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# Study of [1,3] sigmatropic hydrogen migration in thymine, thymidine and thymidylic acid by AM1 method

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The geometry and electronic structures of thymine, thymidine and thymidylic acid involving [1,3] sigmatropic hydrogen migration in the formation of tautomers have been fully optimized and evaluated by semi-empirical molecular orbital AM1 method. In this connection, the heats of formation ($\Delta H_f°$), dipole moments ($\mu$), full atomic charges, and energies of frontier molecular orbitals ($E_{HOMO}$ and $E_{LUMO}$) have been calculated and discussed. The mechanistic investigation of [1,3] sigmatropic rearrangement in thymine affected in the conformational changes of thymidine and thymidylic acid has been studied by the comparison of net charges of atoms in different positions of the molecule. All tautomers of thymine, thymidine and thymidylic acid exist within the energy of 28.054 kcal/mol, 20.889 kcal/mol, and 21.124 kcal/mol respectively. Furthermore, dipole moment and atomic charges of all tautomers indicated that the dipole-dipole interactions play a vital role during the hydrogen bonding with adenine.

**Keywords**: Frontier molecular orbital, AM1, [1,3] sigmatropic rearrangement, tautomers, conformations

UV and ionizing radiations damage DNA duplex at the molecular level and in turn it modifies living cells, due to dimerization of pyrimidine ring in polynucleotides, which are involved in loss or alteration in biological activity. Purines are more radio resistant then pyrimidines. Thymine is more readily dimerized and reverts to thymine on reirradiation[1]. In solution, thymine is photochemically more slowly altered then uracil[2]. The yeast photo-reactivating enzyme splits pyrimidine dimer in irradiated DNA[3]. Thymine dimer (TT) and heterodimers (CT, CC, and UT) are formed through cross links[4] in irradiated DNA or irradiated microorganisms from *E. coli* and possible dimers are isolated[5]. The [1,3] sigmatropic hydrogen migration in the formation of tautomers of thymine, thymidine and thymidylic acid may change the hereditary character and play a vital role in all phases of life. Many side effects of chemical therapy prompted medical and biological scientists to lean towards biological therapy. In this connection, the advanced technology of genetic engineering for the synthesis of genes and discovery of miracle enzymes are required to cure many diseases[6].

In view of these observations in the application of AM1 study for conformational analyses[7], the present investigation on photochemical and thermal [1,3] sigmatropic hydrogen migration in the formation of tautomeric forms of thymine, thymidine and thymidylic acid have been evaluated by the relative values of the net charges of atoms at different positions of the molecule. The heats of formation ($\Delta H_f°$), dipole moments ($\mu$), and energies of frontier molecular orbitals ($E_{HOMO}$ and $E_{LUMO}$) have been determined by full optimization calculations using semi-empirical molecular orbital AM1 method and discussed.

## Computational Methodology[8]

Semi-empirical molecular orbital calculations were performed using AM1 (Austin Model 1) method included in the MOPAC93 on Intel Celron 333 MHz PC. Geometries in the ground state were completely optimized (keyword PRECISE, equivalent to GNORM=1.0) until the lowest energy conformations were found. The keyword MMOK was also used to correct the increase in the barrier to rotation of the amide linkage. The position of the atom in the molecule is mentioned as subscript. The initial molecular geometry was adopted as Pople's standard data[9]. The conformations were designated by Klyne-Prelog terms[10] using *s=syn, a=anti, c=clinal, p=periplanar* ($0\pm30°$ and $180\pm30°$) and all other angles.

## Results and Discussion

### Electronic structures of uracil, uridine and uridylic acid

The electronic structures of thymine, thymidine and thymidylic acid along with the numbering of the system in this context are shown in **Figure 1**. The calculated heats of formation ($\Delta H_f°$), dipole moments ($\mu$), the energies of frontier orbitals ($E_{HOMO}$ and $E_{LUMO}$), and the net charges on typical atoms of thymine tautomers (**a** to **f**) (**Table I**), thymidine **1-3a** and thymidylic acid **1-3b** are presented (**Table II**).

Photochemical or thermal [1,3] sigmatropic rearrangement[11] will take place by shifting of a hydrogen atom with its $\sigma$-bond within a $\pi$-bond

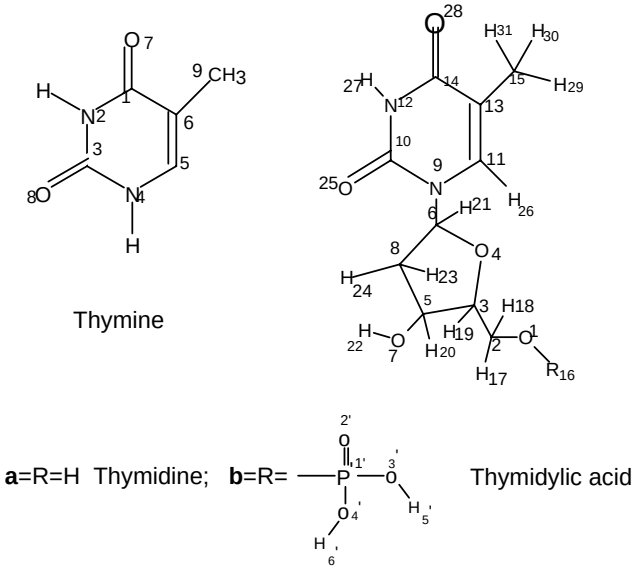



**Figure 1**

frame-work to a new site in two pathways: *i.e.* the hydrogen moves along the top or bottom face of the $\pi$ -system or across the $\pi$-system from top to bottom or *vice versa*. The former is called suprafacial and later antarafacial migration respectively. But in a photochemical reaction, promotion of an electron from HOMO to LUMO, the suprafacial pathway is allowed in the case of **a** to **f** tautomers (**Figure 1** and **Scheme I**). [1,3] Sigmatropic hydrogen migration in tautomers of **b**, **d** and **f** tautomers is easily converted to **c** tautomer, because of an aromatic sextet. The net charges of $O_7$ are more in the case of **a, d**, and $O_8$ is more in the case of **a**, **b** and **f** then the shifting of proton is more susceptible to form tautomers. According to the heat of formation ($\Delta H_f°$) data, the stability of tautomers follow the order **a < d < f < b < c < e** (**Table I**). The value of dipole moment ($\mu$) is in the order **e > b > f > a > c > d**. The strong kind of dipole-dipole interactions make hydrogen bonding in the formation of the double helix of DNA, and it permits the self duplication of the molecule, which is the basis of heredity[12]. Polar bonds allow molecules to interact in various ways with each other. Such secondary interactions are relatively weak and play a vital role in the chemistry of life. When the 2-deoxyribose is united with $N_4$-atom of thymine through a glycosidic bond, the tautomeric forms of thymine are strongly favored in the solid and solution. The tautomeric forms are important in determining the nature of hydrogen bonding in nucleic acids[13].

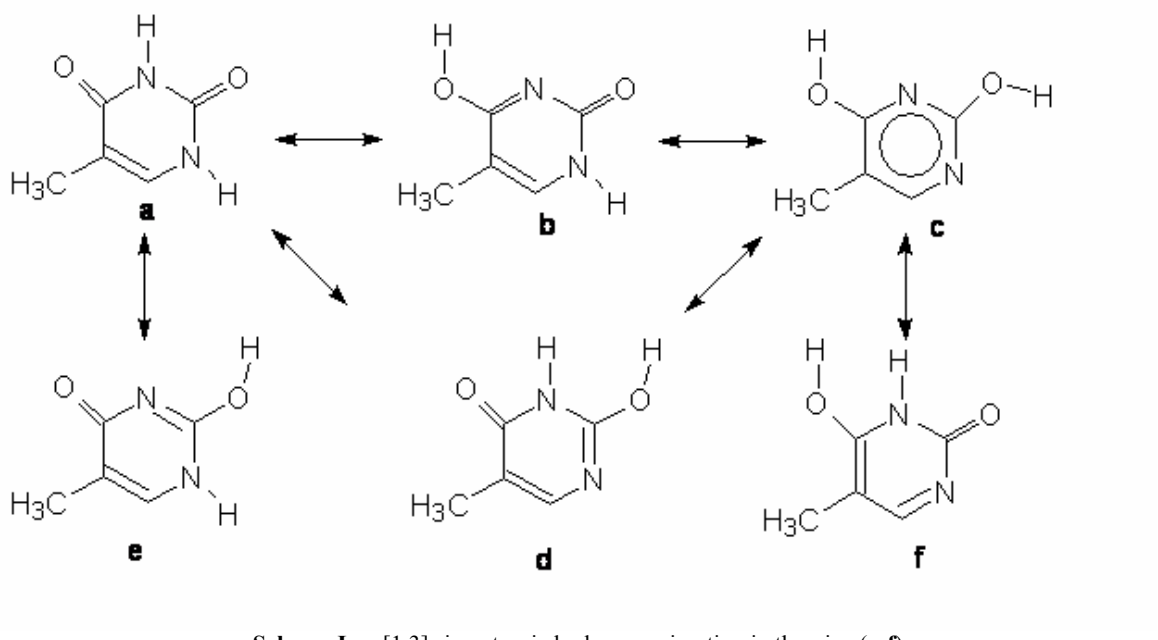
The thymidine tautomers **1-3a** are formed by attachment of 2-deoxy (-) ribose at $N_9$-position of thymine, through a glycosidic bond (**Figure 1** and

**Table I** — Heats of formation $\Delta H_f°$ (in kcal/mol), dipole moment (in Debye), energies of frontier molecular orbitals ($E_{HOMO}$ and $E_{LUMO}$ ) (in eV), and the atomic charges on typical-atoms for thymine tautomers **a** to **f** from AM1 calculation.

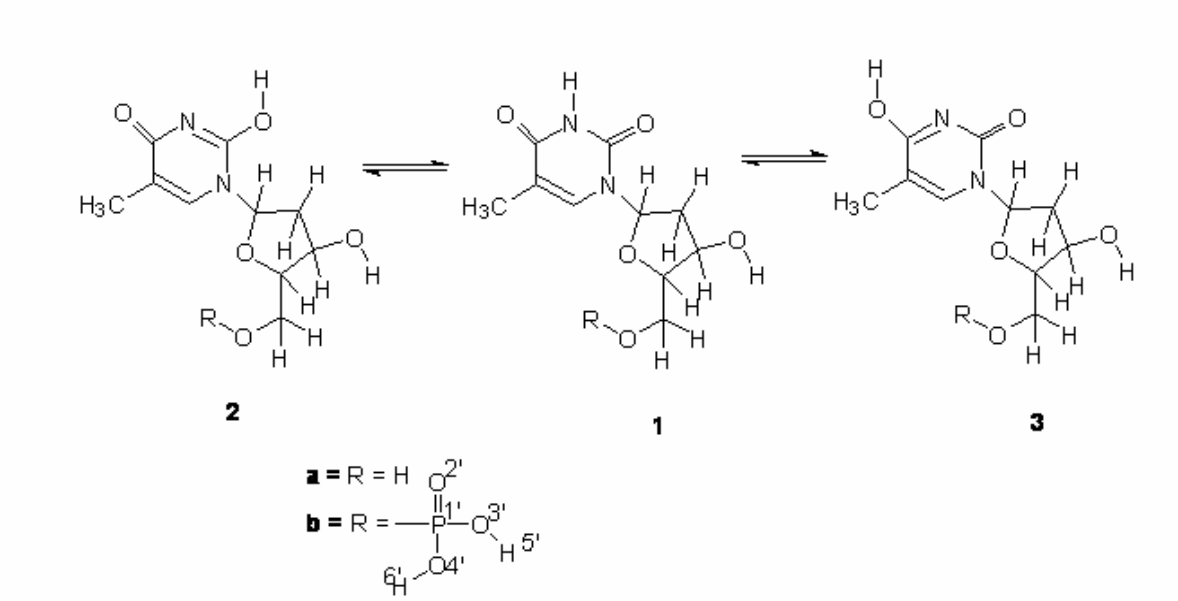
| Property | **a** | **b** | **c** | **d** | **e** | **f** |
|---|---|---|---|---|---|---|
| $\Delta H_f°$ (kcal/ mol) | -61.241 | -43.457 | -42.125 | -52.111 | -33.187 | -45.250 |
| $\mu$(Debye) | 4.219 | 7.274 | 4.089 | 2.507 | 8.107 | 4.882 |
| $E_{HOMO}$(in eV) | -9.607 | -9.507 | -9.713 | -9.247 | -9.473 | -9.173 |
| $E_{LUMO}$(in eV) | -0.278 | -0.472 | -0.330 | -0.439 | -0.028 | -0.475 |
| $C_1$(atomic charge) | 0.3547 | 0.2192 | 0.1802 | 0.3427 | 0.2987 | 0.2289 |
| $C_3$ | 0.3931 | 0.3394 | 0.1752 | 0.2468 | 0.2490 | 0.3392 |
| $C_5$ | 0.0353 | 0.0696 | 0.0276 | 0.0058 | -0.0074 | 0.0591 |
| $C_6$ | -0.2307 | -0.3051 | -0.2870 | -0.2358 | -0.2171 | -0.2743 |
| $C_9$ | -0.1533 | -0.1617 | -0.1651 | -0.1549 | -0.1602 | -0.1413 |
| $N_2$ | -0.3637 | -0.2183 | -0.1708 | -0.3132 | -0.2417 | -0.3558 |
| $N_4$ | -0.3153 | -0.3163 | -0.2555 | -0.2741 | -0.3253 | -0.2072 |
| $O_7$ | -0.3305 | -0.2109 | -0.2094 | -0.3391 | -0.2926 | -0.2339 |
| $O_8$ | -0.3629 | -0.3199 | -0.2035 | -0.2491 | -0.2100 | -0.3198 |

**Table II** — Heats of formation $\Delta H_f°$ (in kcal/mol), dipole moment (in Debye), energies of frontier molecular orbitals ($E_{HOMO}$ and $E_{LUMO}$) (in eV), and the atomic charges on typical-atoms for thymidine **1** to **3a** and thymidylic acid **1** to **3b** tautomers from AM1 calculation.

| Property | **1a** | **2a** | **3a** | **1b** | **2b** | **3b** |
|---|---|---|---|---|---|---|
| $\Delta H_f°$ (kcal/mol) | -192.385 | -171.496 | -175.347 | -412.439 | -391.314 | -394.520 |
| μ(Debye) | 5.8815 | 7.0508 | 8.4079 | 5.6151 | 7.0653 | 2.5246 |
| $E_{HOMO}$(in eV) | -9.293 | -9.136 | -9.205 | -9.614 | -9.242 | -9.414 |
| $E_{LUMO}$(in eV) | 0.025 | 0.219 | -0.217 | -0.286 | 0.109 | -0.441 |
| $C_2$ (atomic charge) | -0.0302 | -0.0291 | -0.0349 | -0.0013 | 0.0063 | -0.0009 |
| $C_8$ | -0.02306 | -0.2323 | -0.2291 | -0.2305 | -0.2336 | -0.2229 |
| $C_{10}$ | 0.3965 | 0.2688 | 0.3463 | 0.4015 | 0.2704 | 0.3432 |
| $C_{13}$ | -0.2427 | -0.2334 | -0.3177 | -0.2467 | -0.2330 | -0.3262 |
| $C_{14}$ | 0.3551 | 0.3088 | 0.2223 | 0.3569 | 0.3126 | 0.2229 |
| $C_{15}$ | -0.1482 | -0.1549 | -0.1567 | -0.1598 | -0.1575 | -0.1660 |
| $N_9$ | -0.2745 | -0.2393 | -0.2825 | -0.2746 | -0.2448 | -0.2887 |
| $N_{12}$ | -0.3634 | -0.3218 | -0.2270 | -0.3639 | -0.3228 | -0.2266 |
| $P_{1'}$ | — | — | — | 2.6041 | 2.6083 | 2.6157 |
| $O_1$ | -0.3445 | -0.3433 | -0.3457 | -0.7526 | -0.7465 | -0.7722 |
| $O_4$ | -0.2755 | -0.2709 | -0.2778 | -0.2739 | -0.2705 | -0.2761 |
| $O_7$ | -0.3197 | -0.3199 | -0.3212 | -0.3163 | -0.3193 | -0.3206 |
| $O_{25}$ | -0.3750 | -0.2624 | -0.3318 | -0.3626 | -0.2630 | -0.3344 |
| $O_{28}$ | -0.3369 | -0.3089 | -0.2138 | -0.3326 | -0.3051 | -0.2122 |
| $O_{2'}$ | — | — | — | -1.0692 | -1.0725 | -1.0462 |
| $O_{3'}$ | — | — | — | -0.8102 | -0.8199 | -0.8113 |
| $O_{4'}$ | — | — | — | -0.7770 | -0.7730 | -0.7895 |
| $(N_{12})H$ | 0.2661 | — | — | 0.2677 | — | — |
| $(O_{25})H$ | — | 0.2695 | — | — | 0.2701 | — |
| $(O_{28})H$ | — | — | 0.2317 | — | — | 0.2330 |




**Scheme I** — [1,3] sigmatropic hydrogen migration in thymine (**a-f**)




**Scheme II** — [1,3] Sigmatropic hydrogen migration in thymidine (**1a-3a**) and thymidylic acid (**1b-3b**)

**Scheme II)**. But the promotion of an electron from HOMO to LUMO, a photochemical reaction is allowed in the suprafacial pathway in case of **3a** tautomer and all others allowed antarafacial thermal [1,3] sigmatropic rearrangement (**Figure 1** and **Scheme II)**. Stereochemically, migration of hydrogen can be suprafacial or antarafacial in the biological systems and natural reactions. In the transition state, a three-center bond is required to involve overlap between the *s* orbital of the hydrogen and lobes of *p* orbitals of the two terminal atoms. But the *s* orbital of the hydrogen and lobes of *p* orbitals in opposite phase cannot be overlapped or bonded simultaneously to both terminal orbitals and therefore, [1,3] shift of hydrogen is symmetry-forbidden.

A sigmatropic rearrangement depends on the symmetry of terminal orbitals and on the geometry of the system. Thus, the transition state would be extremely strained[14], when thermal [1, 3] sigmatropic migration is allowed to take place *via* antarafacial [1, 3] shift. Since they would require the π-framework to be twisted far from the planarity, it requires delocalization of electrons. It can be shown that the net charge of $O_{25}$ is more in case of **1a** and **3a** and $O_{28}$ is more in case of **1a** and **2a**. The [1,3] sigmatropic hydrogen migration is more susceptible to form tautomers **1a** and **3a**. Usually the oxygen atom with larger value of net charge accepts proton shifts more easily, when the proton is shifting from $N_{12}$- to $O_{25}$ in the case of **1a** to form **2a** with decreasing net charges at $O_{25}$, $O_{28}$, $N_9$, $N_{12}$, $C_{10}$, $C_{13}$ and $C_{14}$ – atoms. If the proton is shifting from $N_{12}$- to $O_{28}$ in the case of tautomers **1a** to **3a** with decreasing net charges at $O_{25}$, $O_{28}$, $N_{12}$, $C_{10}$ and $C_{14}$ atoms and increasing at $N_9$, $C_{13}$, and $C_{15}$ atoms (**Table II**). The electron density is highest at $O_{25}$ in case of tautomer **1a**.

According to the heats of formation ($\Delta H_f°$) data, the stability of thymidine tautomers is in the order of **1a < 3a < 2a**. These tautomers are formed with the difference in the heats of formation of 17.038k.cal/mol and 20.889k.cal/mol respectively in the case of **1a** to **3a** and **1a** to **2a**. The value of dipole moment (μ) is in the order of **3a > 2a > 1a**. The hydrogen bonding is a strong kind of dipole-dipole attraction, in which a hydrogen atom stands as a bridge between the electronegative atoms by holding one with a covalent bond and the other by purely electrostatic forces. Tautomer **3a** has more polarity than the other tautomers (**2a** and **3a**). The position of equilibrium depends upon the polarity of the solution and also the presence of tautomers.

Tautomers of thymidylic acid **1-3b** are formed by attachment of phosphate at $O_1$-atom position of thymidine (**Figure 1** and **Scheme II**). But, a photochemical reaction allows the promotion of an electron from HOMO to LUMO, in suprafacial pathway in the case of **1b** and **3b** tautomers. Thymidylic acid tautomer **2b** is allowed antarafacial thermal [1,3] sigmatropic rearrangement. The net charge of $O_1$- is more in the case of **1-3b** tautomers

**Table III** — Bond lengths (Å) of thymidine **1-3a** and thymidylic acid **1-3b** from AM1 calculation

| Bond lengths (Å) | **1a** | **2a** | **3a** | **1b** | **2b** | **3b** |
|---|---|---|---|---|---|---|
| $O_1$-$C_2$ | 1.4186 | 1.4179 | 1.4194 | 1.4149 | 1.4151 | 1.4125 |
| $C_3$-$O_4$ | 1.4309 | 1.4282 | 1.4324 | 1.4314 | 1.4325 | 1.4348 |
| $O_4$-$C_6$ | 1.4405 | 1.4410 | 1.4318 | 1.4398 | 1.4401 | 1.4347 |
| $C_6$-$N_9$ | 1.4602 | 1.4562 | 1.4601 | 1.4599 | 1.4575 | 1.4661 |
| $N_9$-$C_{10}$ | 1.4217 | 1.4061 | 1.4496 | 1.4251 | 1.4059 | 1.4491 |
| $N_9$-$C_{11}$ | 1.3855 | 1.3946 | 1.3686 | 1.3866 | 1.3940 | 1.3657 |
| $C_{10}$-$N_{12}$ | 1.4009 | 1.3234 | 1.4093 | 1.4021 | 1.3197 | 1.4081 |
| $N_{12}$-$C_{14}$ | 1.4077 | 1.4175 | 1.3280 | 1.4059 | 1.4183 | 1.3292 |
| $C_{14}$-$O_{28}$ | 1.2421 | 1.2419 | 1.3718 | 1.2419 | 1.2416 | 1.3713 |
| $C_{10}$-$O_{25}$ | 1.2516 | 1.3825 | 1.2457 | 1.2495 | 1.3827 | 1.2459 |
| $N_{12}$-$H_{27}$ | 0.9774 | — | — | 0.9980 | — | — |
| $O_{25}$-H | — | 0.9745 | — | — | 0.9746 | — |
| $O_{28}$-H | — | — | 0.9745 | — | — | 0.9704 |
| $O_{1'}$-$P_{1'}$ | — | — | — | 1.6062 | 1.6042 | 1.6063 |
| $O_{2'}$-$P_{1'}$ | — | — | — | 1.4504 | 1.4505 | 1.4473 |
| $O_{3'}$-$P_{1'}$ | — | — | — | 1.5916 | 1.5924 | 1.5918 |
| $O_{4'}$-$P_{1'}$ | — | — | — | 1.5829 | 1.5841 | 1.5879 |
| $O_{4'}$-$H_{6'}$ | — | — | — | 0.9577 | 0.9567 | 0.9565 |
| $O_{3'}$-$H_{5'}$ | — | — | — | 0.9541 | 0.9537 | 0.9539 |

than respective thymidine tautomers **1-3a**. The proton shifting from $N_{12}$- to $O_{25}$ in the case of **1b** to **2b** is considered by increasing the atomic charges at $C_2$-, and $C_8$-and decreasing at $O_1$-, $O_{25}$- $O_{28}$-, $N_9$- $N_{12}$-, $C_{10}$- and $C_{14}$-atoms (**Table II**).

The proton shifting from $N_{12}$- to $O_{28}$ in the case of tautomers **1b** to **3b** is considered by decreasing net charges at $O_{25}$, $O_{28}$, $N_{12}$, $C_2$, $C_8$, $C_{10}$ and $C_{14}$ atoms and increasing at $O_1$-, $N_9$-, $C_{13}$- and $C_{15}$-atoms. The net charges are highest at oxygen atoms (*i.e*., $O_{2'}$, $O_{3'}$ and $O_{4'}$), when they are attached to phosphorus atom.

According to the heats of formation ($\Delta H_f°$ ) data, the stability of thymidylic acid tautomers is in the order of **1b > 3b > 2b**. These tautomers are formed with the difference in the heats of formation of 21.125k.cal/mol and 17.919k.cal/mol respectively in the case of **1b** to **2b** and **1b** to **3b**. From this data, it can be predicted that the conversion of **1b** to **3b** is a lower energy process than the conversion of **1b** to **2b**. The value of dipole moment ($\mu$) is more in the case of tautomer **2b**, and it may exist in more polar medium.

**The molecular geometry of thymidine 1-3a**

The [1,3] sigmatropic hydrogen migration in thymine of thymidine can be shown in the **Scheme II** as per the results of AM1 calculations. The molecular deformations will depend on the changes in the parameters of bond lengths, bond angles, dihedral angles and the change in energy content of the molecule. The spatial arrangement of atoms in a molecule is considered for the [1,3] sigmatropic hydrogen migration in thymine of thymidine and its conformations are shown in **Scheme II**. The main data of bond lengths (**Table III**), bond angles (**Table IV**), and dihedral angles (**Table V**) of thymidine tautomers **1-3a** and **Table VI** (**1-3b**) of tautomers are only listed for the sake of simplicity from full-optimized AM1 calculations.

When [1,3] sigmatropic hydrogen migration is involved from $N_{12}$- to $O_{25}$- and $N_{12}$- to $O_{28}$- then respective tautomers **2a** and **3a** will be formed**.** From **Table III**, it is found that the bond length of $N_{12}$-H in **1a** (0.9774 Å) is larger than $O_{25}$-H bond in **2a** (0.9745 Å) and $O_{28}$-H bond in **3a** (0.9745 Å). The proton shifting from $N_{12}$- to $O_{25}$- is in the formation of **2a** from **1a,** the bond lengths are decreased in the case of $C_3$-$O_4$**,** $C_6$-$N_9$**,** $N_9$-$C_{10}$ and $O_{12}$-$N_{12}$ by 0.0027 Å, 0.004 Å, 0.0156 Å, and 0.0775 Åand increased in the case of $N_9$-$C_{11}$, $N_{12}$-$C_{14}$ and $C_{10}$-$O_{25}$ by 0.0091 Å, 0.0098 Å and 0.1309 Å. According to the **Table IV**, bond angles of $C_2C_3O_4$, $C_6N_9C_{10}$ and $N_9C_{10}N_{12}$, are increased by 1.24°, 4.09° and 7.76° and decreased in case of bond angle of $C_{10}N_{12}C_{14}$, $N_9C_{10}O_{25}$ and $N_{12}C_{14}O_{28}$ by 4.61°, 7.64° and 1.51°. As per the

**Table IV** — Bond angles (° ) of thymidine **1-3a** and thymidylic acid **1-3b** from AM1 calculation

| Bond angle (°) | **1a** | **2a** | **3a** | **1b** | **2b** | **3b** |
|---|---|---|---|---|---|---|
| $C_2C_3O_4$ | 109.99 | 111.23 | 109.56 | 109.87 | 110.15 | 110.13 |
| $C_2C_3O_5$ | 113.70 | 112.88 | 114.37 | 114.67 | 114.59 | 114.33 |
| $C_6N_9C_{10}$ | 117.88 | 121.97 | 118.86 | 118.48 | 122.30 | 117.99 |
| $C_6N_9C_{11}$ | 122.01 | 121.73 | 121.68 | 120.87 | 121.53 | 122.45 |
| $N_9C_{10}N_{12}$ | 118.77 | 126.53 | 119.90 | 118.30 | 126.39 | 119.91 |
| $C_{10}N_{12}C_{14}$ | 122.92 | 118.31 | 117.82 | 123.29 | 118.84 | 117.79 |
| $N_9C_{10}O_{25}$ | 121.18 | 113.54 | 117.66 | 121.32 | 113.25 | 117.22 |
| $C_{10}N_{12}H_{27}$ | 117.10 | — | — | 116.97 | — | — |
| $N_{12}C_{14}O_{28}$ | 118.47 | 119.98 | 114.35 | 118.70 | 120.14 | 114.36 |
| $C_{10}O_{25}H$ | — | 108.29 | — | — | 108.32 | — |
| $C_{14}O_{28}H$ | — | — | 107.81 | — | — | 107.82 |
| $O_{2'}P_{1'}O_1$ | — | — | — | 116.36 | 115.63 | 114.75 |
| $O_{2'}P_{1'}O_{3'}$ | — | — | — | 114.49 | 113.73 | 121.42 |
| $O_{2'}P_{1'}O_{4'}$ | — | — | — | 121.28 | 122.34 | 119.37 |
| $P_{1'}O_{3'}H_{5'}$ | — | — | — | 117.39 | 117.93 | 118.54 |
| $P_{1'}O_{4'}H_{6'}$ | — | — | — | 117.08 | 116.77 | 117.02 |

**Table V** — Dihedral angles (° ) of thymidine tautomers (**1** to **3)a** from AM1 calculation.

| Dihedral angles (° ) | **1a** | | **2a** | | **3a** | |
|---|---|---|---|---|---|---|
| | Angle | * | Angle | * | Angle | * |
| $O_1C_2C_3O_4$ | -71.23 | -*sc* | -67.45 | -*sc* | -79.94 | -*sc* |
| $O_1C_2C_3C_5$ | 50.56 | +*sc* | 54.91 | +*sc* | 42.02 | +*sc* |
| $C_2C_3C_5O_7$ | 107.35 | +*ac* | 109.95 | +*ac* | 110.13 | +*ac* |
| $C_3O_4C_6N_9$ | -125.84 | -*ac* | -126.09 | -*ac* | -123.51 | -*ac* |
| $O_4C_6N_9C_{10}$ | -125.19 | -*ac* | -119.52 | -*ac* | -136.35 | -*ac* |
| $O_4C_6N_9C_{11}$ | 44.57 | +*sc* | 55.72 | +*sc* | 40.12 | +*sc* |
| $C_6N_9C_{10}N_{12}$ | 173.69 | +*ap* | 178.30 | +*ap* | 177.18 | +*ap* |
| $N_9C_{10}N_{12}C_{14}$ | -1.96 | -*sp* | -1.36 | -*sp* | 0.06 | +*sp* |
| $C_3C_2O_1H_{16}$ | 168.71 | +*ap* | 153.62 | +*ap* | -178.47 | -*ap* |
| $C_3C_5O_7H_{22}$ | -178.13 | -*ap* | -179.00 | -*ap* | 179.56 | +*ap* |
| $C_6N_9C_{10}O_{25}$ | -7.98 | -*sp* | -3.14 | -*sp* | -3.53 | -*sp* |
| $C_6N_9C_{11}H_{26}$ | 6.85 | +*sp* | 1.59 | +*sp* | 2.07 | +*sp* |
| $C_{10}N_{12}C_{14}O_{28}$ | -179.62 | -*ap* | 179.85 | +*ap* | 179.85 | +*ap* |
| $N_9C_{10}N_{12}H_{27}$ | 178.88 | +*ap* | -- | -- | -- | -- |
| $N_9C_{10}O_{25}H$ | -- | -- | 179.36 | +*ap* | -- | -- |
| $N_{12}C_{14}O_{28}H$ | -- | -- | -- | -- | 179.11 | +*ap* |

* Conformational analyses[10] using prefixes *a = anti, s = syn, p = peri-planar, c = clinal, and* + & - signs.

**Table V**, dihedral angle is changed from -*ap* to +*ap*, in the conformation of tautomers **1a** to **2a** in the case of $C_{10}N_{12}C_{14}O_{28}$, +a*p* conformation is observed in the case of $N_9C_{10}N_{12}H$ of **1a** and $N_9C_{10}O_{25}H$, of tautomer **2a**.

[1,3] Sigmatropic hydrogen migration from $N_{12}$- to $O_{28}$- is involved in the formation of **3a** from **1a**. The bond lengths of $N_9$-$C_{11}$, $N_{12}$-$C_{14}$, and $C_{13}$-$C_{15}$ are decreased by 0.0169 Å, 0.0797 Å, and 0.0021 Å and increased in the case of $N_9$-$C_{10}$, $C_{10}$-$N_{12}$, $C_{10}$-$O_{25}$ and $C_{14}$-$O_{28}$ by 0.0279 Å, 0.0084 Å, 0.0059 Å and 0.1297 Å (**Table III**). **Table IV** shows that the bond angles are decreased by 5.1°, 3.52° and 4.12° respectively in the case of $C_{10}N_{12}C_{14}$, $N_9C_{10}O_{25}$ and $N_{12}C_{14}O_{28}$ and increased in case of bond angle of $N_9C_{10}N_{12}$ by 1.13°. The bond angle of $C_{10}N_{12}H$ in **1a** (117.10°) is changed

**Table VI** — Dihedral angles (° ) of thymidylic acid tautomers (**1** to **3**)**b** from AM1 calculation.

| Dihedral angles (° ) | **1b** | | **2b** | | **3b** | |
|---|---|---|---|---|---|---|
| | Angle | * | Angle | * | Angle | * |
| $O_1C_2C_3O_4$ | -78.48 | -*sc* | -81.47 | -*sc* | -78.50 | -*sc* |
| $O_1C_2C_3C_5$ | 43.59 | +*sc* | 41.05 | +*sc* | 43.46 | +*sc* |
| $C_2C_3C_5O_7$ | 108.10 | +*ac* | 104.16 | +*ac* | 111.99 | +*ac* |
| $C_3O_4C_6N_9$ | -117.62 | -*ac* | -123.52 | -*ac* | -112.96 | -*ac* |
| $O_4C_6N_9C_{10}$ | -102.71 | -*ac* | -130.76 | -*ac* | -171.44 | -*ap* |
| $O_4C_6N_9C_{11}$ | 64.35 | +*sc* | 43.61 | +*sc* | 5.46 | +*sp* |
| $C_6N_9C_{10}N_{12}$ | 170.74 | +*ap* | 177.72 | +*ap* | 177.23 | +*ap* |
| $N_9C_{10}N_{12}C_{14}$ | -1.97 | -*sp* | -0.66 | -*sp* | 0.09 | +*sp* |
| $C_2C_3C_5H_{20}$ | -12.03 | -*sp* | -16.11 | -*sp* | -7.54 | -*sp* |
| $C_3O_4C_6H_{21}$ | 126.58 | +*ac* | 120.52 | +*ac* | 131.59 | +*ac* |
| $C_3C_5O_7H_{22}$ | -177.93 | -*ap* | -177.52 | -*ap* | 174.93 | +*ap* |
| $C_6N_9C_{10}O_{25}$ | -11.29 | -*sp* | -3.38 | -*sp* | -2.91 | -*sp* |
| $C_6N_9C_{11}H_{26}$ | 9.98 | +*sp* | 1.95 | +*sp* | 2.88 | +*sp* |
| $C_{10}N_{12}C_{14}O_{28}$ | -179.68 | -*ap* | 178.43 | +*ap* | 179.77 | +*ap* |
| $N_9C_{10}N_{12}H_{27}$ | 178.71 | +*ap* | -- | -- | -- | -- |
| $N_9C_{10}O_{25}H$ | -- | -- | 179.04 | +*ap* | -- | -- |
| $N_{12}C_{14}O_{28}H$ | -- | -- | -- | -- | 176.65 | +*ap* |
| $P_{1'}O_{2'}O_1C_2$ | -157.98 | -*ap* | -177.98 | -*ap* | -157.84 | -*ap* |
| $O_1O_{2'}P_{1'}O_{4'}$ | 122.81 | +*ac* | 123.53 | +*ac* | 121.95 | +*ac* |
| $O_1O_{2'}P_{1'}O_{3'}$ | -116.98 | -*ac* | -118.38 | -*ac* | -116.04 | -*ac* |
| $O_{2'}P_{1'}O_{4'}H_{6'}$ | 175.12 | +*ap* | 152.70 | +*ap* | 145.10 | +*ac* |
| $O_{2'}P_{1'}O_{3'}H_{5'}$ | 1.58 | +*sp* | 3.33 | +*sp* | 106.01 | +*ac* |

* Conformational analyses[10] using prefixes *a = anti, s = syn, p = peri-planar, c = clinal, and* + & - signs.

to $C_{14}O_{25}H$ in tautomer **3a** (107.81°). **Table V** presents that the change of dihedral angles are -*sp* to +*sp*, +*ap* to -*ap*, -*ap* to +*ap*, and -*ap* to +*ap*, in the conformation of tautomer **1a** to **3a** in the case of $N_9C_{10}N_{12}C_{14}$, $C_3C_2O_1H_{16}$, $C_3C_5O_7H_{22,}$ and $C_{10}N_{12}C_{14}O_{28}$. The dihedral angle is +*ap* conformation in the case of $N_9C_{10}N_{12}H$ tautomer **1a** and $N_{12}C_{14}O_{28}H$ of tautomer **3a**. It can be predicted that the sequence of [1,3] sigmatropic hydrogen migration in thymine of thymidine from **1a** to **2a** or **3a**, changes the conformation and dipole moment. The polar bonds may interact with other molecules in various media. Further, it is relatively weak in the secondary interactions and play vital role in the replication, translation, transcription, recombination and mutation will take place among the genes[15].

### The molecular geometry of thymidylic acid 1-3b

**Table III** represents that the bond length of $N_{12}$-H in **1b** (0.9980 Å) is decreased to $O_{25}$-H bond in **2b** (0.9746 Å) and $O_{28}$-H bond in **3b** (0.9704 Å), if the [1,3] sigmatropic hydrogen migration is involved from $N_{12}$- to $O_{25}$- and $N_{12}$- to $O_{28}$- in the formation of respective tautomers **2b** and **3b.** When the [1,3] migration of proton from $N_{12}$- to $O_{25}$- in thymine of thymidylic acid with the formation of **2b** from **1b**, the bond lengths of $N_9$-$C_{11}$, $N_{12}$-$C_{14}$ and $C_{10}$-$H_{25}$ are increased by 0.0074 Å, 0.0124 Å and 0.1332 Å and decreased in the case of $C_3$-$C_5$**,** $C_6$-$N_9$**,** $N_9$-$C_{10}$ and $C_{10}$-$N_{12}$ by 0.0019 Å, 0.0024 Å, 0.0192 Å and 0.0824 Å. **Table IV** shows that the bond angles of $C_6N_9C_{10}$, $N_9C_{10}N_{12}$, $N_{12}C_{14}O_{28}$, and $O'_2P'_1O'_{4,}$ are increased by 3.82°, 8.09°, 1.44° and 1.06° and decreased in case of bond angle of $C_{10}N_{12}C_{14}$ and $N_9C_{10}O_{25}$ by 4.45° and 8.07° respectively. The bond angle of $C_{10}N_{12}H$ in **1b** (116.97°) is changed to $C_{10}O_{25}H$ with the bond angle of 108.32° in **2b**. As per the **Table VI**, dihedral angle is changed from -*ap* to +*ap* and +*ap* to -*ap* in the conformation of tautomers from **1b** to **2b** in the case of $C_{10}N_{12}C_{14}O_{28}$ and $P'_1O'_2O_1C_2$ respectively. Dihedral angle is +*ap* in the conformation of $N_9C_{10}N_{12}H_{27}$, of **1b** and $N_9C_{10}O_{25}H$, of tautomer **2b**.

When the [1,3] migration of proton from $N_{12}$- to $O_{28}$- in the formation of thymidylic acid tautomer **3b** from **1b**, the bond lengths of $C_3$-$O_4$, $C_6$-$N_9$, $N_9$-$C_{10}$, and $C_{14}$-$O_{28}$ are increased by 0.0034 Å, 0.0062 Å, 0.024 Å and 0.1294 Å and decreased in the case of $N_9$-$C_{11}$, $O_4$-$C_6$ and $N_{12}$-$C_{14}$ by 0.0207 Å, 0.0051 Å and 0.076 Å (**Table III**). From **Table IV**, it is revealed that the bond angle of $O'_2P'_1O'_3$ is increased by 6.93° and decreased in the case of $N_9C_{10}O_{25}$ and $N_{12}C_{14}O_{28}$ by 4.1° and 4.34°. The bond angle of $C_{10}N_{12}H$ in **1b** (116.97°) is changed to $C_{14}O_{28}H$ in **3b** (107.82°) tautomer. **Table VI** presents that dihedral angle is changed the conformation from *-ac* to *-ap*, *+sc* to *–sp*, *-sp* to *+sp*, *+ap* to *-ap*, *+sp* to *+ac* and *+ap* to *+ac* in the case of $O_4C_6N_9C_{10}$, $O_4C_6N_9C_{11}$, $N_9C_{10}N_{12}C_{14}$, $P'_1O'_2O_1C_2$, $O'_2P'_1O'_3H'_5$ and $O'_2P'_1O'_4H'_6$ in the formation of tautomer **3b** from **1b** respectively. The dihedral angle is changed the conformation from *-ap* to *+ap* in the case of $C_3C_5O_7H_{27}$ and $C_{10}N_{12}C_{14}O_{28}$ of tautomer **3b** from **1b**. But the [1,3] sigmatropic migration of proton from $N_{12}^-$ to $O_{28}^-$ in thymine of thymidylic acid with the formation of **3b** from **1b**, the conformation is *+ap* in the case of **1b** ($N_9C_{10}N_{12}H$) and **3b** ($N_{12}C_{14}O_{28}H$) and rests of positions are moderately changed.

## Conclusion

The present work offers a convenient and potentially useful approach to predict weak interactions, which play a vital role in the chemistry of life. Photochemical or thermal [1,3] sigmatropic hydrogen migration in thymine has effects on the conformations of thymidine and thymidylic acid. Thus, the tautomers of thymine studied exist within the energy range of 28.054kcal/mol. Dipole moment and total charge in tautomers portray dipole-dipole interactions for hydrogen bonding in nucleic acids. Further, the utility of theoretical prediction is important for evaluating the nature of hydrogen bonding in nucleic acids and storage / retrieval / transfer of genetic information. This study reveals that the stability of conformations is highly dependent upon the polarity of the medium.

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