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THEORETICAL STUDY ON THE MOLECULAR TAUTOMERISM OF THE 5-HYDROXY-2-HYDROXY METHYL PYRIDINE-4(1H)-ONE

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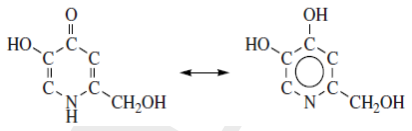
Abstract – 5-hydroxy-2-hydroxy methyl pyridine-4(1H)-one is one of the Hydroxypyridin-4(1H)-one derivatives which are known in coordination as efficient metal ions chelators. In this work, relative stabilities of 5-hydroxy-2-hydroxy methyl pyridine-4(1H)-one tautomers were investigated using two quantum chemical methods: density functional theory and Hartree-Fock in combination with 6-311++G(d,p) basis set. The calculations show that the structure under investigation exists as a mixture of two tautomers with comparable energies. The result indicated that the keto form is more stable than the enol form in all computational methods.

1. Introduction

Hydroxypyridin-4(1H)-one derivatives are widely used in various field of medicinal chemistry for the treatment of metal overload diseases [1,2]. An accurate description of active structures of a chemical compound is essential for modeling the mechanism of drug action. Similar to many other compounds, hydroxypyridin-4(1H)-ones can exist several structures. This is possible because of the phenomenon of tautomerism, in which a compound has several isomers, tautomers that are readily interconvertible. In the case of 3-hydroxypyridin-4(1H)-ones, a single or sometimes two hydrogen atoms can adopt several different positions (Fig. 1) [3]. The composition of the mixture of tautomeric structures depends on relative energies of tautomers. Our aim is to investigate the molecular tautomerism of the 5-hydroxy-2-hydroxy methyl pyridine-4(1H)-one from the molecular approach.



T1 **T2**

Fig.1. Chemical structures of studied tautomers.

2. Computational details

The quantum chemical calculations were performed using the Gaussian 09 software package [4]. The structures and energies of the studied tautomers were examined using the Hartree-Fock and density functional methods (B3LYP, MO6) in combination with 6-311++G(d,p) basis set. Solvent effects were taken into account by the conductor like polarizable continuum model (CPCM). To describe the calculated geometries of the tautomers, frequency calculations were carried out during all the computations. Vibrational frequencies were computed at the fully optimized geometry of the tautomers. Positive values of the obtained Vibrational frequencies indicate that the optimized geometries are at energy minima.

3. Results and Discussion

A statistical thermodynamic formation was used to determine the tautomeric equilibrium constant [5]. In this approach, the equilibrium constant, K_T, for a pair of the tautomers, is related to the standard Gibbs free energy change between the two structures (ΔG) according to this equation: $\Delta G = -RT \ln K_T$. In order to calculate the energies of the tautomers with high accuracy, we used several quantum-machanical methods. The results are listed in Table 1. In all cases, T1 tautomer is more stable than T_2 about 30 kJ.mol^{-1}.

Table 1. Difference in free Gibbs energy and tautomeric equilibrium constant (K_T) for the studied tautomers.

Method	ΔG (kJ.mol^{-1})	$K_T = [T_2]/[T_1]$
B3LYP	33.50	1.3×10^{-6}
MO6	29.54	6.7×10^{-6}
HF	20.93	2.1×10^{-4}

4. Conclusion

In this work we performed a theoretical study on the molecular tautomerism of 5-hydroxy-2-hydroxy methyl pyridine-4(1H)-one. The calculated energy differences between T_2 and T_1 tautomers, indicates that the T_1 structure is more stable than T_2. Consequently, the population of T_2 structure in the tautomeric mixture should be low. We also concluded that T_1 tautomer for metal complexation by single protonation of its hydroxyl group is better than T_2 tautomer which should be doubly deprotonated.

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