Computational Methods and Molecular Modelling for Some Predicted Tautomers of Pyrimidine Compounds

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Abstract: Introduction: Several molecular modelling techniques and quantum chemical methods have been performed to correlate the chemical structures of the compounds with their physical molecular properties.

Methods: Theoretical parameters were used to characterize the molecular structure of the investigated ligands and to study their equilibria mechanism. Molecular modelling data such as the bond length, bond order, bond angles and dihedral angles values were estimated for some pyrimidine compounds, where the data suggested the presence of tautomerism and dynamic equilibria were deduced between all the detected tautomers in the solid state.

Results: Four main tautomers were predicted for barbital and thiobarbituric acid, while three tautomers were for thiouracil. Quantum chemical parameters such as the highest occupied molecular orbital energy (E_{HOMO}), the lowest unoccupied molecular orbital energy (E_{LUMO}), energy gap (ΔE), dipole moment (µ), sum of the total negative charge (STNC), electronegativity (χ), chemical potential (P), global hardness (η) and softness (γ) were calculated.

Conclusion: These studies display a good correlation between the theoretical and experimental data.

Keywords: Molecular orbital energy, molecular modelling data, pyrimidines tautomers, quantum chemical parameters.

1. INTRODUCTION

The molecular modelling calculations are widely increasing nowadays for the expectation of the mechanism of the reactions and identification of the products [1]. This saves time and money for understanding the biological phenomena and exploiting artificial models [2].

The common feature of molecular modelling [3] techniques is the atomistic level description of the molecular systems; the lowest level of information is individual atoms (or a small group of atoms), in contrast to quantum chemistry, where electrons are considered explicitly. The benefit of molecular modelling is that it reduces the complexity of the system, allowing many more particles (atoms) to be considered during simulations. Molecular modelling methods [4] are used to investigate the structure, dynamics and thermodynamics of inorganic, biological, polymeric, drug discovery, medicinal chemistry and pharmaceutical research. The latter has been formalized as a field of study known as Computer Assisted Drug Design (CADD) or Computer Assisted Molecular Design (CAMD) [5].

The stability of DNA and RNA structure is due to the H-bond base pairing and the base stacking, which is actually an interaction between π-orbital of the aromatic rings of the bases and London dispersion forces [6]. The interesting information about their electronic structure and the weakly held molecular complexes can be obtained by quantum chemical treatment [7].

In general, ab initio methods are able to reproduce laboratory measurements for properties such as the heat of formation, ionization potential and molecular geometry [5]. Semiempirical methods utilize approaches that are similar to ab initio methods, but several approximations are introduced to simplify the calculations. These methods include the Huckel approach for aromatic compounds (in which the outer electrons in conjugated systems are treated, but the inner (or core) electrons are ignored) and the Neglect of Differential Overlap formalisms found in the CNDO
Table 1. Colour, m.p (°C) and sources of ligands.

| Compound                                      | Colour | m.p(°C) | M.wt  | Formula       | Sources                |
|-----------------------------------------------|--------|---------|-------|---------------|------------------------|
| Barbital (H2L), 5,5'-Diethyl-Barbituric acid  | White  | > 360   | 184.20| C4H12N2O3     | MERCK                  |
| 2-Thiobarbituric acid (H2L) [2-SBA], 4,6-Dihydroxy-2-mercapto-pyrimidin. N:C(SH)N:C(OH)CH:COH | Rose   | 245     | 144.15| C4H12N2S      | Fluka AG , Buchs SG    |
| 2-Thiouracil (H2L), [2-TU].2,3-dihydro-2-thiao-pyrimidin-4(1H)-one. | White  | 300     | 128.15| C4H6N2OS      | Riedel-de Haën AG, SEELZE-HANNOVER |

(Complete Neglect of Differential Overlap) and INDO (Intermediate Neglect of Differential Overlap). Lesions in DNA are caused by electrons with high and low energy resulting in cancer cell formation [8]. Electron correlation is necessary to obtain accurate charge distribution and dipole moments. The valence adiabatic ionization potential (AIP) calculated by the difference between the energies of the appropriate cation radical and neutral species at their respective optimized geometries was reported for pyrimidines [9]. The technique known as energy minimization is used to find positions of zero gradient for all atoms, i.e., a local energy minimum. Lower energy states are more stable and are commonly investigated because of their role in chemical and biological processes. A molecular dynamics simulation computes the behaviour of a system as a function of time.

The phenomena of tautomerization of pyrimidines compounds were examined by Masoud et al. [10-16] to study the structural chemistry and the chemical equilibria of such compounds in the solid state. Applying software opened the door for the powerful use of theoretical chemistry to study the phenomena of tautomerization research. The possible tautomeric forms: imin-enamine, thiol-thion and keto-enol tautomerism were calculated as gaseous for the compounds under study. The corresponding geometries were optimized without any geometry constraints for full geometry optimizations. In the present manuscript, it is aimed to give spotlight for structural configurations from the view of molecular modelling data, including geometries (bond lengths, bond orders, bond angles, torsion angles); energies (total energy, heat of formation, binding energy, highest occupied molecular orbital energy [E_{HOMO}], the lowest unoccupied molecular orbital energy [E_{LUMO}], energy gap [ΔE]), electronic properties (dipole moments, charges, electronegativity, chemical potential, global hardness and softness) for different biologically active pyrimidine compounds.

2. MATERIALS AND METHODS

2.1. Compounds

The color, m.p (°C) and sources of investigated ligands are given in Table 1. Their chemical structures and predicted tautomers are presented (Figs. 1,3,5).

2.2. Simulations and Computer Programs

The molecules were built with the ChemBio3D Ultra 11.0., where geometrical structures and electronic properties of the free ligands (Barbital, SBA and TU) and their possible tautomers [10-14] were assigned by optimizing their bond lengths, bond orders, bond angles, dihedral angles and close contact using the MM2 calculation to minimizing energy, (Figs. 1-6) and (Tables 2-4). The structural chemistry was investigated by applying the HyperChem.v8.0.x Professional program using PM3 semi-empirical method to speed up the calculations of quantum chemical parameters such as the highest occupied molecular orbital energy (E_{HOMO}), the lowest unoccupied molecular orbital energy (E_{LUMO}), energy gap (ΔE), dipole moment (μ). Also, electronegativity (χ), chemical potential (Pi), global hardness (η), softness (σ) and the sum of the total negative charge (STNC) were calculated to study some nucleic acid bases and their predicted tautomers [15] (Fig. 1-6) and (Tables 5,6).
3. RESULTS AND DISCUSSION

3.1. Molecular Modelling Geometries

The molecular modelling calculations [5] are based on neglecting the possibility of hydrogen bonding using different parameters like (Heat of formation, Gradient norm, Dipole, Charges, Solvation in water, Electrostatic potential, Molecular surface, Spin density, Hyperfine coupling constants and Polarizabilities) which are of major importance to control the modelling of the compounds. The optimized geometries of selected pyrimidines, their predicted tautomers and molecular modelling data are given (Figs. 1-6) and (Tables 2-4).

3.1.1. Barbital

The parent pyrimidine barbituric acid compound possesses three main tautomers through the π-charge density on pyrimidine ring and the imino moiety [10,11,14]. Four tautomers are predicted for barbital (Fig. 1). The bond length and bond order values for all forms are given (Table 2a) and (Fig. 2), respectively, where the data suggested the presence of tautomerism. The bond lengths of the same functional groups atoms show more similarities, where the ethyl groups atoms in different tautomers (1, 2, 3, and 4) are approximately similar in their bond lengths (Table 2a). This lies in two categories: 1.1106–1.1173 (Å) for C(12)-H(21), C(12)-H(20), C(11)-H(19), C(10)-H(17), C(10)-H(16), C(12)-H(22), C(13)-H(23), C(13)-H(24), C(13)-H(25) and C(11)-H(18); 1.5354–1.5507 (Å) for C(11)-C(13), C(10)-C(12), C(5)-C(11) and C(5)-C(10), also, C(4)-C(5) and C(5)-C(6) lie in this range. The new bond lengths of enol atoms that appeared in tautomers (2, 3 and 4), (Table 2a) are approximately similar: 0.9708–0.9714 (Å) for O(7)-H(14) in tautomers (3 and 4) and O(9)-H(15) in tautomers (2 and 4), respectively. This leads to the disappearance of N(1)-H(14) bond length in tautomers (3 and 4), also N(3)-H(15), bond length was absent in tautomers (2 and 4) to form keto-enol tautomerization. Tautomer (1) is detected in keto form only, with the reduction of N(1)-C(6) bond length in tautomers (3 and 4) than tautomers (1 and 2), and the reduction of C(2)-N(3) bond length in tautomers (2 and 4) than tautomers (1 and 3) due to formation of N=C. All the above observations are taken as an argument of tautomerism (Fig. 1).

Table 2. Molecular modelling data of barbital tautomers.

| Atoms     | Tautomer (1) | Tautomer (2) | Tautomer (3) | Tautomer (4) |
|-----------|--------------|--------------|--------------|--------------|
| C(6)-O(7) | 1.2079       | 1.2073       | 1.3627       | 1.3617       |
| C(5)-C(6) | 1.5366       | 1.5322       | 1.5257       | 1.5214       |
| N(1)-C(6) | 1.3692       | 1.3571       | 1.2820       | 1.2866       |
| C(2)-O(9) | 1.2067       | 1.3597       | 1.2253       | 1.3620       |
| C(2)-N(3) | 1.3655       | 1.2781       | 1.3650       | 1.2904       |
| N(1)-C(2) | 1.3657       | 1.3436       | 1.3857       | 1.4095       |
| C(4)-O(8) | 1.2085       | 1.2257       | 1.2076       | 1.2263       |
| C(4)-C(5) | 1.5367       | 1.5379       | 1.5350       | 1.5364       |
| N(3)-C(4) | 1.3688       | 1.3983       | 1.3659       | 1.3868       |
| C(13)-H(25) | 1.1131   | 1.1123       | 1.1128       | 1.1133       |
| C(13)-H(24) | 1.1122   | 1.1133       | 1.1123       | 1.1124       |
| C(13)-H(23) | 1.1146   | 1.1147       | 1.1146       | 1.1146       |
| C(12)-H(22) | 1.1111   | 1.1129       | 1.1127       | 1.1129       |
| C(12)-H(21) | 1.1127   | 1.1116       | 1.1106       | 1.1111       |
| C(12)-H(20) | 1.1148   | 1.1146       | 1.1149       | 1.1149       |
| C(11)-H(19) | 1.1154   | 1.1164       | 1.1158       | 1.1155       |
| C(11)-H(18) | 1.1166   | 1.1153       | 1.1173       | 1.1168       |
| C(10)-H(17) | 1.1162   | 1.1169       | 1.1169       | 1.1168       |
| C(10)-H(16) | 1.1170   | 1.1161       | 1.1156       | 1.1153       |
| C(10)-C(12) | 1.5374   | 1.5371       | 1.5373       | 1.5374       |
| C(11)-C(13) | 1.5360   | 1.5358       | 1.5357       | 1.5354       |
| C(5)-C(11) | 1.5486       | 1.5472       | 1.5480       | 1.5468       |
| C(5)-C(10) | 1.5492       | 1.5474       | 1.5507       | 1.5500       |
| N(1)-H(14) | 1.0068       | 1.0063       | ——           | ——           |
| N(3)-H(15) | 1.0068       | ——           | 0.9708       | ——           |
| O(9)-H(15) | ——           | 0.9708       | ——           | 0.9714       |
| O(7)-H(14) | ——           | ——           | 0.9709       | 0.9708       |
(b) Bond Angle (degree °)

| Atoms          | Tautomer (1) | Tautomer (2) | Tautomer (3) | Tautomer (4) |
|----------------|--------------|--------------|--------------|--------------|
| H(25)-C(13)-H(24) | 107.9491     | 108.0354     | 108.0763     | 107.9883     |
| H(25)-C(13)-H(23) | 107.0231     | 107.0457     | 106.7770     | 106.9449     |
| H(25)-C(13)-C(11) | 111.7857     | 112.1880     | 111.8102     | 111.6498     |
| H(24)-C(13)-H(23) | 107.0412     | 106.9896     | 107.0816     | 107.0941     |
| H(24)-C(13)-C(11) | 112.0924     | 111.6666     | 112.1273     | 112.1691     |
| H(23)-C(13)-C(11) | 110.6919     | 110.6598     | 110.7010     | 110.7376     |
| H(22)-C(12)-H(21) | 107.7233     | 107.7020     | 107.8588     | 107.6493     |
| H(22)-C(12)-H(20) | 106.8359     | 106.5889     | 106.5839     | 106.5260     |
| H(22)-C(12)-C(10) | 112.8748     | 111.9109     | 112.0498     | 111.9291     |
| H(21)-C(12)-H(20) | 106.5294     | 107.0352     | 106.4868     | 106.8800     |
| H(21)-C(12)-C(10) | 112.0333     | 112.6798     | 113.1116     | 112.9916     |
| H(20)-C(12)-C(10) | 110.5036     | 110.6086     | 110.3870     | 110.5225     |
| H(19)-C(11)-H(18) | 105.3281     | 105.3592     | 105.7428     | 105.5902     |
| H(19)-C(11)-C(13) | 108.9087     | 107.3690     | 108.5242     | 109.0558     |
| H(19)-C(11)-C(5)  | 109.4915     | 110.0903     | 109.6083     | 109.4727     |
| H(18)-C(11)-C(13) | 107.5313     | 109.0256     | 107.7301     | 107.4880     |
| H(18)-C(11)-C(5)  | 109.9151     | 109.3080     | 109.1748     | 109.8684     |
| C(13)-C(11)-C(5)  | 115.1933     | 115.2190     | 115.5972     | 114.9396     |
| H(17)-C(10)-H(16) | 105.7855     | 105.6733     | 105.6180     | 105.4600     |
| H(17)-C(10)-C(12) | 106.2378     | 108.9302     | 109.0017     | 109.1924     |
| H(17)-C(10)-C(5)  | 110.0571     | 108.6155     | 108.3240     | 108.6804     |
| H(16)-C(10)-C(12) | 108.8029     | 106.6724     | 105.5634     | 105.8831     |
| O(7)-C(6)-C(5)    | 125.4048     | 125.1245     | 120.9393     | 121.6004     |
| N(1)-C(6)-O(7)    | 119.4373     | 120.5515     | 117.3077     | 118.3318     |
| N(1)-C(6)-C(5)    | 115.1432     | 114.2843     | 121.6312     | 119.9036     |
| N(3)-C(4)-O(8)    | 119.6583     | 121.0361     | 119.3094     | 121.3244     |
| N(3)-C(4)-C(5)    | 115.2132     | 116.4636     | 115.1776     | 115.9673     |
| O(8)-C(4)-C(5)    | 125.1083     | 122.4953     | 125.4808     | 122.7078     |
| C(2)-N(1)-C(6)    | 124.4061     | 126.5950     | 121.8867     | 120.9793     |
| C(2)-N(3)-C(4)    | 124.3179     | 119.5889     | 124.8633     | 118.9409     |
| O(9)-C(2)-N(3)    | 120.7271     | 120.4584     | 118.2354     | 117.5279     |
| O(9)-C(2)-N(1)    | 120.7456     | 118.5549     | 122.6826     | 119.5567     |
| N(3)-C(2)-N(1)    | 118.1233     | 120.9664     | 118.9419     | 122.9153     |
| H(16)-C(10)-C(5)  | 108.3417     | 110.0355     | 109.9791     | 110.0873     |
| C(12)-C(10)-C(5)  | 117.0464     | 116.3865     | 117.7006     | 116.9285     |
| C(6)-C(5)-C(4)    | 110.7301     | 107.1196     | 111.5105     | 107.6156     |
| C(6)-C(5)-C(11)   | 106.6690     | 108.3184     | 108.3273     | 108.9027     |
| C(6)-C(5)-C(10)   | 110.1915     | 109.3567     | 109.0201     | 109.9060     |
| C(4)-C(5)-C(11)   | 107.4541     | 107.4386     | 105.7907     | 107.2239     |
| C(4)-C(5)-C(10)   | 109.0135     | 111.2938     | 108.8233     | 109.9055     |
| C(11)-C(5)-C(10)  | 112.7445     | 113.0945     | 113.3781     | 113.1091     |
| C(2)-N(1)-H(14)   | 117.7344     | 113.0665     | ——           | ——           |
| C(6)-N(1)-H(14)   | 117.7521     | 120.3363     | ——           | ——           |
| C(2)-N(3)-H(15)   | 117.7721     | ——           | 117.5295     | ——           |
| H(15)-N(3)-C(4)   | 117.7987     | ——           | 117.5941     | ——           |
| H(15)-O(9)-C(2)   | ——           | 111.7869     | ——           | 110.5648     |
| C(6)-O(7)-H(14)   | ——           | ——           | 111.2713     | 111.1853     |
| Atoms                        | Tautomer (1) | Tautomer (2) | Tautomer (3) | Tautomer (4) |
|-----------------------------|--------------|--------------|--------------|--------------|
| C(10)-C(5)-C(6)-N(1)       | 156.2454     | -153.0810    | -143.5002    | 148.7960     |
| C(10)-C(5)-C(6)-O(7)       | -25.1661     | 29.2101      | 40.6217      | -35.9406     |
| C(11)-C(5)-C(6)-N(1)       | -81.0625     | 83.2599      | 92.6977      | -86.7867     |
| C(11)-C(5)-C(6)-O(7)       | 97.5259      | -94.4490     | -83.1804     | 88.4767      |
| C(4)-C(5)-C(6)-N(1)        | 35.5591      | -32.3532     | -23.3217     | 29.1330      |
| C(4)-C(5)-C(6)-O(7)        | -145.8525    | 149.9379     | 160.8002     | -155.6036    |
| C(2)-N(1)-C(6)-C(5)        | -13.4408     | 8.1856       | 4.9236       | -3.6831      |
| C(2)-N(1)-C(6)-O(7)        | 167.8803     | -173.3604    | -179.0550    | -179.1001    |
| N(1)-C(2)-N(3)-C(4)        | 11.2195      | 4.0127       | -11.0013     | -1.2883      |
| O(9)-C(2)-N(3)-C(4)        | -176.0217    | -177.6486    | 173.1842     | 178.5852     |
| C(6)-N(1)-C(2)-N(3)        | -11.3859     | 8.3942       | 13.4271      | -13.3726     |
| C(6)-N(1)-C(2)-O(9)        | 175.8568     | -169.9755    | -170.9545    | 166.7563     |
| N(3)-C(4)-C(5)-C(10)       | -157.1087    | 164.0730     | 144.4733     | -161.7457    |
| N(3)-C(4)-C(5)-C(11)       | 80.4106      | -71.6148     | -93.3820     | 74.9370      |
| N(3)-C(4)-C(5)-C(6)        | -35.7251     | 44.5826      | 24.1791      | -42.0824     |
| O(8)-C(4)-C(5)-C(10)       | 24.5404      | -15.1257     | -37.6182     | 18.0143      |
| O(8)-C(4)-C(5)-C(11)       | -97.9403     | 109.1865     | 84.5265      | -105.3030    |
| O(8)-C(4)-C(5)-C(6)        | 145.9240     | -134.6161    | -157.9123    | 137.6776     |
| C(2)-N(3)-C(4)-C(5)        | 13.7409      | -32.1986     | -8.9399      | 30.3667      |
| C(2)-N(3)-C(4)-O(8)        | -167.8115    | 147.0127     | 173.0132     | -149.3969    |
| C(5)-C(11)-C(13)-H(23)     | 177.7158     | 177.2575     | 176.0043     | -176.7844    |
| C(5)-C(11)-C(13)-H(24)     | 58.2830      | -63.6764     | 56.4909      | -57.2023     |
| C(5)-C(11)-C(13)-H(25)     | -63.0764     | 57.7774      | -65.0760     | 64.1650      |
| H(18)-C(11)-C(13)-H(23)    | -59.3703     | 53.9588      | -61.6163     | 60.5669      |
| H(18)-C(11)-C(13)-H(24)    | -178.8032    | 173.0249     | 178.8703     | -179.8511    |
| H(18)-C(11)-C(13)-H(25)    | 59.8374      | -65.5213     | 57.3033      | -58.4838     |
| H(19)-C(11)-C(13)-H(23)    | 54.2858      | -59.7081     | 52.4341      | -53.4462     |
| H(19)-C(11)-C(13)-H(24)    | -65.1470     | 59.3580      | -67.0793     | 66.1359      |
| H(19)-C(11)-C(13)-H(25)    | 173.4936     | -179.1882    | 171.3537     | -172.4968    |
| C(5)-C(10)-C(12)-H(20)     | -175.0508    | -173.4645    | -178.1611    | 174.1814     |
| C(5)-C(10)-C(12)-H(21)     | 66.3276      | -53.7047     | -58.9659     | 54.7071      |
| C(5)-C(10)-C(12)-H(22)     | -55.4874     | 67.8486      | 63.2157      | -67.0191     |
| H(16)-C(10)-C(12)-H(20)    | -51.8843     | 63.3186      | 58.6896      | -62.5539     |
| H(16)-C(10)-C(12)-H(21)    | -170.5058    | -176.9215    | 177.8847     | 177.7348     |
| H(16)-C(10)-C(12)-H(22)    | 67.6791      | -55.3683     | -59.9336     | 56.0086      |
| H(17)-C(10)-C(12)-H(20)    | 61.5986      | -50.3124     | -54.3573     | 50.5563      |
| H(17)-C(10)-C(12)-H(21)    | -57.0229     | 69.4474      | 64.8378      | -69.1549     |
| H(17)-C(10)-C(12)-H(22)    | -178.8379    | -168.9993    | -172.9805    | 169.1189     |
| C(10)-C(5)-C(11)-C(13)     | -61.2451     | -61.6696     | -60.4173     | 62.1577      |
| Atomic Bonds | Tautomer (1) | Tautomer (2) | Tautomer (3) | Tautomer (4) |
|--------------|--------------|--------------|--------------|--------------|
| C(10)-C(5)-C(11)-H(18) | 177.1206 | 61.4793 | 177.9750 | -176.4812 |
| C(10)-C(5)-C(11)-H(19) | 61.8757 | 176.7555 | 62.5821 | -60.9581 |
| C(11)-C(5)-C(10)-C(12) | -47.5270 | -48.4472 | -46.7486 | 47.2113 |
| C(11)-C(5)-C(10)-H(16) | -170.9296 | 73.0067 | 74.1365 | -73.6257 |
| C(11)-C(5)-C(10)-H(17) | 73.8475 | -171.7626 | -170.8920 | 171.3339 |
| C(4)-C(5)-C(10)-C(12) | -166.7664 | 72.6081 | 70.6753 | -72.5846 |
| C(4)-C(5)-C(10)-H(16) | 69.8310 | -165.9379 | -168.4396 | 166.5783 |
| C(4)-C(5)-C(10)-H(17) | -45.3918 | -50.7072 | -53.4681 | 51.5379 |
| C(4)-C(5)-C(11)-C(13) | 58.8954 | 175.1172 | -179.5964 | -176.5207 |
| C(4)-C(5)-C(11)-H(18) | -62.7390 | -61.7339 | 58.7959 | -55.1596 |
| C(4)-C(5)-C(11)-H(19) | -177.9838 | 53.5423 | -56.5970 | 60.3635 |
| C(6)-C(5)-C(10)-C(12) | 71.5227 | -169.2414 | -167.5035 | 169.1580 |
| C(6)-C(5)-C(10)-H(16) | -51.8799 | -47.7874 | -46.6184 | 48.3209 |
| C(6)-C(5)-C(10)-H(17) | -167.1028 | 67.4433 | 68.3531 | -66.7195 |
| C(6)-C(5)-C(11)-C(13) | 177.6769 | 59.7121 | 60.7281 | -60.3495 |
| C(6)-C(5)-C(11)-H(18) | 56.0425 | -177.1390 | -60.8796 | 61.0116 |
| C(6)-C(5)-C(11)-H(19) | -59.2023 | -61.8629 | -176.2725 | 176.5347 |
| H(14)-N(1)-C(6)-C(5) | 170.4215 | -170.6185 | —— | —— |
| H(14)-N(1)-C(6)-O(7) | -8.2574 | 7.2055 | —— | —— |
| H(14)-N(1)-C(2)-N(3) | 164.7525 | -172.1367 | —— | —— |
| H(14)-N(1)-C(2)-O(9) | -8.0049 | 9.4936 | —— | —— |
| O(9)-C(2)-N(3)-H(15) | 7.9075 | —— | -8.1669 | —— |
| N(1)-C(2)-N(3)-H(15) | -164.8512 | —— | 167.6476 | —— |
| H(15)-N(3)-C(4)-C(5) | -170.1893 | —— | 172.4121 | —— |
| H(15)-N(3)-C(4)-O(8) | 8.2583 | —— | -5.6349 | —— |
| N(1)-N(2)-C(2)-O(9)-H(15) | —— | -173.7835 | —— | 171.7559 |
| N(3)-C(2)-O(9)-H(15) | —— | 7.8383 | —— | -8.1221 |
| C(5)-C(6)-O(7)-H(14) | —— | —— | 11.8984 | -13.6013 |
| N(1)-C(6)-O(7)-H(14) | —— | —— | -164.1522 | 161.7341 |

| Atoms | Tautomer (1) | Tautomer (2) | Tautomer (3) | Tautomer (4) |
|-------|--------------|--------------|--------------|--------------|
| N(1), C(4) | 2.7973 | 2.6619 | 2.8267 | 2.7277 |
| C(2), C(5) | 2.8215 | 2.8126 | 2.8188 | 2.7740 |
| C(6), N(3) | 2.7936 | 2.8148 | 2.7386 | 2.7847 |
| O(7), H(22) | 2.4321 | —— | —— | —— |
| O(8), H(17) | 2.4824 | —— | —— | —— |
| O(8), H(21) | —— | 2.4679 | 2.3879 | 2.4272 |
Fig. (1). The optimized molecular structure of barbital tautomers.
Fig. (2). Molecular modelling of barbital tautomers.
The magnitude of the bond order is associated with the bond length. The bond order concept is used in molecular dynamics and bond order potentials.[17] The bond orders of the same functional groups atoms show more similarities, where the ethyl groups atoms in different tautomers (1, 2, 3, and 4) (Fig. 1) are approximately similar in their bond orders (Fig. 2). This lies between ~0.95~1 (Å) to prove that all ethyl groups atoms are held together via a single bond. The newly born bond orders of enol atoms that appeared in tautomers (2, 3 and 4), (Fig. 2) were approximately similar ~ 0.9 (Å) for O(7)-H(14) in tautomers (3 and 4) and O(9)-H(15) in tautomers (2 and 4), respectively. The phenomena of enolization lead to a reduction in bond orders of O(7)-C(6) in tautomers (3 and 4) and O(9)-C(2) in tautomers (2 and 4) to ~ 1.1 (Å). However, the bond orders of O(7)-C(6) in tautomers (1 and 2) and O(9)-C(2) in tautomers (1 and 3) were increased to ~ 1.8 (Å), proving the formation of double bond and keto-form. This leads to the disappearance of N(1)-H(14) bond order in tautomers (3 and 4), also N(3)-H(15), and in tautomers (2 and 4) to form keto-enol tautomerization. Tautomer (1) is detected in keto form only (Fig. 2), with the reduction of N(1)-C(6) bond order in tautomers (1 and 2) ~ 1 (Å) than tautomers (3 and 4) ~ 1.7 (Å), accompanied with the reduction of C(2)-N(3) bond order in tautomers (1 and 3) ~ 1 (Å) than tautomers (2 and 4) ~ 1.6 (Å). These bond orders are near ~ 2 (Å) with the formation of N=C. All the above observations are taken as an argument of tautomerism.

Meanwhile, the bond angles between atoms in barbital for all its tautomers (Fig. 1) and (Table 2b) pointed that most of them lie in the range: 105.3281° ~ 126.5950° referring to distorted sp² hybridization due to distortion in electronic configuration. The perfect sp³ hybridization at ~ 120° was detected in tautomer (1) at O(9)-C(2)-(N(1)), while in tautomer (2) at N(1)-C(6)-O(7), N(3)-C(2)-N(1) and C(6)-N(1)-(H(14)) and in both tautomers (1 and 2) at O(9)-C(2)-N(3) while in tautomer (3) at O(7)-C(6)-C(5) and in tautomer (4) at C(2)-N(1)-C(6). A remarkable feature for the bond angles data of keto form of barbital (tautomer 1) proved by the presence of the bond angles at ~ 117.7° for C(2)-N(1)-H(14), C(6)-N(1)-H(14), C(2)-N(3)-H(15) and H(15)-N(3)-C(4). The bond angles of H(15)-O(9)-(C(2)) and C(6)-O(7)-H(14) cannot be detected in tautomer (1), while the presence of H(15)-O(9)-(C(2)) in tautomers (2 and 4) and C(6)-O(7)-H(14) in tautomers (3 and 4) lie in the range 110.5648° ~ 111.7869° which exhibited the enol-form in the concerned tautomers. The above observations proved the phenomenon of tautomerization. Again the dynamic equilibria are deduced between all the detected tautomers of barbital in the solid state. [10]

From the dihedral (torsion) angle (τ) [18], a positive value of (τ) is assigned to the clockwise rotation of up to 180° necessary to bring the front atoms into an eclipsed position with the rear atom, while the negative value of (τ) is assigned to anti-clockwise rotation less than 180° to bring the front atoms into an eclipsed position with the rear atom. It is a very useful descriptive tool as it can describe all combinations of tetrahedral, trigonal and diagonal atoms. The most dihedral angles of barbital in all its tautomers (Fig. 1) lie in the range: 153.0810° ~ 179.8511°, (Table 2e), referring to the distortion in the linearity of sp³ hybridization.

The approximately zero dihedral angles lie in the range -1.2883° ~ 29.2101° in barbital tautomers pointing that some groups of angles are with +ve sign and others are with –ve sign of the same value, i.e., cancel other. The dihedral angles lie in the range -105.3030° ~ 149.9379° in barbital tautomers, referring to deviation from sp³ hybridization due to distorted electronic effects. However, the dihedral angles lie between 30.3667° ~ -97.9403° referring to the strong deviation from the perpendicular angle attributed to the distortion effect. Detected dihedral angles between 164.7525° ~ -172.1367° for H(14)-N(1)-(C(2)-N(3) and H(14)-N(1)-(C(6)-C(5) and 7.2055° ~ 9.4936° for H(14)-N(1)-(C(6)-O(7) and H(14)-N(1)-(C(2)-O(9) in tautomers (1 and 2) only proved the phenomenon of tautomerization. This explains the absence of the dihedral angles C(5)-(C)-(O)-(H)-(H(14) and N(1)-(C)-(O)-(H)-(H(14) in both tautomers (1 and 2 only). Also, the detected dihedral angles N(1)-(C)-(O)-(H)-(H(15) and N(3)-(C)-(O)-(H)-(H(15) in both concerned tautomers (2 and 4) to assign the phenomenon of tautomerization. The close contact between C(2), C(5); N(1), C(4) and C(6), N(3) in the four tautomers referred to steric hindrance effects between the given atoms. The close contact pointed to O(7), H(22) and O(8); H(17) in tautomer (1) only. Nothing is recorded between O(8), H(21), and vice versa for tautomers (2, 3 and 4), indicating the phenomenon of tautomerization. From the foregoing close contact data (Table 2d), the tautomer (1) is more steric hindered between its atoms and less stable than other tautomers (2, 3 and 4), (Fig. 1).

3.1.2. Thiobarbituric Acid

In sequence for studying the four predicted tautomers of SBA [10,11,14] from the different views: bond length, bond order, bond angles, dihedral angles and close contacts for all forms are given (Figs. 3, 4) and (Table 3). The data suggested the presence of tautomerism. The bond lengths of thione atoms, C(6)-(S)(7), are approximately similar for tautomers (2, 3, and 4), (Table 3a), and lie in the range 1.8179~1.8374 Å, while in tautomer (1), it was shortened to 1.5792 Å due to C(6) of that tautomer and lies between N(1)-(H(13) and N(5)-(H(12) causing steric effect, while in other three tautomers N(1)-(H(13) were disappeared, (Table 3a). The newly formed bond lengths of thiol atoms that appeared in tautomers (3 and 4) are approximately similar: 1.3464 and 1.3537 Å for S(7)-(H(13) and S(7)-(H(12), respectively, (Table 3). This leads to the disappearance of N(5)-(H(12) bond length in tautomer (4) only, also O(9)-(H(13) bond length was absent in tautomers (1 and 3) to form thione-keto in tautomer (1). However, tautomer (2) gives thione-enol form with the reduction of C(2)-O(9) bond length for tautomers (1 and 3) than tautomers (2 and 4). All the above observations indicated the phenomenon of tautomerization between thione (in tautomers 1 and 2) and thiol (in tautomers 3 and 4). Also, the phenomenon of tautomerization takes place between thiol-keto in tautomer (3) and thiol-enol in tautomer (4) (Fig. 3).

This gives reasons for the reduction in bond lengths of N(1)-C(6) in tautomer (3) and N(1)-C(2) in tautomer (4) than the other tautomers due to the formation of N=C.
Fig. (3). The optimized molecular structure of SBA tautomers.

Table 3. Molecular modelling data of SBA tautomers.

| Atoms      | Tautomer (1) | Tautomer (2) | Tautomer (3) | Tautomer (4) |
|------------|--------------|--------------|--------------|--------------|
| N(5)-C(6)  | 1.3725       | 1.4608       | 1.3432       | 1.3075       |
| C(4)-O(8)  | 1.2079       | 1.4129       | 1.2073       | 1.2080       |
| C(4)-N(5)  | 1.3670       | 1.4579       | 1.3562       | 1.3838       |
| C(3)-C(4)  | 1.5174       | 1.5257       | 1.5157       | 1.5090       |
| C(6)-S(7)  | 1.5792       | 1.8220       | 1.8179       | 1.8374       |
| N(1)-C(6)  | 1.3725       | 1.4609       | 1.2959       | 1.4175       |
| C(2)-O(9)  | 1.2081       | 1.4129       | 1.2300       | 1.3550       |
| C(2)-C(3)  | 1.5174       | 1.5257       | 1.5234       | 1.4970       |
| N(1)-C(2)  | 1.3669       | 1.4576       | 1.3858       | 1.2600       |
| C(3)-H(11) | 1.1152       | 1.1165       | 1.1153       | 1.1130       |
| C(3)-H(10) | 1.1147       | 1.1155       | 1.1150       | 1.1130       |
| N(5)-H(12) | 1.0094       | 1.0498       | 1.0076       | ——           |
| N(1)-H(13) | 1.0094       | ——           | ——           | ——           |
| O(9)-H(13) | ——           | 0.9605       | ——           | 0.9720       |
| S(7)-H(13) | ——           | ——           | 1.3464       | ——           |
| S(7)-H(12) | ——           | ——           | ——           | 1.3537       |
(b) Bond Angle (degree °)

| Atoms      | Tautomer (1) | Tautomer (2) | Tautomer (3) | Tautomer (4) |
|------------|--------------|--------------|--------------|--------------|
| C(6)-N(5)-C(4) | 124.7903    | 112.6033     | 126.8883     | 119.1576     |
| O(8)-C(4)-N(5) | 120.4819    | 107.8931     | 121.0098     | 123.8092     |
| O(8)-C(4)-C(3) | 124.1353    | 109.8365     | 124.0481     | 121.0871     |
| N(5)-C(4)-C(3) | 115.3648    | 110.3865     | 114.9390     | 115.0989     |
| C(4)-C(3)-C(2) | 115.1148    | 110.0779     | 115.0659     | 109.7358     |
| C(4)-C(3)-H(11) | 107.7638    | 109.2134     | 108.0665     | 111.1666     |
| C(4)-C(3)-H(10) | 108.9707    | 110.3290     | 108.3654     | 111.1401     |
| C(2)-C(3)-H(11) | 107.7641    | 109.2242     | 108.4978     | 110.4180     |
| C(2)-C(3)-H(10) | 108.9679    | 110.3330     | 108.2679     | 106.9856     |
| H(11)-C(3)-H(10) | 108.0416    | 107.6130     | 108.4081     | 107.2891     |
| S(7)-C(6)-N(5) | 120.7923    | 109.7525     | 117.7200     | 121.1912     |
| N(5)-C(6)-N(1) | 118.2468    | 110.7973     | 121.8668     | 121.8103     |
| S(7)-C(6)-N(1) | 120.7934    | 108.9543     | 120.4123     | 116.9769     |
| C(6)-N(1)-C(2) | 124.7861    | 112.5742     | 122.0468     | 120.7094     |
| O(9)-C(2)-C(3) | 124.1354    | 109.8629     | 119.1885     | 118.4400     |
| O(9)-C(2)-N(1) | 120.4746    | 107.9430     | 122.1069     | 120.8647     |
| C(3)-C(2)-N(1) | 115.3719    | 110.1729     | 118.7040     | 119.5482     |
| H(13)-N(1)-C(2) | 115.8915    | —           | —           | —           |
| H(13)-N(1)-C(6) | 119.3074    | —           | —           | —           |
| H(13)-O(9)-C(2) | —           | 106.3453     | —           | 112.2586     |
| H(13)-S(7)-C(6) | —           | —           | 110.2575     | —           |
| H(12)-N(5)-C(6) | 119.3142    | 109.4637     | 114.4028     | —           |
| H(12)-N(5)-C(4) | 115.8808    | 109.0281     | 118.7087     | —           |
| H(12)-S(7)-C(6) | —           | —           | —           | 113.5718     |

(c) Dihedral Angle (degree °)

| Atoms      | Tautomer (1) | Tautomer (2) | Tautomer (3) | Tautomer (4) |
|------------|--------------|--------------|--------------|--------------|
| C(4)-N(5)-C(6)-N(1) | 10.3612    | -57.1311     | 1.6755       | 5.014        |
| C(4)-N(5)-C(6)-S(7) | -174.3065  | -177.4995    | -177.9778    | -176.2401    |
| C(3)-C(4)-N(5)-C(6) | 8.1902     | 55.8838      | 1.5023       | 24.9509      |
| O(8)-C(4)-N(5)-C(6) | -173.2906  | 175.9100     | -179.1223    | -154.2650    |
| C(6)-N(1)-C(2)-C(3) | -8.2078    | -56.4053     | -5.7532      | -3.2252      |
| C(6)-N(1)-C(2)-O(9) | 173.2787   | -176.3689    | 174.5518     | -170.7941    |
| C(2)-N(1)-C(6)-N(5) | -10.3520   | 57.4589      | 0.6220       | -17.8809     |
| C(2)-N(1)-C(6)-S(7) | 174.3157   | 178.3014     | -179.7339    | 163.7906     |
| N(1)-C(2)-C(3)-C(4) | 25.7375    | 53.9681      | 8.3335       | 31.1431      |
| N(1)-C(2)-C(3)-H(10) | 148.4723   | 175.9679     | -113.0447    | -89.5352     |
| N(1)-C(2)-C(3)-H(11) | -94.5271   | -65.9347     | 129.4975     | 154.0230     |
| O(9)-C(2)-C(3)-C(4) | -155.8103  | 172.7639     | -171.9625    | -160.9875    |
| O(9)-C(2)-C(3)-H(10) | -33.0755   | -65.2363     | 66.6593      | 78.3342      |
| O(9)-C(2)-C(3)-H(11) | 83.9251    | 52.8610      | -50.7984     | -38.1075     |
| H(10)-C(3)-C(4)-O(8) | 33.0803    | 65.3850      | -64.1820     | -104.1705    |
The bond orders of thione atoms, C(6)-S(7) in tautomers (1 and 2), are 1.5266 and 1.6478 (Å), respectively, which indicate the formation of a double bond between these atoms (Fig. 4). For tautomers (3 and 4), these were shortened to 1.014 and 1.0532 (Å), referring to form a single bond between these atoms. The detected bond orders of thiol atoms assigned in tautomers (3 and 4) at ~ 0.98 (Å) for S(7)-H(13) and S(7)-H(12), respectively (Fig. 4). This leads to the disappearance of N(5)-H(12) bond order in tautomer (4) only. The O(9)-H(13) bond order was absent in tautomers (1 and 4). The perfect sp² hybridization at ~120 ° was detected at O(8)-C(4)-N(5) and S(7)-C(6)-N(5) in tautomer (1); at S(7)-C(6)-N(1) in both tautomers (1 and 3); at O(9)-C(2)-N(1) in both tautomers (1 and 4); and at C(6)-N(1)-C(2) in tautomer (4). A remarkable feature for tautomers (3 and 4) in SBA (Table 3b), where the bond angles detected at 110.2575 ° for H(13)-S(7)-C(6) in tautomer (3) and at 113.5718 ° for H(12)-S(7)-C(6) in tautomer (4) proved the thiol form in tautomers (3 and 4) only. However, these bond angles disappeared in both tautomers (1 and 2), which indicated the thione form in tautomers (1 and 2). This leads to the disappearance of H(12)-N(5)-C(4) and H(12)-N(5)-C(6) bond angles in tautomer (4) only. Also, H(13)-O(9)-C(2) bond angle was not detected in tautomers (1 and 3). This is valid for tautomers (2 and 4), giving the thione-enol and thiol-enol forms in tautomers (2 and 4), respectively. The formation of enol forms in tautomers (2 and 4) and thiol forms in tautomers (3 and 4) explained the disappearance of H(13)-N(1)-C(2) and H(13)-N(1)-C(6) bond angles in tautomers (2, 3 and 4) and these bond angles take place in tautomer (1) only. All the above observations indicated the phenomenon of tautomeration between thione-keto in tautomer (1), thione-enol in tautomer (2), thiol-keto in tautomer (3) and thiol-enol in tautomer (4), (Fig. 3).
Fig. (4). Molecular modelling of SBA tautomers.
Meanwhile, the most dihedral angles of SBA in all its tautomers (Fig. 3) lie in the range: 154.0230° – 179.7339°, referring to the distortion in the linearity of sp3 hybridization. These angles lie in the range -104.1705° – 148.4723° in tautomers (1, 3 and 4), referring to deviation from sp3 hybridization due to distorted electronic effects. Such hybridization is invalid in tautomer (2), which means that the tautomer (2) is more stable than the other three tautomers SBA. However, the dihedral angles that lie in between 24.9509° – 94.5366° in all SBA tautomers are attributed to the strong deviation from a perpendicular angle attributed to the distortion effect (Table 3c). The approximately zero dihedral angles lie in the range 0.6220° – 17.8809° in tautomers (1, 3 and 4) pointing that some groups of angles are with +ve sign and others are with −ve sign of the same value, i.e., cancel other. This zero dihedral angle is invalid in tautomer (2), indicating again its stability than the other three tautomers. Detected dihedral angles N(1)-C(6)-S(7)-H(13) and N(5)-C(6)-S(7)-H(13) in tautomer (3) only, in addition to N(1)-C(6)-S(7)-H(12) and N(5)-C(6)-S(7)-H(12) in tautomer (4) only, indicating the presence of thiol form in both structures (3 and 4) proved the phenomenon of tautomerization. The absence of the two dihedral angles C(3)-C(2)-O(9)-H(13) and N(1)-C(2)-O(9)-H(13) in tautomers (1 and 3), while in (2 and 4) indicating the presence of enol form in tautomers (2 and 4) only. Also, the detected dihedral angles H(13)-N(1)-C(6)-S(7), H(13)-N(1)-C(6)-N(5), H(13)-C(2)-C(3) and H(13)-N(1)-C(2)-O(9) in tautomer (1) only, while the absence of the dihedral angles H(12)-N(5)-C(6)-N(1), H(12)-N(5)-C(6)-S(7), C(3)-C(4)-N(5)-H(12) and O(8)-C(4)-N(5)-H(12) in tautomer (4) only proved the phenomenon of tautomerization between thione-keto in structure (1), thione-enol for (2), thiol-keto in (3) and thiol-enol in tautomer (4), (Fig. 3).

The close contact between C(2), C(5); N(1), C(4) and C(6), N(3) with the approximately same degree in tautomers (1, 3 and 4) referred to steric hindrance effects between those atoms in these three tautomers, (Table 3d). While that close contact is invalid in tautomer (2), i.e., no steric hindrance in tautomer (2) of SBA, indicating the stability of tautomer (2) than other tautomers of SBA (1, 3 and 4) (Fig. 3).

3.1.3. 2-Thiouracil

Three tautomers are predicted for 2-TU [13,14] (Fig. 5). The bond length and bond order values for three forms are given in (Table 4a) and (Fig. 6), respectively, where the data suggested the presence of tautomerism. The bond lengths of thione atoms, C(2)-S(8), are approximately similar for tautomers (1 and 2) (Table 4a). However, for tautomer (3), the longer bond length 1.8204 (Å) is due to S(8) of that tautomer forming a new bond with H(10), giving thiol tautomer, while this S(8)-H(10) bond length was disappeared in tautomers (1 and 2). This explains the disappearance of N(3)-H(10) bond length in tautomer (3) only. Also, O(7)-H(9) bond length is absent in tautomer (1) to form thione-keto in tautomer (1) (Table 4a). This is valid for tautomers (2 and 3) with the same bond length in both giving thione-enol and thiol-enol forms, respectively (Table 4a). The formation of enol forms in tautomers (2 and 3) explained the disappearance of N(1)-H(9) bond length in that tautomers. However, this bond length is assigned in tautomer (1) only. All the above observations indicated the phenomenon of tautomerization between thione-keto in tautomer (1), thione-enol in tautomer (2) and thiol-enol in tautomer (3) (Fig. 5).

The bond orders of thione atoms, C(2)-S(8), are approximately similar for tautomers (1 and 2), 1.4533 and 1.5151 (Å), (Figs. 5 and 6), indicating the formation of a double bond between C(2)-S(8) and proved the thione tautomer. However, for tautomer (3), it was reduced to 1.0454 (Å) due to that tautomer forms a new bond S(8)-H(10) with bond order 0.98749 (Å) giving thiol tautomer, while this S(8)-H(10) bond order was absent in tautomers (1 and 2). This explains the disappearance of N(3)-H(10) bond order in tautomer (3) only while it appeared in tautomers (1 and 2) at ~ 0.94 (Å). Also, O(7)-H(9) bond order is absent in tautomer (1) to form thione-keto in tautomer (1) (Fig. 6). This is valid for tautomers (2 and 3) with the approximately same bond order ~ 0.9 (Å) in both giving thione-enol and thiol-enol forms, respectively (Fig. 6). The keto form in tautomer (1) can be proved by assigning a bond order for C(6)-O(7) at 1.8113 (Å), which referred to form a double bond between those two atoms. However, for its tautomers...
Table 4. Molecular modelling data of 2-TU tautomers.

(a) Bond Length (Å)

| Atoms          | Tautomer (1) | Tautomer (2) | Tautomer (3) |
|----------------|--------------|--------------|--------------|
| C(5)-H(12)     | 1.1013       | 1.1008       | 1.1008       |
| C(4)-H(11)     | 1.0991       | 1.0985       | 1.0914       |
| C(5)-C(6)      | 1.4839       | 1.4167       | 1.3972       |
| C(4)-C(5)      | 1.3604       | 1.3750       | 1.3966       |
| N(3)-C(4)      | 1.3963       | 1.3691       | 1.3389       |
| C(2)-N(3)      | 1.3130       | 1.3544       | 1.3538       |
| C(6)-O(7)      | 1.2146       | 1.3606       | 1.3605       |
| N(1)-C(6)      | 1.3692       | 1.3443       | 1.3455       |
| N(1)-C(2)      | 1.3755       | 1.3220       | 1.3539       |
| C(2)-S(8)      | 1.5777       | 1.5796       | 1.8204       |
| N(1)-H(9)      | 1.0087       | ——           | ——           |
| N(3)-H(10)     | 1.0497       | 1.0490       | ——           |
| O(7)-H(9)      | ——           | 0.9715       | 0.9714       |
| S(8)-H(10)     | ——           | ——           | 1.3446       |

(b) Bond Angle (degree °)

| Atoms          | Tautomer (1) | Tautomer (2) | Tautomer (3) |
|----------------|--------------|--------------|--------------|
| C(4)-N(3)-C(2) | 122.1682     | 120.9181     | 117.2145     |
| H(11)-C(4)-C(5)| 123.8628     | 124.5419     | 120.8428     |
| H(11)-C(4)-N(3)| 116.0280     | 116.8105     | 117.0491     |
| C(5)-C(4)-N(3) | 120.1091     | 118.6476     | 122.1080     |
| H(12)-C(5)-C(6)| 120.3277     | 120.7088     | 120.9069     |
| H(12)-C(5)-C(4)| 120.4100     | 120.7801     | 121.0370     |
| C(6)-C(5)-C(4) | 119.2621     | 118.5105     | 118.0561     |
| C(5)-C(6)-O(7) | 124.3650     | 121.7281     | 122.0936     |
| C(5)-C(6)-N(1) | 114.9655     | 120.1127     | 119.4630     |
| O(7)-C(6)-N(1) | 120.6695     | 118.1591     | 118.4434     |
| C(6)-N(1)-C(2) | 120.3039     | 120.3615     | 119.5326     |
| N(3)-C(2)-N(1) | 119.1877     | 121.4347     | 123.6257     |
| S(8)-C(2)-N(3) | 118.4622     | 118.1036     | 117.8326     |
| S(8)-C(2)-N(1) | 122.3501     | 120.4607     | 118.5415     |
| H(10)-N(3)-C(4)| 118.2424     | 119.0240     | ——           |
| H(10)-N(3)-C(2)| 119.5893     | 120.0575     | ——           |
| H(9)-N(1)-C(6) | 116.0985     | ——           | ——           |
| H(9)-N(1)-C(2) | 119.5974     | ——           | ——           |
| C(6)-O(7)-H(9) | ——           | 109.2594     | 109.3017     |
| H(10)-S(8)-C(2)| ——           | ——           | 109.4017     |

(c) Dihedral Angle (degree °)

| Atoms          | Tautomer (1) | Tautomer (2) | Tautomer (3) |
|----------------|--------------|--------------|--------------|
| C(4)-C(5)-C(6)-N(1) | 0.3087       | 0.1824       | -0.0136      |
| C(4)-C(5)-C(6)-O(7)  | -179.6930    | -179.9200    | 179.9164     |
| H(12)-C(5)-C(6)-N(1) | -179.8226    | 179.9037     | -179.9913    |
|        | Tautomer (1) | Tautomer (2) | Tautomer (3) |
|--------|--------------|--------------|--------------|
| (d) Close Contacts |               |              |              |
| Atoms  | Tautomer (1) | Tautomer (2) | Tautomer (3) |
| C(6), N(3) | 2.7875       | 2.7080       | 2.7671       |
| N(1), C(4) | 2.7273       | 2.7478       | 2.7166       |
| C(2), C(5) | 2.7786       | 2.7246       | 2.7004       |
In tautomer (3), where a bond angle at \( \angle C(2) \), at \( C(6) \) and \( O(7) \) hybridiza...

...the perfect sp\(^3\) hybridization at \( \approx 120^\circ \) was detected at C(5)-C(4)-N(3) and O(7)-C(6)-N(1) in tautomer (1); at C(4)-N(3)-C(2), C(5)-C(6)-N(1), C(6)-N(1)-C(2), S(8)-C(2)-N(1) and H(10)-N(3)-C(2) in tautomer (2); at H(12)-C(5)-C(6) in both tautomers (1 and 2); at H(11)-C(4)-C(5) in both tautomers (2 and 3) and at H(12)-C(5)-C(6) in all tautomers of 2-TU. A remarkable feature in tautomer (3), where a bond angle at 109.4017° for H(10)-S(8)-C(2) in that tautomer only proved the thiol tautomer, while the H(10)-S(8)-C(2) bond angle was disappeared in both tautomers (1 and 2) which indicated the thione tautomers. This leads to the disappearance of H(10)-N(3)-C(4) and H(10)-N(3)-C(2) bond angles in tautomer (3) only. Also, C(6)-O(7)-H(9) bond angle was vanished in tautomer (1) to form thione-keto in tautomer (1) only. This is valid for tautomers (2 and 3) with approximately the same bond angle giving thione-enol and thiol-enol forms in tautomers (2 and 3), respectively. The formation of enol forms in tautomers (2 and 3) explained the disappearance of H(9)-N(1)-C(6) and H(9)-N(1)-C(2) bond angles in that tautomers, while these bond angles take place in tautomer (1) only. All the above observations indicated the phenomenon of tautomerization between thione-thione in tautomer (1), thione-enol in tautomer (2) and thiol-enol in tautomer (3), (Fig. 5).

However, from the view of the bond angles between atoms in 2-TU for all its tautomers, (Fig. 5), it is pointed that most of them lie in the range: 109.2594° – 124.5419°, (Table 4b), referring to distorted sp\(^3\) hybridization due to distortion in electronic configuration. The perfect sp\(^3\) hybridization...

Meanwhile, the most dihedral angles of 2-TU in all its predicted tautomers (Fig. 5) lie in the range -170.7076° – -179.9917°, (Table 4c), referring to a slight deviation from the linearity of sp\(^3\) hybridization. The approximately zero dihedral angles lie in the range -0.0136° – 9.1349° in 2-TU tautomers pointing that some groups of angles are with +ve sign and others are with –ve sign of the same value, i.e., cancel other. Detected dihedral angles at \( \approx 179^\circ \) for N(1)-C(2)-N(3)-H(10) and H(10)-N(3)-C(4)-C(5), in addition to...
H(10)-N(3)-C(4)-H(11) and S(8)-C(2)-N(3)-H(10) dihedral angles in tautomers (1 and 2) only, indicating the presence of thione form in both concerned tautomers proved the phenomenon of tautomerization. This gives the reason for the absence of the two dihedral angles N(1)-C(2)-S(8)-H(10) and N(3)-C(2)-S(8)-H(10) in both tautomers (1 and 2), while detected in tautomer (3) only, indicating the presence of thiol form in tautomer (3) only. Also, the detected dihedral angles N(1)-C(6)-O(7)-H(9) and C(5)-C(6)-O(7)-H(9) in tautomers (2 and 3) only, while vanished the dihedral angles H(9)-N(1)-C(2)-S(8), H(9)-N(1)-C(2)-N(3), H(9)-N(1)-C(6)-O(7) and H(9)-N(1)-C(6)-C(5) in tautomers (2 and 3) proving the presence of enol form in only tautomers (2 and 3). All these observations indicated the phenomenon of tautomerization. The close contact exhibits between N(1),C(4); C(2),C(5) and C(6),N(3) with the approximately same degree in all three tautomers of 2-TU (Table 4d), referring to steric hindrance effects between those atoms in all these tautomers (Fig. 5).

3.2. Quantum Chemical Parameters of Pyrimidine Tautomers

Quantum chemical methods have been performed to correlate the chemical structures of the compounds with their physical molecular properties [19], using theoretical parameters to characterize the molecular structure of the investigated ligands and to study their tautomerization phenomena, (Figs. 1-6). The calculated quantum chemical parameters such as the highest occupied molecular orbital energy (E\text{HOMO}), the lowest unoccupied molecular orbital energy (E\text{LUMO}), energy gap (\Delta E), dipole moment (\mu) and those parameters that give valuable information about the reactive behavior such as sum of the total negative charge (STNC), electronegativity (\chi), chemical potential (\Pi), global hardness (\eta) and softness (\sigma) were calculated (Tables 5,6). The concepts of these parameters are related to each other [15] where:

\[ \Pi = -\chi \]

\[ \Pi = \frac{(E_{\text{HOMO}} + E_{\text{LUMO}})}{2} \]

\[ \eta = \frac{(E_{\text{LUMO}} - E_{\text{HOMO}})}{2} \]

The inverse of the global hardness is designated as the softness \(\sigma\) as follows:

\[ \sigma = \frac{1}{\eta} \]

3.2.1. Barbital

Four main tautomers for barbital are expected depending on molecular orbital calculations [10] (Fig. 1). Their charge distributions are represented (Fig. 2). Most of the parameters given (Table 5) are the same for the four tautomers of barbital. The major difference lies in the dipole moment values. The dipole moment, \mu, was used to discuss and rationalize the structure [20], where the order here is in the sequence for the tautomers (4) > (3) > (2) > (1). The calculated quantum chemical parameters for the barbital tautomers calculated by the PM3 method are given (Table 6).

3.2.2. Thio Barbitalic Acid

Four tautomers are predicted [10,11,14] for SBA (Fig. 3) and their charge distribution given in Fig. (4). The four energy parameters (Table 5) are the same, such that slight variations in the heat of formation values denote the presence of four tautomers. The electronegativity (\chi), chemical potential (\Pi), global hardness (\eta) and softness (\sigma) parameters were calculated by the PM3 method for the SBA tautomers (Table 6).

3.2.3. 2-Thiouracil

In a similar way, three main tautomers are expected for the entitled compound [13,14]: KETO-imino-thione Tautomer (1), Enol-thione-imino Tautomer (2) and Enol-thiol Tautomer (3). Their charge distributions are given in Fig. (6). Most of the energy parameters (Table 5) are more or less the same, with slight variation in the three tautomers of thiouracil. The major difference lies through the heat of formation and the dipole moment values to assign the presence of different tautomers. The calculated quantum chemical parameters for the three tautomers of TU calculated by the PM3 method are given (Table 6).

According to the Frontier Molecular Orbital theory, FMO, the chemical reactivity is a function of the interaction between HOMO and LUMO levels of the reacting species. [21] The E\text{HOMO} indicates the ability of the molecule to donate electrons to an appropriated acceptor empty molecular orbitals, and E\text{LUMO} indicates its ability to accept electrons. The lower the value of E\text{LUMO}, the more ability of the molecule to accept electrons. [22] While the higher the E\text{HOMO} value of the ligand, the easier is its offering electrons to the unoccupied d-orbital of the transition metals center and the greater is its ability to complexation. Furthermore, the HOMO level is mostly localized on the pyrimidine moiety, especially with imino groups indicating that the preferred sites for an electrophilic attack at the metal center are through the nitrogen atoms. So, the pyrimidine compounds with high coefficients of HOMO density were oriented toward the metal center leading to easier complexation through the \pi-electrons of the pyrimidine ligands and the lone pair of nitrogen. The HOMO–LUMO energy gap, \Delta E approach, which is an important stability index, was applied to develop theoretical models for explaining the structure and conformation barriers in many molecular systems. The smaller value of \Delta E means that the compound has more probable complexation ability. [22]

The recorded values (Table 6) pointed that tautomer (2) in SBA, TU and tautomer (4) in barbital have the smallest HOMO–LUMO gap (8.317487, 7.350207, 7.541028 and 9.209023 eV obtained by PM3 semi-empirical method) compared with the other tautomers. Accordingly, it could be expected that the above-mentioned tautomers (2 and 4) of molecules have more ability to complexation with the metal ion than the other tautomers of molecules.

Absolute hardness, \eta and softness, \sigma are important properties to measure the molecular stability and reactivity. A hard molecule has a large energy gap and a soft molecule has a small energy gap. Soft molecules are more reactive than hard ones because they could easily offer electrons to an acceptor. In the above system, the tautomer (2) in SBA,
Table 5. Some energetic properties of the ligands calculated by the PM3 method.

| Ligands   | Total Energy (Kcal/mol) [a.u.] | Binding Energy (Kcal/mol) | Isolated Atomic Energy (Kcal/mol) | Electronic Energy (Kcal/mol) | Heat of Formation (Kcal/mol) | Dipole Moment [µ] (Debyes) | STNC (e) |
|-----------|--------------------------------|---------------------------|----------------------------------|------------------------------|-------------------------------|-----------------------------|-------------------------|
| Barbital (1) | -53961.3172 [-85.9928]       | -2535.9790                | -51425.3382                      | -311604.1517                | -138.9580                     | 1.633                       | -1.576997 |
| Barbital (2) | -53947.7049 [-85.9711]       | -2522.3667                | -51425.3382                      | -310970.6229                | -125.3457                     | 2.207                       | -1.694286 |
| Barbital (3) | -53947.1835 [-85.9703]       | -2521.8453                | -51425.3382                      | -312100.0495                | -124.8244                     | 5.343                       | -1.600444 |
| Barbital (4) | -53933.9553 [-85.9492]       | -2508.6172                | -51425.3382                      | -311222.9027                | -111.5962                     | 5.387                       | -1.661873 |
| SBA (1)    | -37666.4091 [-60.0252]       | -1355.0659                | -36311.3432                      | -159282.7169                | -51.5799                      | 2.538                       | -1.092464 |
| SBA (2)    | -37654.3555 [-60.0060]       | -1343.0122                | -36311.3432                      | -158989.8757                | -39.5262                      | 4.080                       | -1.030607 |
| SBA (3)    | -37669.1898 [-60.0296]       | -1357.8465                | -36311.3432                      | -158073.3756                | -54.3605                      | 1.916                       | -1.099139 |
| SBA (4)    | -37656.1096 [-60.0088]       | -1344.7663                | -36311.3432                      | -157761.0577                | -41.2803                      | 5.229                       | -1.044754 |
| TU (1)     | -30880.2232 [-49.2107]       | -1241.3958                | -29638.8274                      | -126837.5946                | 2.531204                      | 4.892                       | -1.082484 |
| TU (2)     | -30871.4921 [-49.1968]       | -1232.6647                | -29638.8274                      | -126636.2532                | 11.2622513                    | 6.243                       | -1.040525 |
| TU (3)     | -30886.4485 [-49.2207]       | -1247.6211                | -29638.8274                      | -125821.4038                | -3.6941130                    | 3.919                       | -0.839059 |

Table 6. The calculated quantum chemical parameters for the ligands calculated by the PM3 method.

| Ligands   | HOMO (eV) | LUMO (eV) | ΔE = E_{LUMO} - E_{HOMO} (eV) | η = ΔE / 2 (eV) | σ = 1 / η (eV) | Πi = (E_{HOMO} + E_{LUMO}) / 2 (eV) | χ = - Πi (eV) |
|-----------|-----------|-----------|--------------------------------|-----------------|--------------|-------------------------------|-----------------|
| Barbital (1) | -10.726065 | -0.317471 | 10.408594                      | 5.204297        | 0.192149     | -5.521768                     | 5.521768 |
| Barbital (2) | -10.183420 | -0.558735 | 9.624685                       | 4.812343        | 0.207799     | -5.3710775                    | 5.371078 |
| Barbital (3) | -10.568722 | -0.637949 | 9.930773                       | 4.965387        | 0.201394     | -5.6033355                    | 5.603336 |
| Barbital (4) | -10.169500 | -0.960477 | 9.209023                       | 4.604511        | 0.217178     | -5.5649885                    | 5.5649885 |
| SBA (1)    | -9.530299  | -1.751704 | 7.778595                       | 3.889297        | 0.257115     | -5.640015                     | 5.640015 |
| SBA (2)    | -9.230345  | -1.880138 | 7.350207                       | 3.675104        | 0.272101     | -5.5552415                    | 5.5552415 |
| SBA (3)    | -10.039382 | -1.064465 | 8.974917                       | 4.487458        | 0.222843     | -5.5519235                    | 5.5519235 |
| SBA (4)    | -9.597355  | -1.300401 | 8.296954                       | 4.148477        | 0.241052     | -5.448878                     | 5.448878 |
| TU (1)     | -9.278298  | -1.344439 | 7.933859                       | 3.969029        | 0.252084     | -5.3113685                    | 5.3113685 |
| TU (2)     | -8.822793  | -1.281765 | 7.541028                       | 3.770514        | 0.265215     | -5.052279                     | 5.052279 |
| TU (3)     | -9.282817  | -0.729537 | 8.55328                       | 4.27664         | 0.233828     | -5.006177                     | 5.006177 |

TU and tautomer (4) in barbital have the highest σ value (0.240457, 0.272101, 0.265215 and 0.217178 eV obtained by PM3 semi-empirical method) be more soft molecule compared with the other tautomers, i.e., more reactive than hard ones because they could easily offer electrons to an acceptor metal and possess high ability for complexation, (Table 6).

**CONCLUSION**

Mulliken population analysis is mostly used for the calculation of the charge distribution over the whole skeleton of the molecule [22] to explain that the more negatively charged heteroatom is more able to complexation with the metal center through a donor-acceptor type reaction. Variation in the complexation ability of the pyrimidine
compounds depends on the presence of electronegative O- and N-atoms. The calculated Mulliken charges [22] of the atoms are presented (Figs. 2, 4, 6). The sites of ionic reactivity can be estimated from the net charges on a molecule. Thus, the calculations of the summation total negative charge, STNC (Table 5), were calculated, where the ligand of more active sites has higher STNC and is more reactive toward the metal center.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

Declared none.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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