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Moroxydine Tautomers - A DFT Treatment

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Abstract

Moroxydine is an orally active non-nucleoside type antiviral agent of biguanide structure. Biguanides constitute an important class of therapeutic agents suitable for the treatment of a wide spectrum of diseases. In the present density functional study (B3LYP/6-311++(d,p)) tautomers of moroxydine have been investigated within the constraints of the theory and the basis set employed. Moroxydine may exhibit 1,3- and 1,5-type proton tautomerism. Presently, all those possible tautomeric forms are considered. All the tautomers are electronically stable and have thermo chemically favorable formation values at the standard conditions. Some quantum chemical and spectral properties of those tautomeric systems have been obtained and discussed. The effect of tautomeric variations on the chemical function descriptors have been determined. Also, the variation of polar surface areas of the tautomers have been considered in relation to their ability to penetrate the blood-brain barrier.

1. Introduction

Moroxydine (4-morpholinecarboximidoylguanide) (Figure 1) is an orally active non-nucleoside antiviral agent of biguanide structure. Moroxydine hydrochloride (Mor) was discovered as an antiviral agent with biguanide structure in the 1950's and it has been reported having a number of antiviral activities against various DNA and RNA viruses, including influenza symptoms, herpes simplex, varicella-zoster, measles, mumps disease, hepatitis C virus, *etc*. [1-5]. Schersten reported the use of moroxydine against herpes zoster virus [6]. In 1960, Melander published a report on the synthesis and activity of moroxydine against influenza virus in mice and further explored the pharmacological actions in animals and humans [7]. Sjoberg reported the prophylactic and suppressive

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activity in clinical influenza [8]. Later, in 1962, Nasemann et al., reported the in vitro inhibitory activity of N',N-anhydrobis (2-hydroxyethyl)- biguanide HC1 (ABOB) in herpes simplex virus [7]. In 1966 Kaji et al., tested the activity of ABOB against adeno virus [9]. The authors, further, reported its use in the treatment of pharyngoconjuctival fever. This drug exhibits reduction in the duration of fever and pharyngitis [10]. Nakao synthesized and tested the benzene sulphonyl derivatives of moroxydine which showed inhibitory action against poliovirus [11]. Moroxydine was also tested in measles [12], chickenpox [13] and different dermatological diseases [14] but the results were found negative.

Biguanides have attracted considerable attention a century ago and showed resurgent interest in recent decades after a long period of dormancy. Biguanides are compounds in which structurally two guanidine moieties are fused to form a highly conjugated system. Biguanides are highly basic and hence they are available as salts (mostly hydrochloride salts). They constitute an important class of therapeutic agents which have been suitably used for the treatment of a wide spectrum of diseases. Biguanide derivates usually have an antihyperglycemic effect, and therefore some biguanides are used in the treatment of diabetes mellitus. In addition, heterocyclic guanidine derivatives were found to have an inhibitory effect on viral growth, which led to the marketing of the first antiviral drugs, moroxydine (as trade name of Flumidin, Virustat, Influmin, Spenitol, Morgalin).

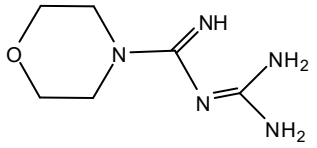


Figure 1. 2D- structure of moroxydine.

Other aspects of moroxydine and some other biguanidine derivatives have been the focus of investigations [15-20]. Although mechanism of action of moroxydine is not fully known the effects seem to be due to an influence on the virus host-cell system.

In the present density functional study, tautomers of moroxydine have been investigated within the constraints of the theory and the basis set employed.

2. Method of Calculations

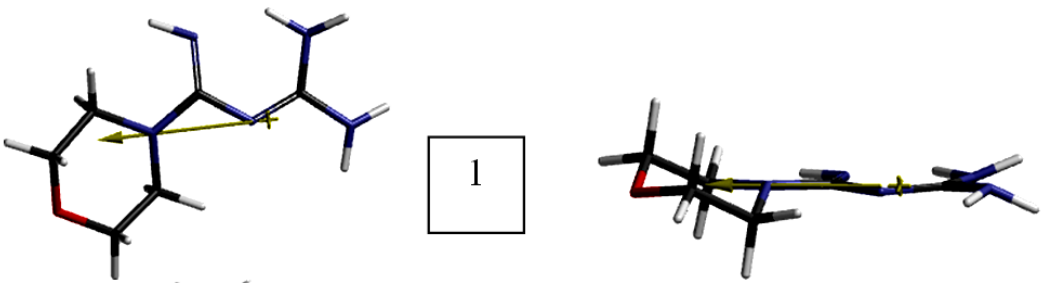
In the present DFT study, all the initial geometry optimizations of the moroxydine tautomers leading to energy minima have been achieved by using molecular mechanics (MM2) method then the structures were subjected to semi empirical PM3 self consistent

fields molecular orbital (SCF MO) method [21,22] at the restricted level [23]. Afterwards, the structure optimizations have been managed within the framework of Hartree-Fock (HF) and finally by using density functional theory (DFT) at the level of B3LYP/6-311++G(d,p) [24,25]. Note that the exchange term of B3LYP consists of hybrid Hartree-Fock and local spin density (LSD) exchange functions with Becke's gradient correlation to LSD exchange [26]. Also note that the correlation term of B3LYP consists of the Vosko, Wilk, Nusair (VWN3) local correlation functional [27] and Lee, Yang, Parr (LYP) correlation correction functional [28]. In the present treatment, the normal mode analysis for each structure yielded no imaginary frequencies for the 3*N*–6 vibrational degrees of freedom, where *N* is the number of atoms in the system. This search has indicated that each structure corresponds to at least a local minimum on the potential energy surface. Furthermore, all the bond lengths have been thoroughly searched in order to find out whether any bond cleavages have occurred or not during the geometry optimization process. All these computations were performed by using SPARTAN 06 program [29].

3. Results and Discussion

Figure 2 shows the optimized structures of the tautomers of present interest. They are 1,3- and 1,5-type proton tautomers. However, in the figure, structures-1 and 5 are actually different conformers of the same tautomer detected.

Table 1 lists some thermo chemical values of the tautomers considered. As seen in the table all the tautomers possess exothermic heat of formation and favorable Gibb's energy of formation values at the standard states. The orders of H^o and G^o values (algebraically) are 5<1<2<4<3 and 1<5<2<4<3, respectively. The change of positions of tautomer-1 and 5 in the orders of H^o and G^o values is due to their entropy values. Tautomer-3 is less exothermic and less favorable than the others.



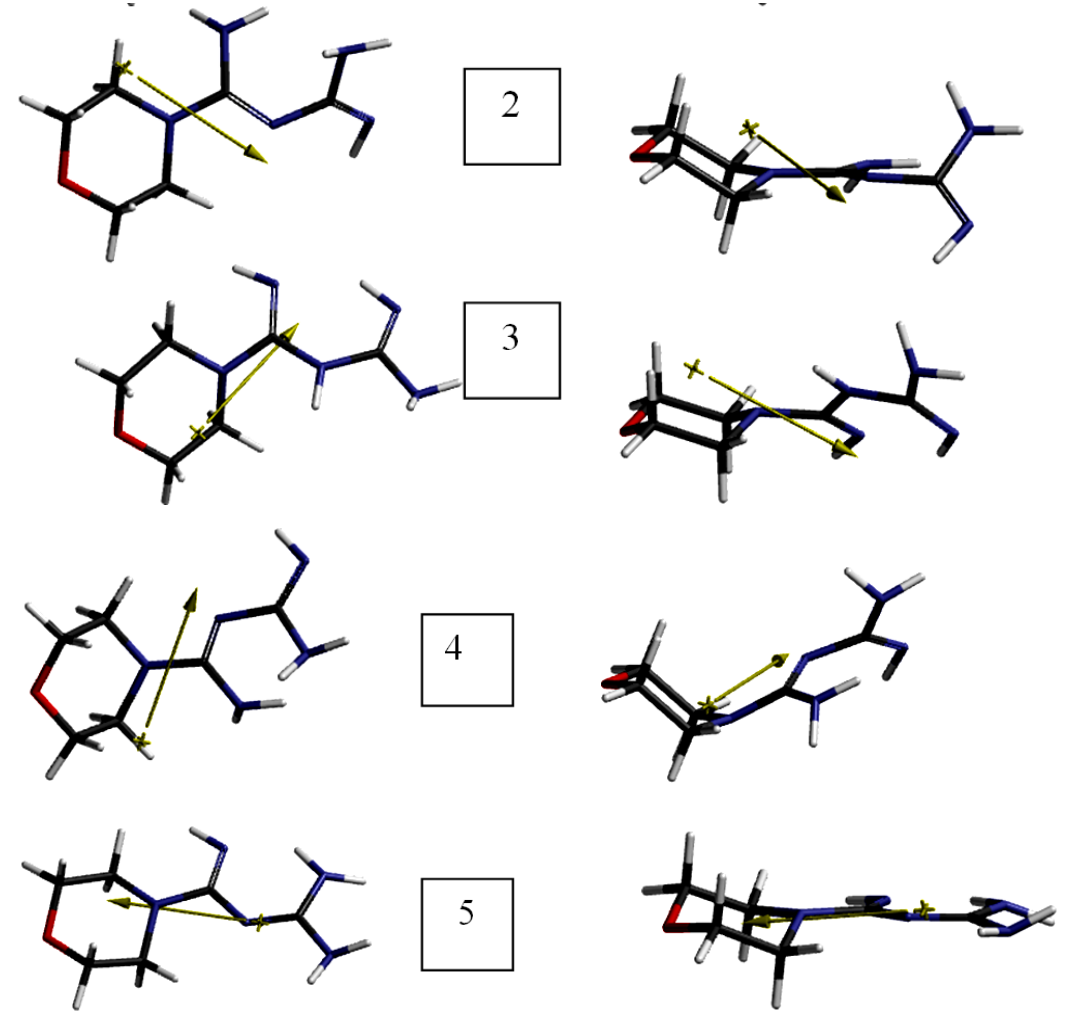


Figure 2. Optimized structures of the tautomers of present interest (Top and side views).

Table 1. Some thermo chemical values of the tautomers considered.

Tautomer	Hº	Sº (J/molº)	Gº
1	-1536977.077	409.98	-1537099.313
2	-1536949.288	409.79	-1537071.467
3	-1536926.596	409.71	-1537048.754
4	-1536948.220	406.79	-1537069.506
5	-1536977.221	408.83	-1537099.116

Energies in kJ/mol.

Table 2 lists some energies of the tautomers considered where E, ZPE and E_C stand for the total electronic energy, zero point vibrational energy and the corrected total electronic energy, respectively. As seen in the table all the tautomers considered are electronically stable and the stability order is 5>1>2>4>3.

Table 2. Some energies of the tautomers considered.

Tautomer	E	ZPE	E_C
1	-1537550.85	558.48	-1536992.37
2	-1537524.77	560.26	-1536964.51
3	-1537501.95	560.17	-1536941.78
4	-1537523.92	560.84	-1536963.08
5	-1537551.58	559.18	-1536992.40

Energies in kJ/mol.

Table 3 displays some calculated properties of the tautomers considered. The data in Table 3 reveal that in aqueous solution the stability order is 5>1>2>4>3. Note that tautomer-5 is solvated better than tautomer-1 while keeping in mind that relationship between those are conformational. The order of dipole moments is 3>2>4>5>1.

Table 3 . Some calculated properties of the tautomers considered.

Tautomer	E_{aq} (kJ/mol)	Solvation Energy (kJ/mol)	Dipole	PSA (Å²)	Area (Å²)	Volume (Å³)	Pol.
1	-1537618.71	-67.86	2.45	77.067	194.40	167.45	53.65
2	-1537594.17	-69.40	4.18	79.574	196.45	168.52	53.74
3	-1537587.38	-85.43	4.59	79.987	196.34	168.60	53.64
4	-1537592.44	-68.52	3.85	80.588	197.22	168.78	53.75
5	-1537619.66	-68.08	2.46	77.178	194.45	167.46	53.64

E_{aq} : Aqueous energy, Pol.: Polarizability, Polarizabilities in 10^{-30} m^3 units. Dipoles in debye units.

Polar surface areas (PSA) of the tautomers is defined as the amount of molecular surface area arising from polar atoms (N,O) together with their attached hydrogen atoms. Molecules with PSA values greater than 140 Å² tend to be poor at permeating cell

membranes whereas to penetrate the blood-brain barrier a PSA value of a molecule should be less than 90 Å² [30,31]. All the tautomers of present interest seem to have quite good penetrating ability the blood-brain barrier having the order of ease of 1>5>2>3>4.

Table 4 lists the Boltzmann distributions and the relative energies of the tautomers considered. As seen in the table, structure-5 associated with a greater value of the distribution than structure-1 both in vacuum and aqueous conditions. Since, the relative energy of tautomer-5, (actually a conformer of tautomer-1) is a negative quantity then its contribution to the distribution is greater than the corresponding value of tautomer-1.

Table 4. The Boltzmann distributions and the relative energies of the tautomers considered.

Tautomer	Boltzmann Dist	Rel. E (kJ/mol)	Boltzmann Dist (aq)	Rel. E_{aq} (kJ/mol)
1	0.427	0.000	0.406	0.000
2	0.000	26.08	0.000	24.54
3	0.000	48.90	0.000	31.33
4	0.000	26.93	0.000	26.27
5	0.573	-0.73	0.594	-0.95

Figures 3 and 4 show the electrostatic potential (ESP) charges on atoms of the tautomers and the ESP maps of the tautomers, respectively. Note that the ESP charges are obtained by the program based on a numerical method that generates charges that reproduce the electrostatic potential field from the entire wavefunction [29]. It is seen from the figure that tautomerism in moroxydine affects the conformation (even in the morpholine ring system) and the ESP charges appreciably.

The ESP maps of the tautomers are shown in Figure 4 where the red and blue colors stand for negative and positive potential regions, respectively. In the figure, note the influence of tautomerism on the potential field over the whole system such that even the morpholine ring (which is not directly involved in the tautomerism) has been affected by the location of the tautomeric proton, thus possesses varying colors from one tautomer to other.

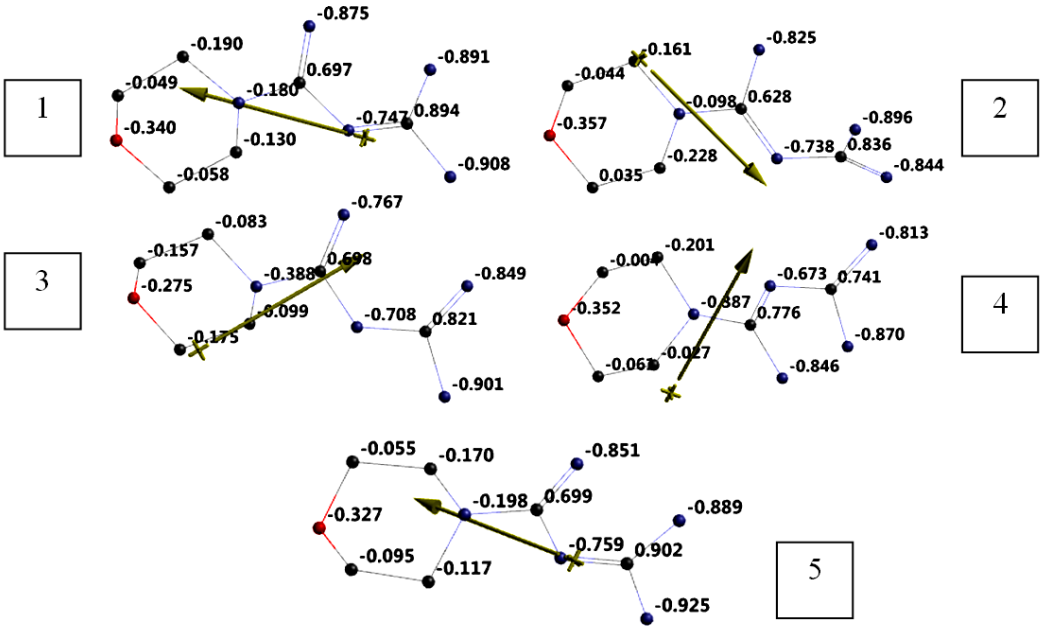


Figure 3. The ESP charges on atoms of the tautomers (Hydrogens not shown).

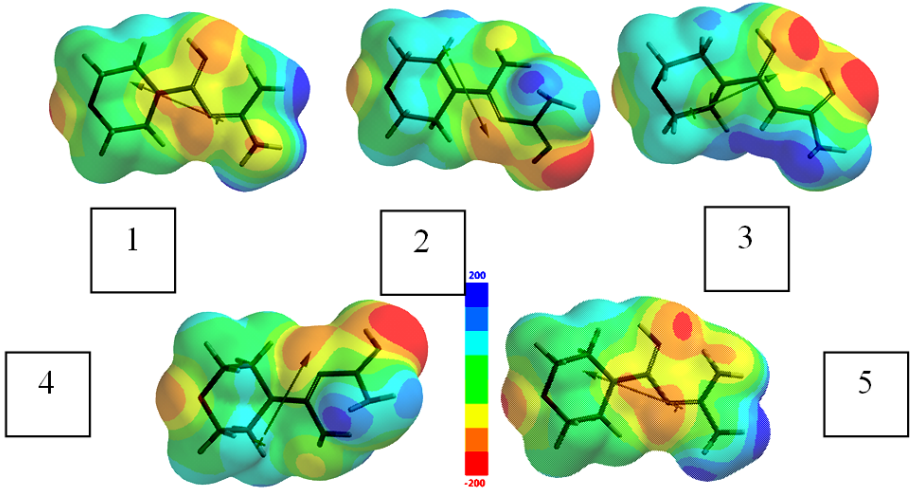


Figure 4. The ESP maps of the tautomers considered.

Figure 5 shows some of the of molecular orbital energy levels of the tautomers considered. The distribution patterns of the molecular orbitals are quite different for each tautomer, especially for tautomer-3.

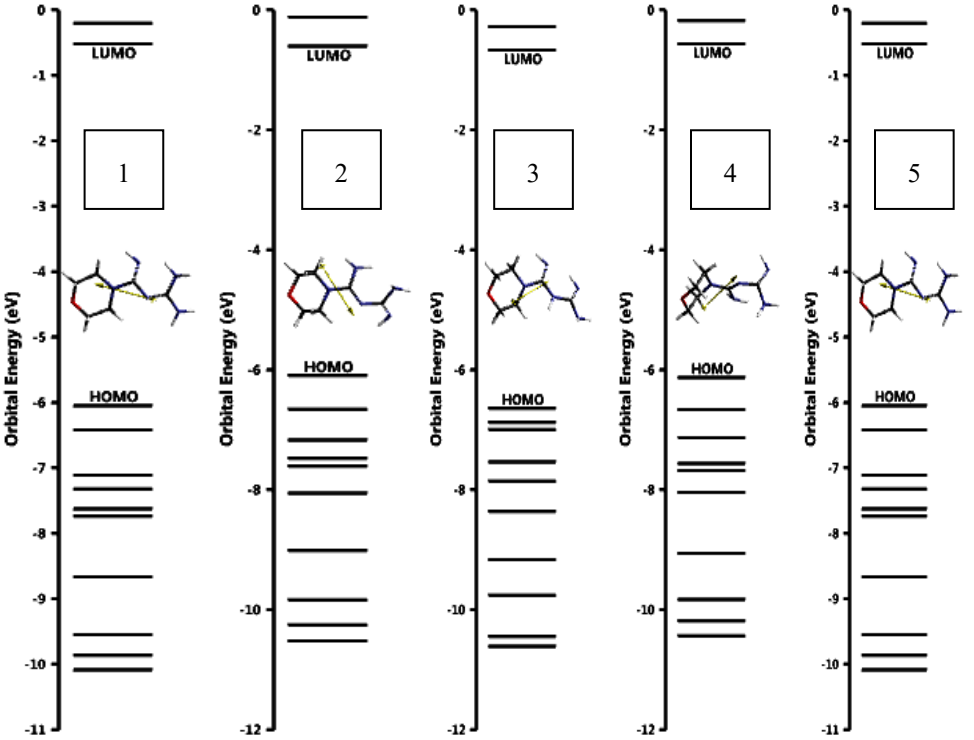


Figure 5. Some of the of molecular orbital energy levels of the tautomers considered.

The HOMO, LUMO energies (ε_{HOMO} and ε_{LUMO}, respectively) and intermolecular orbital energy gap $\Delta\varepsilon$ ($\Delta\varepsilon = \varepsilon_{LUMO}-\varepsilon_{HOMO}$) values of the tautomers are shown in Table 5. The data in the table reveal that the orders of the HOMO and LUMO energies are 3<4<2<5<1 and 3<2<4<1<5, respectively. Whereas, the order of $\Delta\varepsilon$ values is 3>4>5>1>2. Tautomer-3 is characterized with the lowest lying HOMO and LUMO energies, resulting in the largest intermolecular molecular orbital gap value.

The appearance of UV-VIS spectra of the tautomers are similar to each other. Table 6 shows the calculated λ_{max} values of the tautomers (the λ_{max} values follow the order of 4>5>1>2>3) and Figure 6 displays two representatives of the spectra. The spectra of the tautomers are not very different from each other in contrast to expectation based on their $\Delta\varepsilon$ values. That is because of the fact that the calculated spectra are not merely based on the HOMO and LUMO orbital energies but also some other molecular orbital energies are involved. Their UV-VIS spectra occur in the ultraviolet region only because there is no greatly extended conjugation in the structures.

Table 5. The HOMO, LUMO energies and Δε values of the tautomers considered.

Tautomer	HOMO	LUMO	Δε
1	-583.44	-50.13	533.31
2	-588.58	-58.30	530.28
3	-641.21	-64.41	576.8
4	-591.57	-54.36	537.21
5	-585.38	-48.43	536.95

Energies in kJ/mol.

Table 6. The calculated λ_{max} values of the tautomers.

1	2	3	4	5
220.15	218.01	209.53	226.58	223.04

λ_{max} values in nm.

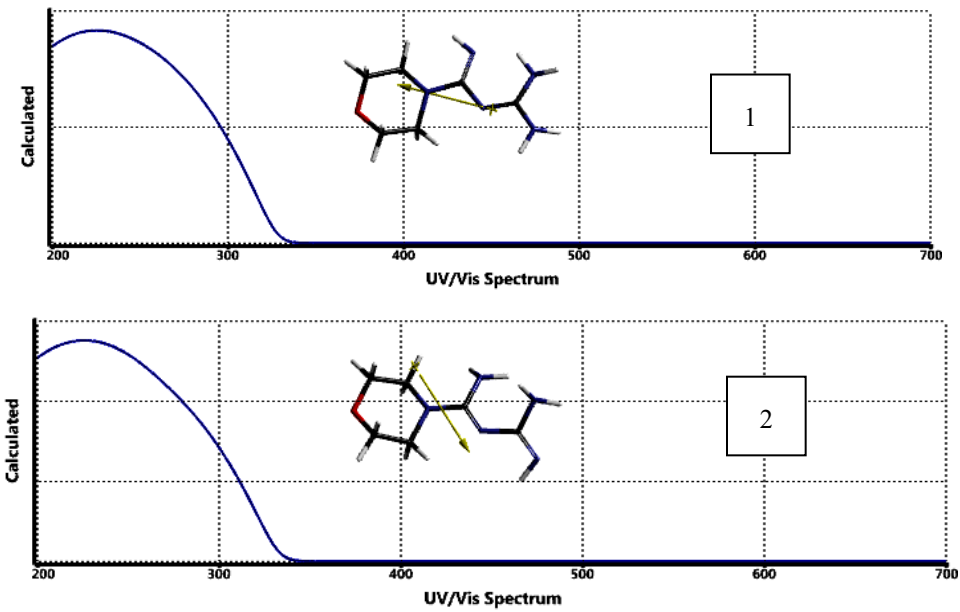


Figure 6. Two of the calculated UV-VIS spectrums of the tautomers considered.

The effect of tautomerism on the chemical function descriptors (CFD) of the tautomers are shown in Figure 7. Note that CFDs are attributes given to a molecule in order to characterize or anticipate its chemical behavior. In the figure different colors stand for different descriptors. Note that HBA and HBD mean hydrogen bond acceptor and donors, respectively.

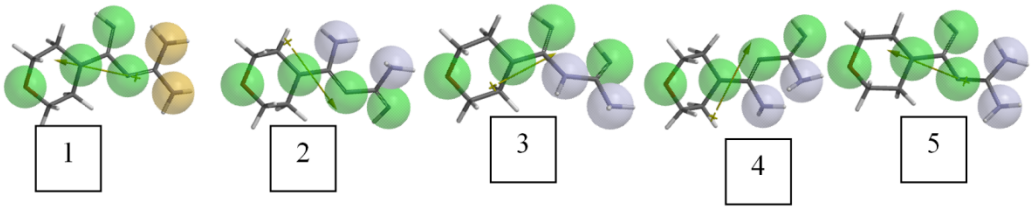


Figure 7. CFDs of the tautomers considered (Green: HBA; Yellow: HBA and HBD; Bluish: HBA , HBD and +ionizable).

4. Conclusion

Within the limitations of the theory and basis set employed, the present DFT treatment of moroxydine tautomers considered has indicated that in vacuum as well as in aqueous conditions, they are electronically stable and have thermo chemically favorable formation values. Their calculated properties are highly dependent on the tautomeric form, especially their solvation energies, dipole moments and polar surface areas whereas their UV-VIS spectra are similar to each other and occur in the ultraviolet region only.

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