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COMPUTATIONAL STUDIES OF STABILITY AND MOLECULAR DESCRIPTORS OF 2-PYRIDONE AND 2-PYRIDINETHIONE TAUTOMERS BY DENSITY FUNCTIONAL THEORY (DFT)

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ABSTRACT

Density functional theory (DFT) calculations were carried out to investigate the relative energies, thermodynamic properties, equilibrium constants and molecular descriptors of 2-pyridone and 2-pyridinethione tautomers in the gas phase. All possible tautomers are optimized with B3LYP/6- 311++G (d,p) basis set. It can be seen from the results that two are keto (P43HO & P34HO) and (P43HT & P34HT) tautomers have highest energy, with relative energy about 28-33 kcal mol^{-1}. From the HOMO and LUMO orbital energies, in order to determine, the global reactivity descriptors namely, the chemical hardness (η), chemical potential (μ), electrophilicity index (ω), softness (S), nucleofugality(ΔE_n), and electrofugality(ΔE_e), values for the prediction of the reactivity of the tautomers. From the electrophilicity index (ω) results, the tautomer P34HT is a good electrophile and P43HO is good nucleophile in gas phase.

KEYWORDS: Molecular descriptors, 2-pyridone and 2-pyridinethione tautomers, HOMO-LUMO energies and DFT calculations.

INTRODUCTION

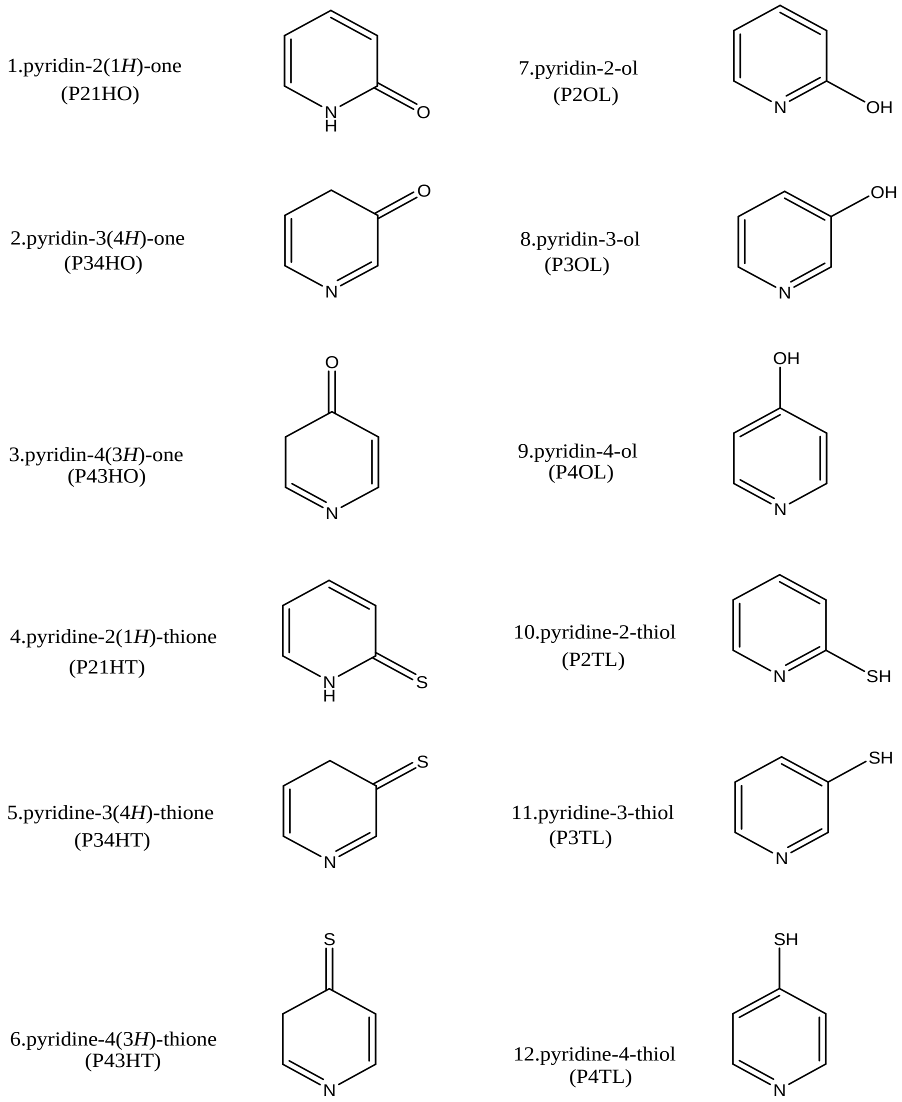
The heterocyclic skeleton containing nitrogen atom is the basis of many essential pharmaceuticals and of many physiologically active natural products. Molecules containing heterocyclic substructures continue to be attractive targets for synthesis since they often exhibit diverse and important biological properties. Accordingly, novel strategies for the stereo selective synthesis of hetero polycyclic ring systems continue to receive considerable attention in the field of synthetic organic chemistry.

Pyridine-2(1H)-one (2-Pyridone) is colorless crystalline solid is used in peptide synthesis. It is well known to form hydrogen bonded structures somewhat related to the base-pairing mechanism found in RNA and DNA. The most prominent feature of 2-pyridone is the amide group; a nitrogen with a hydrogen bound to it and a keto group next to it. In peptides, amino acids are linked by this pattern, a feature responsible for some remarkable physical and chemical properties. 2-Pyridone is rapidly degraded by microorganisms in the soil environment, with a half life less than one week.[1] Organisms capable of growth on 2-pyridone as a sole source of carbon, nitrogen, and energy have been isolated by a number of researchers. The most extensively studied 2-pyridone degrader is the gram positive bacterium Arthrobacter crystallopoietes,[2] a member of the phylum Actinobacteria which includes numerous related organisms that have been shown to degrade pyridine or one or more alkyl-, carboxyl-, or hydroxyl-substituted pyridines. Generally speaking, degradation of pyridones, dihydroxypyridines, and pyridinecarboxylic acids is commonly mediated by oxygenases, whereas degradation of pyridine solvents often is not, and may in some cases involve an initial reductive step.[3]

2-pyridinethione (2-Mercaptopyridine) is an organosulfur compound and this yellow crystalline solid is a derivative of pyridine. The compound and its derivatives serve primarily as acylating agents. A few of 2-mercaptopyridine's other uses include serving as a protecting group for amines and imides as well as forming a selective reducing agent. Pyridinethione derivatives belong to a class of cyclic sulfur organo products containing sulfur atom (S) and often oxygen (O), nitrogen (N), hydrogen (H), as well as other elements, can find application for making biologically active agents such as antiviral, antibacterial, antifungal, antituberculous, antbody and antifungal agents. Pyridinethione inhibits the growth of fungi, yeast, mold and bacteria. Sodium and zinc salt of pyrithione N-oxide are widely used in cosmetics and shampoo. In acidic media, amines N-oxides are cationic and can act as a mild conditioner. They are used in body care products.

COMPUTATIONAL DETAILS

Pyridine-2(1H)-one and pyridine-2(1H)-thione were existing three keto and three enol tautomers theoretically for each of them. Considering the position of oxygen atom (= O) and hydroxyl group (- OH), the number of the tautomers ascends to 12, and Scheme.1, illustrates the 12 tautomers.



Scheme 1. Pyridine-2(1H)-one and pyridine-2(1H)-thione possible tautomers.

All the geometries of the tautomers have been fully optimized using the B3LYP method within the framework of density functional theory (DFT) in conjunction with the 6-311++G (d,p) basis set, i.e., Becke's three parameter non-local hybrid exchange potential with the non-local correlation functional of Lee, Yang, and Parr.[4,5] Following the geometry optimizations, analytical frequency calculations were proceeded at the DFT/6-311++G (d,p) level, using following standard procedures, to obtain the thermochemical properties. All these calculations were carried out on a Pentium V personal computer by means of GAUSSIAN09 program package and for our computations.[6]

Density functional theory (DFT)[7] has been found to be successful in providing theoretical insights into the chemical reactivity and selectivity, in terms of popular qualitative chemical concepts like absolute electronegativity (χ), hardness (η), softness(S), electrophilicity index (ω), fractions of electrons transferred (ΔN), electron affinity (EA) , ionization potential (IP). These quantities have been calculated and were used to understand the chemical reactivity of molecular systems. The important quantities to be obtained are the frontier orbitals; the highest occupied orbital (HOMO) and the lowest unoccupied orbital (LUMO).

The basic relationship of the density functional theory of chemical reactivity is precisely, the one established by Parr, Donnelly, Levy and Palke[8], that links the chemical potential of DFT with the first derivative of the energy with respect to the number of electrons, and therefore with the negative of the electronegativity (χ).

$$\chi = -\mu = \left(\frac{\partial E}{\partial N}\right)_{V(\vec{r})} \quad (1)$$

Where μ is the chemical potential, E is the total energy, N is the number of electrons, and v(r) is the external potential of the system. Hardness (η) has been defined within the DFT as the second derivative of the E with respect to N as (v_r) property which measures both the stability and reactivity of the molecule.[9]

$$\eta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{V(\vec{r})} \quad (2)$$

Where, v(r) and μ are, respectively, the external and electronic chemical potentials.

According to, the Koopmans' theorem[10] for closed-shell molecules, ionization potential (IP) and electron affinity (EA) can be expressed as follows in terms of E_{HOMO} and E_{LUMO} the highest occupied molecular orbital energy, and the lowest unoccupied molecular orbital energy, respectively:

$$IP = -E_{HOMO} \text{ and } EA = -E_{LUMO} \quad (3)$$

When the values of IP and EA are known, one can determine through the following expressions[11] the values of the absolute electronegativity χ, the absolute hardness (η) and the softness (S):

$$\chi = \frac{I+A}{2} \text{ and } \eta = \frac{I-A}{2} \quad (4)$$

The global softness(s) is the inverse of the global hardness[12]

$$S = \frac{1}{\eta} \quad (5)$$

The electrophilicity is a descriptor of reactivity that allows a quantitative classification of the global electrophilic nature of a molecule within a relative scale. Parr have proposed electrophilicity index as a measure of energy lowering due to maximal electron flow between donor and acceptor and defined electrophilicity index (ω) as follows.[13]

$$\omega = \frac{\mu^2}{2\eta} \quad (6)$$

According to the definition, this index measures the propensity of chemical species to accept electrons. A good, more reactive, nucleophile is characterized by lower value of μ, ω and conversely a good electrophile is characterized by a high value of μ, ω. This new reactivity index measures the stabilization in energy when the system acquires an additional electronic charge Δ_{Nmax} from the environment.[13]

$$\Delta N_{\max} = -\frac{\mu}{\eta} \quad (7)$$

The maximum charge transfer ΔN_{max} towards the electrophile was evaluated using Eq. (7). Thus, while the quantity defined by Eq. (6) describes the propensity of the system to acquire additional electronic charge from the environment; the quantity defined in Eq. (7) describes the charge capacity of the molecule. Very recently, Ayers and coworkers[14,15] have proposed two new reactivity indices to quantify nucleophilic and electrophilic capabilities of a leaving group, nucleofugality (ΔE_n) and electrofugality (ΔE_e), defined as follows,

$$\Delta E_n = EA + \omega = \frac{(\mu+\eta)^2}{2\eta} \text{ and } \Delta E_e = IP + \omega = \frac{(\mu-\eta)^2}{2\eta} \quad (8)$$

RESULTS AND DISCUSSION

The equilibrium geometry optimization for the isomers has been achieved by energy minimization, using DFT at the B3LYP level, employing the basis set 6-311++G (d,p). The optimized geometry of the tautomers of 2-pyridone and 2- pyridinethione under study are confirmed to be located at the local true minima on potential energy surface, as the calculated vibrational spectra has no imaginary frequency. Optimized structures of the allopurinol predicted isomers are shown in Fig. 1.

The total and relative energies of 12 tautomers are presented in Table 1, among the 12 tautomers, six are keto (P21HO, P34HO, P43HO, P21HT, P34HT and P43HT) tautomers and six are (P2OL, P3OL, P4OL, P2TL, P3TL andP4TL) enol tautomers for of Pyridine-2(1H)-one and pyridine-2(1H)-thione respectively.

The most stable tautomer P21HO (Pyridine-2(1H)-one) and P21HT (pyridine-2(1H)-thione) are taken as reference to obtain the relative energetic stability of other tautomers. It can be seen from the results that two are keto (P43HO & P34HO) and (P43HT & P34HT) tautomers have highest energy, with relative energy about 28-33 kcal mol^{-1}, because of the possibility of formation of hydrogen bond between hydrogen of nitrogen and hetero atom little likely of more than atom, and hydrogen atom between heteroatom spatially close and separate by more than two atoms can be carried out. The total and relative energies of isomers are presented in Table 1, in bracket shows the energies in kcal/mol. In case of Pyridine-2(1H)-one, the order of relative stabilities for isomers in gas phase with respect to stable isomer for as following order respectively: P21HO > P2OL > P4OL > P3OL > P43HO > P34HO and in case of pyridine-2(1H)-thione the order of relative stabilities for isomers in gas phase with respect to stable isomer for as following order respectively: P21HT > P2TL > P4TL > P3TL > P43HT > P34HT.

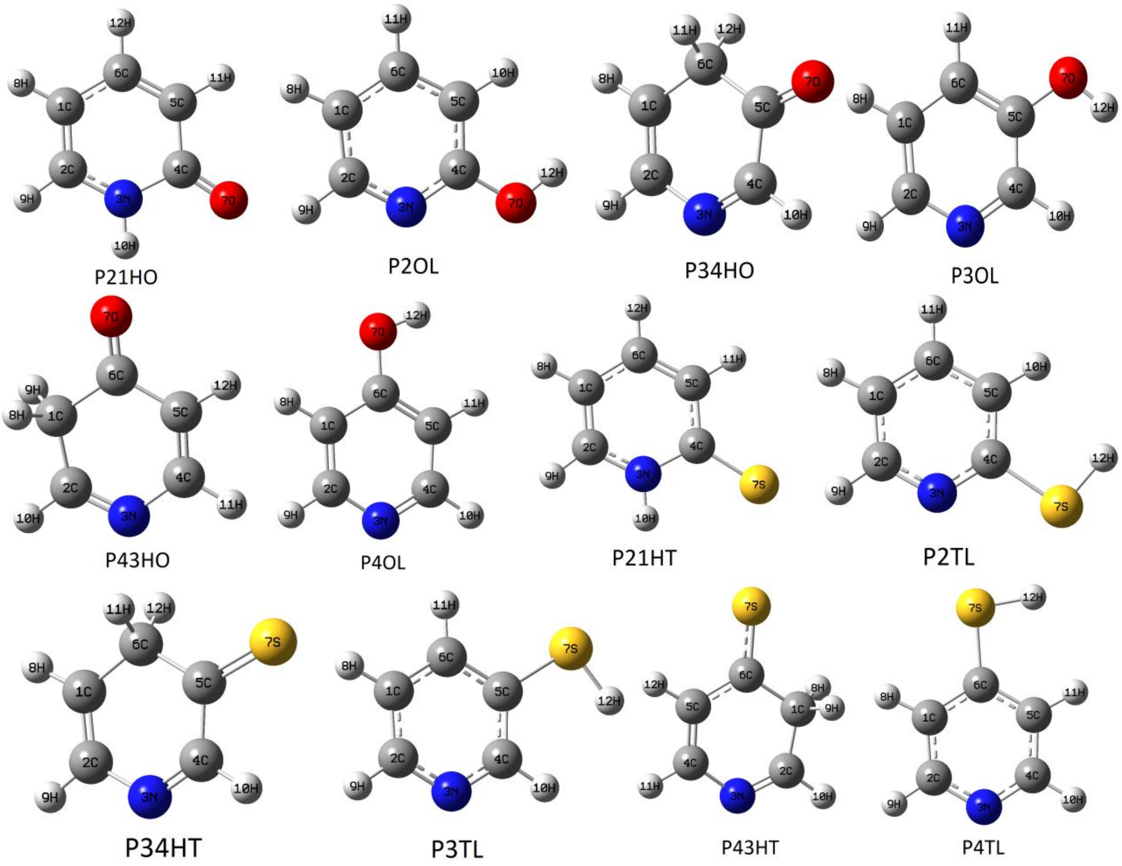


Fig: 1 Optimized structure of of 2-pyridone and 2- pyridinethione tautomers in the gas phase with DFT/(B3LYP) of 6-311++G (d,p) level.

Table 1- The energies of tautomers(a.u) at DFT/6-311++G(d,p) level and the relative energies in brackets in kcal mol^{-1} and dipole moment(μ) debye units and HOMO and LUMO energies in a.u.

S.No	Molecule	E(kcal/mol)	μ	HOMO	LUMO
1	P21HO	-323.614992 (00.00)	4.5103	-0.23333	-0.05875
2	P34HO	-323.562310 (33.06)	3.1074	-0.25792	-0.10994
3	P43HO	-323.570263 (28.07)	1.9952	-0.26753	-0.10107
4	P2OL	-323.604665 (06.48)	3.5811	-0.25222	-0.04196
5	P3OL	-323.597915 (10.71)	1.2458	-0.25079	-0.04282
6	P4OL	-323.601638 (08.38)	2.7399	-0.26724	-0.03084
7	P21HT	-646.574932 (00.00)	5.6854	-0.21246	-0.07284
8	P34HT	-646.522904 (32.64)	3.0291	-0.23739	-0.12871
9	P43HT	-646.530086 (28.14)	2.0568	-0.22997	-0.11801
10	P2TL	-646.568578 (03.98)	3.2666	-0.23941	-0.04582
11	P3TL	-646.565098 (06.17)	1.2639	-0.24069	-0.04728
12	P4TL	-646.566859 (05.06)	2.0639	-0.25197	-0.04414

Thermodynamics analysis

Results provided in Tables 2 are for the Gibbs free energy differences of the keto and enol tautomer in gas phase. Gibbs free energy is evaluated under standard condition, i.e. 298.15 K and 1 atmosphere using the aforementioned methods. Trends are similar to those found on comparing electronic energies. Reactant is lower in Gibbs free energy than the product and product is more stable than reactant. The ΔH is negative, the reaction is exothermic and the bonds formed in the products are stronger than the bonds broken in the reactants and the products are lower in energy than the reactants. The equilibrium constant provides a measure of the degree to which reactants or products are favored during the course of a chemical reaction. The Gibbs free energies of the species provided by Table 2, the equilibrium constant (K) can be readily calculated using equations

$$k = e^{-\Delta G/RT}$$

Table 2- Gas phase change of electronic energies (ΔE), change of enthalpy (ΔH), change of free energy (ΔG), change ofentropy(ΔS) (kcal/mol) and equilibrium constant (K_{eq}) for the keto- enol tautomersim of studying isomers.

S.No	Keto=enol	ΔE	ΔH	ΔG	ΔS	K_{eq}
1	P34HO- P3OL	22.34	21.49	20.54	3.167	0.97
2	P43HO- P4OL	19.69	18.79	17.61	3.931	0.97
3	P21HO- P2OL	-6.48	-6.17	-6.11	-0.183	1.01
4	P34HT- P3TL	26.48	26.83	28.07	-4.155	0.95
5	P43HT- P4TL	23.08	23.46	24.49	-3.432	0.96
6	P21HT- P2TL	-3.99	-1.70	-1.26	-1.482	1.00

Calculation of the HOMO, LUMO and band gaps energies

Energies of HOMO and LUMO are popular quantum mechanical descriptors. The highest occupied molecular orbital (HOMO), it represents the distribution and energy of the least tightly held electrons in the molecule and the lowest unoccupied molecular orbital (LUMO) because it describes the easiest route to the addition of more electrons to the system.

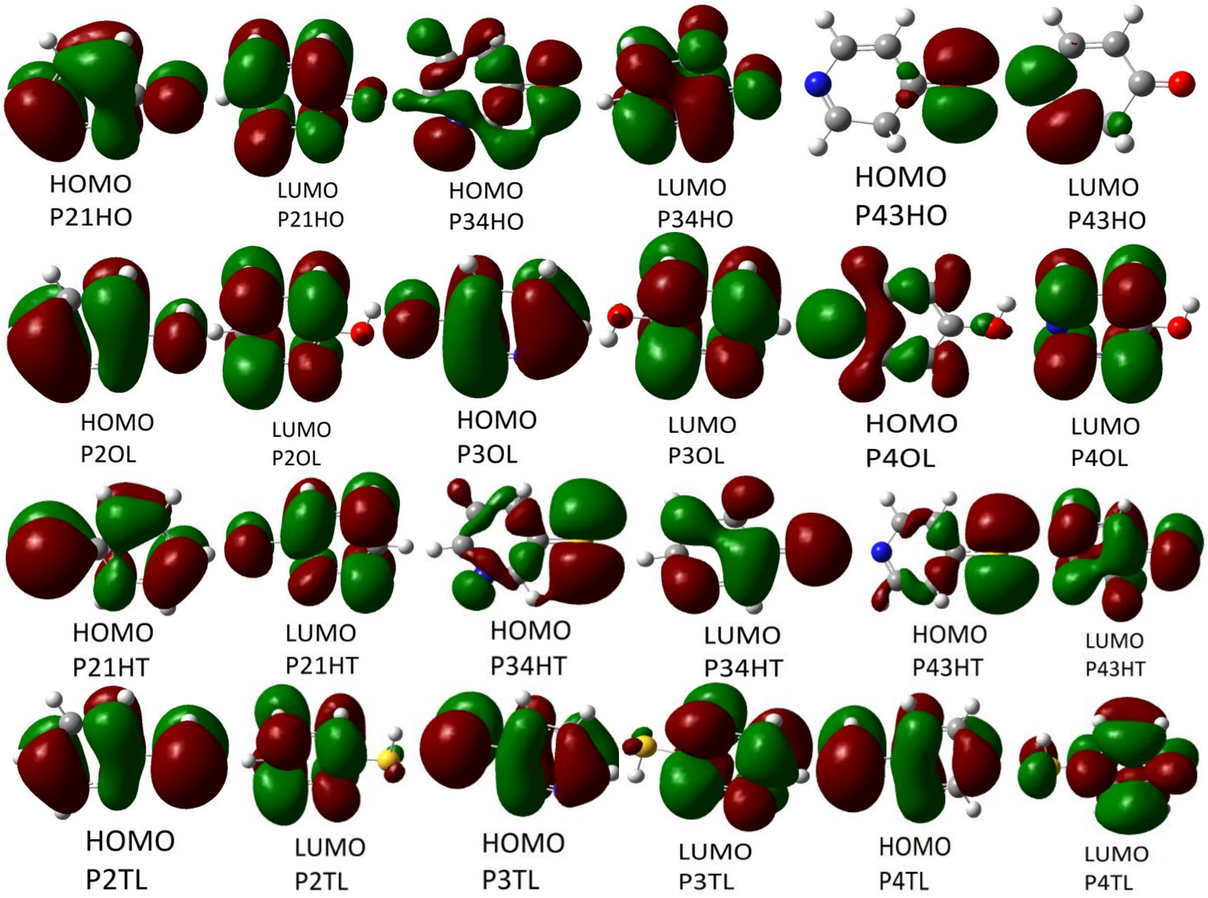


Fig: 2 The HOMO and LUMO frontier molecular orbitals of studied molecules at at DFT/6-311++G (d,p) level in gas phase. In surface box, grey= available; Red= displayed.

In fact, the energy of the HOMO is a good approximation to the lowest ionization potential of the molecule but the energy of the LUMO generally is a poor approximation to the molecule's electron affinity. A molecule whose HOMO is not doubly occupied or that does not have a large HOMO - LUMO energy gap is chemically reactive. High value of HOMO energy is likely to indicate a tendency of the molecule to donate electrons to appropriate acceptor molecule of low empty molecular orbital energy. The lower values of LUMO energy show more probability to accept electrons. The concept of hard and soft nucleophiles and electrophiles has been also directly related to the relative energies of the HOMO and LUMO orbital's. Hard nucleophiles have a low energy HOMO, soft nucleopphiles have a high energy HOMO, hard electrophiles have a high energy LUMO and soft electrophiles have a low energy LUMO.[16] HOMO-LUMO gap is an important stability index.[17] Figure 2 shows that the HOMO and LUMO diagrams of of 2-pyridone and 2- pyridinethione tautomers at B3LYP/6-311++G (d,p) level in gas phase.

The calculated HOMO and LUMO energy level and HOMO-LUMO energy gap (ΔEg) are summarized in Table 2 in gas phase. The HOMO and LUMO energy gap (ΔEg) has great importance to understanding the static molecular reactivity and helps characterize the chemical reactivity and kinetic stability of the molecule. A molecule with a small energy gap is more polarizable and is generally associated with a high chemical reactivity, low kinetic stability and is also termed as soft molecule.[17] The energy gap (E_g) between HOMO and LUMO and reactive descriptors ionization potential (IP), electron affinity (EA), electronegativity (χ), hardness (η), softness (s), chemical potential (μ), softness (S), electrophilicity index (ω), charge transfer (ΔN_{max}), nucleofugality (ΔE_n) and electrofugality (ΔE_e) of 2-pyridone and 2- pyridinethione tautomers calculated by DFT/6-311++g(d,p) basis set in gas phase are presented in Table.3.

Ionization energy is a fundamental descriptor of the chemical reactivity of atoms and molecules. High ionization energy indicates high stability and chemical inertness and small ionization energy indicates high reactivity of the atoms and molecules.[18] The low ionization energy 5.78133 (eV) of P21HT isomer indicates that the isomer is less stable. Absolute hardness and softness are important properties to measure the molecular stability and reactivity. It is apparent that the chemical hardness fundamentally signifies the resistance towards the deformation or polarization of the electron cloud of the atoms, ions or molecules under small perturbation of chemical reaction. A hard molecule has a large energy gap and a soft molecule has a small energy gap.[19] In our present study P34HT isomer have with low hardness values 1.47867 (eV) compared with other isomers respectively. Therefore, P34HT isomer is stable and less reactivity.

Table.3-The theoretical electronic properties (HOMO, LUMO) and energy gap (E_g) and reactive descriptors ionization potential (IP), electron affinity (EA), electronegativity (χ), hardness (η), softness (s), chemical potential (μ), softness (S), electrophilicity index (ω), charge transfer (ΔN_{max}), nucleofugality (ΔE_n) and electrofugality (ΔE_e) of cyanuric acid tautomers calculated by DFT/with different basis set in gas phase.

Tautomer	IP	EA	χ	η	μ	s	ω	ΔN_{max}	ΔE_n	ΔE_e	ΔE_g gap(ev)
P34HO	7.01836	2.99162	5.00499	2.01337	-5.00499	0.49668	6.22090	2.48588	3.22928	13.23926	-4.02674
P3OL	6.82435	1.16519	3.99477	2.82958	-3.99477	0.35341	2.81989	1.41179	1.65470	9.64424	-5.65915
P43HO	7.27987	2.75026	5.01506	2.26480	-5.01506	0.44154	5.55254	2.21435	2.80228	12.83241	-4.52961
P4OL	7.27197	0.83920	4.05559	3.21639	-4.05559	0.31091	2.55687	1.26091	1.71767	9.82885	-6.43277
P21HO	6.34924	1.59867	3.97395	2.37528	-3.97395	0.42100	3.32430	1.67304	1.72563	9.67353	-4.75057
P2OL	6.86326	1.14179	4.00252	2.86073	-4.00252	0.34956	2.80002	1.39912	1.65823	9.66328	-5.72147
P34HT	6.45971	3.50238	4.98105	1.47867	-4.98105	0.67628	8.38959	3.36861	4.88721	14.84930	-2.95733
P3TL	6.54951	1.28655	3.91803	2.63148	-3.91803	0.38001	2.91680	1.48891	1.63024	9.46631	-5.26296
P43HT	6.25781	3.21122	4.73451	1.52329	-4.73451	0.65647	7.35761	3.10807	4.14639	13.61541	-3.04659
P4TL	6.85646	1.20111	4.02878	2.82767	-4.02878	0.35365	2.87005	1.42477	1.66893	9.72650	-5.65535
P21HT	5.78133	1.98208	3.88171	1.89963	-3.88171	0.52642	3.96595	2.04340	1.98387	9.74728	-3.79926
P2TL	6.51468	1.24683	3.88075	2.63393	-3.88075	0.37966	2.85890	1.47337	1.61207	9.37358	-5.26785

The electrophilicity index (ω) has been used as structural depictor for the analysis of the chemical reactivity of molecules.[20,21] It measures the propensity of a species them to accept electrons. A good, more reactive, nucleophile is characterized by a lower value of (ω), in opposite a good electrophile is characterized by a high value of (ω). The electrophilicity index values were calculated by equation (6) and are presented in table 3. The tautomer P34HT is a good electrophile and P43HO is good nucleophile in gas phase. Physically, chemical potential (μ) describes the escaping tendency of electrons from an equilibrium system. The greater the electronic chemical potential, the less stable or more reactive is the compound.

CONCLUSION

A theoretical study of the reactivity and molecular descriptors was carried out at the density functional theory (DFT) calculation level for the tautomers of Pyridine-2(1H)-one and pyridine-2(1H)-thione. The relative stabilities for isomers in gas phase with respect to stable isomer for as following order respectively: P21HO > P2OL > P4OL > P3OL > P43HO > P34HO and in case of pyridine-2(1H)-thione, the order of relative stabilities as following order with respectively: P21HT > P2TL > P4TL > P3TL > P43HT > P34HT. The HOMO and LUMO energies in order to determine, the usefulness of global reactivity descriptors namely, the chemical hardness (η), chemical potential (μ), electrophilicity index (ω), softness (S), nucleofugality (ΔE_n), and electrofugality (ΔE_e), values for the prediction of the reactivity of the tautomers. From electrophilicity index (ω), results the tautomer P34HT is a good electrophile and P43HO is good nucleophile in gas phase.

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