87610	9.85392	9.84940	9.84170	9.83256	9.8190	9.77906	9.83975	9.81857	9.82140	9.84022
$\Delta E$	0.00	13.93	16.75	21.58	27.29	35.83	60.86	22.84	36.08	34.32	22.53
$\mu_m$	0.042	4.544	3.306	3.586	5.902	4.985	1.580	5.346	5.745	3.808	1.547
$\Delta I$	-2.88	-0.02	-3.20	-3.19	-0.96	-3.01	-0.09	-0.35	-0.34	-3.12	-0.18
<b>SCRF-HF/6-31G*</b>											
-E(480+)	7.38245	7.36148	7.35663	7.35049	7.34121	7.32763	7.27135	7.34172	7.32978	7.32864	7.33692
$\Delta E$	0.00	13.16	16.20	20.05	25.88	34.40	69.71	25.56	33.05	33.76	28.57
$\mu_m$	0.201	6.559	5.001	5.332	8.312	7.857	2.108	7.837	8.685	5.717	2.113
$\Delta I$	-2.96	-0.06	-3.30	-2.88	-0.28	-3.25	-0.02	-0.05	-0.17	-3.25	-0.06

\*  $\Delta I = I_C - I_B - I_A$ ,  $I_A = h/(8\pi^2 R_A)$ , etc.

<sup>a</sup>Numbers refer to the labels for tautomers used in Figure 2.

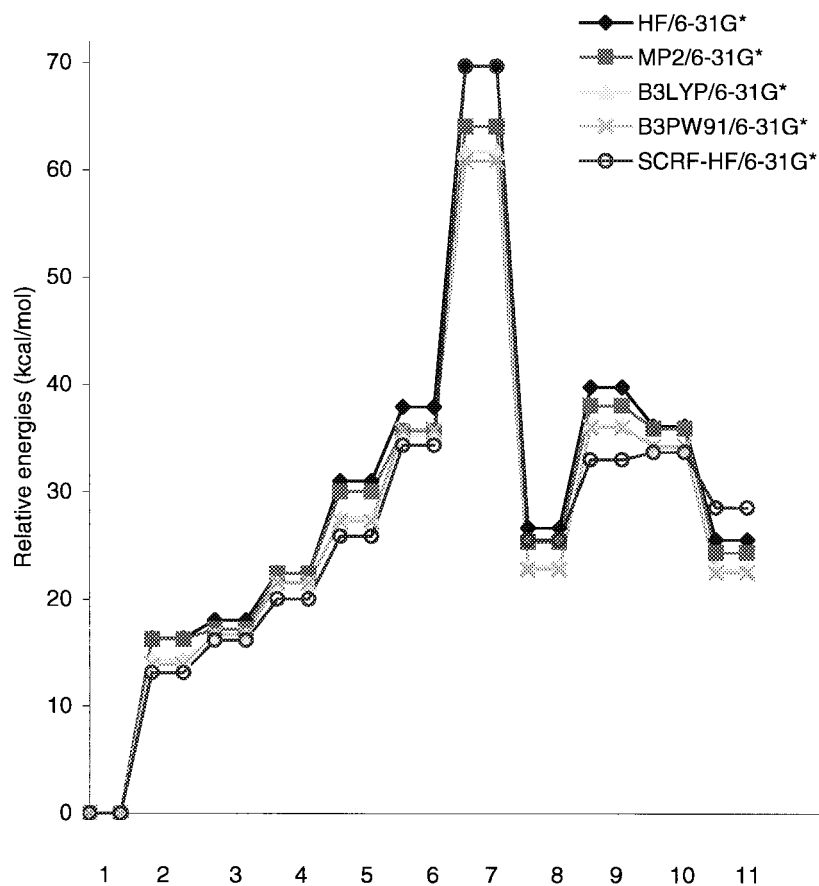


Figure 3. Relative energies of the barbituric acid tautomers calculated at various levels of theory. Numbers in X-axis represents labeling of tautomers as in Figure 2.

Table 3. Chemical hardness (in eV) and Chemical potential (in eV) for the tautomeric forms of barbituric acid in gas and polar mediums.

Tautomers	HF		MP2		HF-SCRF	
	$\eta$	$\mu$	$\eta$	$\mu$	$\eta$	$\mu$
Triketo (1) <sup>a</sup>	7.58	-4.52	7.43	-4.76	7.64	-4.10
2,4-diketo 6-hyd (2)	6.75	-5.97	6.59	-3.21	6.67	-2.62
2,4-diketo 6-hyd (3)	7.24	-4.53	7.02	-4.70	7.36	-4.21
4,6-diketo 2-hyd (4)	7.00	-4.19	6.82	-4.37	7.00	-3.84
2-keto 4,6-dihyd (5)	6.47	-2.99	6.33	-3.22	6.48	-2.65
2-keto 4,6-dihyd (6)	7.07	-4.34	6.82	-4.47	7.13	-4.11
2-keto 4,6-dihyd (7)	5.95	-2.87	5.88	-3.11	6.00	-2.50
4-keto 2,6-dihyd (8)	6.38	-2.75	6.25	-2.95	6.45	-2.50
4-keto 2,6-dihyd (9)	6.83	-2.54	6.64	-2.75	6.78	-2.37
4-keto 2,6-dihyd (10)	6.55	-4.21	6.41	-4.36	6.63	-3.90
Trihyd (11)	6.78	-2.76	6.67	-3.00	6.78	-2.53

<sup>a</sup>Numbers refer to the labels for tautomers used in Figure 2.

the minimum energy structure has the maximum hardness. Recent studies on the structure and conformational stabilities of aldoxime [36] and nitrosoethylene [24] shows that the maximum hardness principle could predict the stable conformer except for the structures stabilized by intra-molecular hydrogen bonding. In the present study  $\eta$  and  $\mu$  of all the tautomers of B.A. are calculated from orbital energies calculated at the HF/6-31G\*, MP2/6-31G\* levels of theory for the gas phase and at HF/6-31G\* level of theory for the aqueous phase, and the values are presented in Table 3. Both in the gas and aqueous phases, the triketo form (1) has the highest value of chemical hardness, which is the minimum energy tautomer, and the less stable tautomer 7 (2,4-diketo 6-hydroxy form) has the lowest value of chemical hardness. In the keto form, the HOMO energy is due to the out of plane orbital of N1, O8 and N3 atoms (for numbering see Figure 1), and the LUMO energy is due to the  $\pi^*$  orbital of carbonyl bonds. The charge transfer from ring carbon atom to oxygen and nitrogen atoms is less and so the energy gap is a maximum in the keto form. The migration of hydrogen to oxygen induces the delocalization of the electrons in the HOMO, which creates the change in external potential. Since, the electrons in the HOMO and LUMO of the enol form are localized with the ring carbon atoms, it decreases the energy gap. The studies on MHP shows that it could predict the stable structure for the geometrical isomers where the chemical potential ( $\mu$ ) and external potential ( $v(r)$ ) are more or less constant and it could not predict the stable structure for the positional isomers where  $\mu$  and  $v(r)$  are not constant [23]. In the present study, the chemical hardness values of tautomers decreases in the following order  $1 > 3 > 6 > 4 > 9 > 11 > 2 > 10 > 5 > 8 > 7$ . It is noted that though the MHP is able to predict the most stable and the least stable tautomers, it could not predict the order of stability. This is due to the fact that, since the tautomers were formed due to the migration of hydrogen atom(s), it makes a rapid change in chemical potential and external potential. Again, the above result confirms that the MHP is not applicable for the positional isomers. It is also observed that the above order is not changed in aqueous phase, which shows that there is no net change in orbital energies due to SCRF calculation.

Study of NMR chemical shift serves several useful purposes and it is useful to detect the presence or absence of particular atom in a particular position of a molecule. The shielding for atoms like carbon is affected greatly by what is bounded and the types

of bonds to neighbours. Identical nuclei (same atoms) give rise to different chemical shift value ( $\delta$ ) when they are in different environments. This study provides a test of theoretical models via a comparison with the experimental data, and the results may be interpreted in such a way that the origin of the chemical shielding is studied. In the present investigation the chemical shift for carbon atoms in 2, 4, 5 and 6 positions of tautomers of B.A. were studied at B3PW91/6-311+G(2d,p)//B3PW91/6-31G(d) level of theory. The shielding ( $\sigma$ ) is related to the chemical shift ( $\delta$ ) by

$$\delta = \text{Shielding for carbon atom in TMS}(\sigma_{\text{TMS}}) - \sigma.$$

The calculated shielding value for carbon atoms in tetramethylsilane (TMS) is 180.67 ppm. The calculated chemical shift value for carbon atoms C2, C4, C5 and C6 in the triketo form of B.A. is presented in Figure 2 along with the experimental values. To test the theoretical values, the  $^{13}\text{C}$ -NMR spectra for B.A. was measured in  $\text{D}_2\text{O}$  solvent. It is found that the difference between theoretical and experimental values is very small (4–6 ppm).

The chemical shift value for each carbon atom in all the other tautomers is also presented in Figure 2. The calculated values agree well quantitatively and qualitatively with the experimental results [44]. Here, for simplicity it is enough to discuss the chemical shift value for carbon atoms in the triketo (1) and 2,4-diketo 6-hydroxy forms (2 and 3). In the triketo form, since the carbon atoms C4 and C6 have the same environment they have a similar chemical shift value (163.74 ppm). For the other keto carbon C2, the chemical shift is 146.67 ppm. In general carbon atoms bonded to the two hetero atoms is more shielded than the carbon atom in which one side is carbon and other side is a hetero atom (N). The chemical shift of the fifth carbon is very small (35.32 ppm) compared with the  $\delta$  value for other carbons. The hybridization involved in C5 is  $\text{sp}^3$  which has a greater ability to oppose the applied field compared with the  $\text{sp}^2$  hybridized orbital and the  $\delta$  value of carbon atoms with a  $\text{sp}^3$  hybridized orbital has a lower value. In other words the methine carbon (C5) is more shielded than the methylene carbon. The hybridization involved in the carbon atoms at 2, 4 and 6 positions is  $\text{sp}^2$ . The carbon atom in the second position of the 2,4-diketo 6-hydroxy form (2) has the same value of  $\delta$  as in the triketo form. Here enolization is due to the migration of H atom from C5 to oxygen atom in C6 and there is a double bond between C5 and C6 atoms. The enolization increases the chemical shift for C5 atom



(79.31 ppm) and decreases it for the carbon atoms at 4 and 6 positions. So the C5 carbon atom is deshielded and the atoms C4 and C6 are shielded. The other 2,4-diketo 6-hydroxy form (3) is formed due to migration of H atom from imine group (N1) to the oxygen atom in C6 and the double bond between the hetero atoms N1 and C6 leads to a increase in the chemical shift for the carbon (C6). Since the nitrogen atom has greater electronegativity, it can attract the electrons centered on the carbon atom, and it leads to down shielding for carbon atom. Moreover, the double bond between C and N atoms decreases the distance between them and it leads to a increase in the chemical shift of the carbon atom. It is interesting to note that for all the tautomers except the 7th tautomer (which is less stable), in general, if the enolization is due to the migration of H atom from methylene group, the enol carbon is shielded and if the H atom migrate from imine group, the enol carbon is deshielded.

## Conclusions

Tautomers of barbituric acid were studied by using *ab initio* and density functional theory methods, and the following conclusions have been reached:

- (i) The triketo form of barbituric acid is found to be the most stable form in the gas phase and in solution, which is in agreement with the experimental result.
- (ii) Since there are no imaginary frequencies in the vibrational spectra, all the tautomers are present at the stationary points corresponding to local minima in the potential energy surface. The agreement between the calculated and experimental structural parameters of triketo form is found to be fairly good. The small discrepancy may be due to the fact that in crystalline state there are crystal forces and inter-molecular hydrogen bonding are present, which are absent in gaseous medium.
- (iii) The maximum hardness principle is able to predict the most stable and least stable tautomers. But, it could not predict the order of stability and this may be due to the change in chemical potential and external potential caused by enolization.
- (iv) Tautomers, which are partially enolized forms, have higher dipole moments in gas phase are stabilized in polar medium.
- (v) The calculated  $^{13}\text{C}$ -NMR chemical shift values agree well with the experimental results. So, the higher level of density functional theory method is a suitable method to study the chemical shift.

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