Tautomerism in Flindersine - A DFT Treatment

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Abstract

Flindersine is a natural product of plant kingdom. Its structure contains a lactam group which could undergo 1,3-type proton tautomerism. It also has an embedded pyran moiety which might show valence tautomerism. Presently, those tautomers are investigated within the restrictions of density functional theory at the level of B3LYP/6-311++G(d,p). Certain quantum chemical output has been collected compared and discussed. Also the possibility of valence tautomerism has been searched by proposing two transition state paths.

1. Introduction

Flindersine is an oxacyclic organonitrogen heterocyclic compound having molecular formula of C_{14}H_{13}NO_{2}. It is a tricyclic compound having an embedded phenylene ring.
too. Flindersine is also called 2,6-dihydro-2,2′-dimethyl-5H-pyrano[3,2-c]quinolin-5-one or 2,2′-dimethyl-α-pyrano(5′,6′,3,4)-2(1H)-quinolone. For a long time it has been on the focus of scientific interest and has been isolated from many natural sources [1-6]. Its bioactivity has been also tested [5-9]. It exhibits some antibacterial and antifungal activity [5, 6].

Bio efficacy of flindersine against Helicoverpa armigera Hübner, Spodoptera litura Fabricius, Anopheles stephensis Liston and Culex quinquefasciatus say was established by Duraipandiyan et al. [7]. Some synthetic works on flindersine have been reported [10-17]. A naturally occurring photochromic chromene, flindersine (FL), has been experimentally investigated and compared with that of a carbonyl group present in a structurally related unreactive heterocyclic compound, 6(5H)-phenanthridinone (PH) by Gentili et al. [15].

2. Method of Calculation

In the present study, the initial geometry optimizations of all the structures leading to energy minima have been achieved by using MM2 method followed by semi-empirical PM3 self-consistent fields molecular orbital (SCF MO) method [18, 19] at the restricted level [20, 21]. Subsequent optimizations were achieved at Hartree-Fock level using various basis sets. Then, geometry optimizations were managed within the framework of density functional theory (DFT) [22, 23] at the level of B3LYP/6-311++G(d,p) [21, 24]. The exchange term of B3LYP consists of hybrid Hartree-Fock and local spin density (LSD) exchange functions with Becke’s gradient correlation to LSD exchange [23, 25]. The correlation term of B3LYP consists of the Vosko, Wilk, Nusair (VWN3) local correlation functional [26] and Lee, Yang, Parr (LYP) correlation correction functional [27]. Also, the vibrational analyses were done. The total electronic energies are corrected for the zero point vibrational energy (ZPE). The normal mode analysis for each structure yielded no imaginary frequencies for the 3N−6 vibrational degrees of freedom, where N is the number of atoms in the system. This indicates that the structure of each molecule corresponds to at least a local minimum on the potential energy surface. For certain structures transition state search has been performed which possesses only a single imaginary vibrational mode. All these calculations were done by using the Spartan 06 package program [28].
3. Results and Discussion

Flindersine molecule is a lactam also having a cyclic ether moiety (α-pyrano ring). Lactams show lactam-lactim type proton tautomerism [29, 30]. Tautomers having different structures exhibit dual reactivity, depending on the tautomer content present (allelotropic mixture [29]). Note that substances which are isomeric under certain conditions can be tautomeric under more drastic conditions [29, 30]. On the other hand, tautomerism plays an important role on some properties of molecules. The proton tautomerism is a special kind of cationotropic tautomeric transformations.

On the other hand, flindersine molecular structure having an embedded α-pyrano moiety invokes one to consider the possibility of valence tautomerism (VT) because many pyran containing examples of it exist in the literature [31-41].

**Proton tautomerism**

Lactam-lactim tautomerism is a 1,3-type proton tautomerism [29]. In flindersine molecule, its structural peculiarity (cross conjugation) precludes any 1,5-type proton tautomerism between N-H of the lactam moiety and pyran oxygen atom. Figure 1 shows the optimized structures of the lactam and lactim forms of flindersine. The figure also displays the direction of the dipole moment vectors.

![Figure 1. Optimized structures of the lactam and lactim forms of flindersine.](image)

Figure 2 shows the electrostatic potential (ESP) charges on atoms of the lactam and lactim tautomers considered. Note that the ESP charges are obtained by the program based on a numerical method that generates charges that reproduce the electrostatic potential field from the entire wavefunction [28].

Note that the tautomers have dipole moments vectors which are directed to different positions. Their numerical values are 3.77 debye and 2.27 debye, respectively for the lactam and lactim forms.
Figure 2. The ESP charges on atoms of some of the tautomers considered (hydrogens omitted).

Figure 3 shows the IR spectra of some of the structures considered. The lactam has N-H stretching at 3594 cm$^{-1}$ followed by aromatic C-H stretchings at 3193 cm$^{-1}$. Next symmetrical and asymmetrical C-H stretchings of the methyl groups occur, respectively at 3118 cm$^{-1}$ and 3028 cm$^{-1}$. Pyran C-H stretchings happen at 3202 cm$^{-1}$ indicating aromatic behavior of it. The strong peak at 1724 cm$^{-1}$ is the amide stretching. The experimental values of lactam form of flindersine were reported (3165, 1665, 1628, 1598, 1500, 1480, 1410 cm$^{-1}$) [42]. In the case of lactim form O-H stretching occurs at 3767 cm$^{-1}$ followed by pyran C-H stretchings which happen at 3203 cm$^{-1}$. The methyl
C-H stretchings occur at 3110-3029 cm\(^{-1}\). The peaks at 1688-1602 cm\(^{-1}\) are due to the skeletal breathing of the aromatic ring overlapped with C=C stretching of the pyran ring.

The keto form dominates in keto-enol equilibrium for common carbonyl-containing structures. However, in many cases enols can be spectroscopically observed or isolated and even in some cases they even dominate the equilibrium [29, 30]. Lactam-lactim tautomerism is similar to keto-enol tautomerism because both of them are 1,3-type proton tautomerism.

Table 1 displays some energies of the tautomeric species considered where E, ZPE and \(E_C\) are the total electronic energy, zero point vibrational energy and the corrected total electronic energy, respectively. As seen in the table the lactim form is the least stable one. The underlying reason for it might be explained by referring to the following resonance structures.

| Structure | E (kJ/mol) | ZPE (kJ/mol) | \(E_C\) (kJ/mol) |
|-----------|-----------|-------------|-----------------|
| Lactam    | -1960571.82 | 630.29      | -1959941.53     |
| Lactim    | -1960546.36 | 629.67      | -1959916.69     |

Energies in kJ/mol.

Both structures B and D are charge separated (four bonds away) but the negative charge on the oxygen atom should be more stable (Structure-B) than the case on the nitrogen because of the greater electronegativity of the former atom, namely oxygen.

Figure 4 shows the time-dependent UV-VIS spectra of some of the species considered. As seen in the figure, both of the \(\lambda_{\text{max}}\) values change their positions in the
spectrum of the lactim form as compared to the lactam case. The overall effect is hypsochromic effect in the lactim form accompanied by some hyperchromic effect. The experimental values for the lactam form are 364, 347, 334, 220 nm [42].

Table 2 displays the HOMO, LUMO energies and the interfrontier molecular orbital energy gaps (\(\Delta\varepsilon\)) of the tautomers of flindersine. The orders of HOMO and LUMO energies are lactim< lactam and lactam< lactim, respectively. Namely, as the lactam converts into the lactim form, its HOMO energy decreases but the LUMO energy increases (see Figure 5). Consequently, the interfrontier molecular orbital energy gap of the lactam is narrower than the respective value of the lactim. Because of that the UV-VIS spectrum of this tautomer as compared to the lactam form exhibits some bathochromic effect.

**Table 2.** The HOMO, LUMO energies and the interfrontier molecular orbital energy gaps (\(\Delta\varepsilon\)).

| Structure | HOMO  | LUMO  | \(\Delta\varepsilon\) |
|-----------|-------|-------|-----------------------|
| Lactam    | -568.45 | -184.81 | 383.64 |
| Lactim    | -576.46 | -165.21 | 411.25 |

Energies in kJ/mol.

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**Figure 4.** UV-VIS spectra of some of the species considered.
Figure 5 shows some of the molecular orbital energy levels of the species considered.

Note that VT stands for the valence tautomer of the lactam form of flindersine (see the next section).

**Valance tautomerism**

Degenerate interconversions can be considered a special case of rearrangements called valence isomerization or valence tautomerization [29-41]. A general scheme is proposed for the interconversions of six-membered oxygen-containing heterocycles (pyrylium salts, pyrans, and pyrones) and their open-chain forms, having selected pyrylium salts as compounds of the key type [41]. The latest data concerning the mechanism of a number of the above transformations are examined. It is shown that ring opening is one of the most characteristic manifestations of the reactivity of six-membered oxygen-containing heterocycles [41]. Note that Flindersine structure also possesses an embedded pyran moiety.
For the formation of the valence tautomer two different paths leading to the transition states can be proposed. Figure 6 shows the interrelationship between the various resonance structures and the valence tautomer VT considered.

Figure 6. Resonance-assisted valance tautomerism in flindersine.

Figure 7 shows the optimized structure of valence tautomer and the transition states TR1 and TR2 leading to VT, valence tautomer, of flindersine.

Figure 7. Optimized structure of VT and the transition states leading to VT, valence tautomer of flindersine.
Figure 8 shows the IR spectra of the transition states considered and the valence tautomer of flindersine. The peak (1738-1736 cm\(^{-1}\)) which is common in all three spectra stands for the carbonyl (lactam) stretching. In transition state TR1 the peak at 1648 cm\(^{-1}\) is the stretching frequency of newly forming carbonyl group originating from the pyran ring. Note that it is also present in the spectrum of the valence tautomer which also has additional strong peaks at 1646 cm\(^{-1}\) (C=C stretching for the double bond in the side chain) and 1584 cm\(^{-1}\) (C=C stretching of the exocyclic double bond).

Figure 9 shows geometries of the transition state of TR1 and TR2. It is noteworthy that in TR2 the C-O bond being broken is longer than the respective bond in TR1. This property makes TR2 to have somewhat greater entropy (see Table 5 in thermochemistry section).
Figure 9. Geometries of the transition states.

Figure 10 shows the ESP charges on atoms of the transition states considered.

Figure 10. The ESP charges on atoms of the transition states considered (hydrogens omitted).

Table 3 includes some energies of the transition states considered and the valence tautomer VT.

Table 3. Some energies of the transition states considered and the valence tautomer VT.

| Structure | E      | ZPE   | E_e'   |
|-----------|--------|-------|--------|
| TR1       | -1960485.31 | 623.15 | -1959862.16 |
| TR2       | -1960518.99  | 623.75 | -1959895.24  |
| VT        | -1960561.00  | 626.07 | -1959934.93  |

Energies in kJ/mol.

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Comparison of $E_C$ values of VT with the respective values of TR1 and TR2 reveals that TR2 resembles the product VT. As the $E_C$ value of VT is compared with the $E_C$ values of the lactam and lactim forms (see Table 1), the order of stabilities appears as lactam>VT>lactim.

A comparison of the charges on the reaction termini in the transition states (see Figure 10) reveals that TR2 requires less amount of charge separation (see Figure 10). In other words the positive charge on the carbon atom at the reaction termini of TR1 and TR2 are 0.989 and 0.701 units, respectively although the negative charge on the oxygen atoms are very comparable. Consequently, TR2 is less energy demanding (more stable) as compared to TR1 (see Table 3).

Table 4 displays the HOMO, LUMO energies and the interfrontier molecular orbital energy gaps ($\Delta\varepsilon$) of some of the species. The data in the table reveal that TR2 is characterized with lower HOMO and LUMO energies compared to TR1. The frontier molecular orbital energies of the valence tautomer, VT, are closer to the respective energies of TR2. When the HOMO and LUMO energies of the tautomers (see Table 2) considered are compared the order is VT<lactim<lactam and VT<lactam<lactim, respectively. The order of $\Delta\varepsilon$ values is lactim>lactam>VT. Consequently, VT formation should be accompanied by some bathochromic shift (see Figure 11).

**Table 4.** The HOMO, LUMO energies and the interfrontier molecular orbital energy gaps ($\Delta\varepsilon$) of some of the species.

| Structure | HOMO    | LUMO    | $\Delta\varepsilon$ |
|-----------|---------|---------|---------------------|
| TR1       | -570.87 | -237.71 | 333.16              |
| TR2       | -627.76 | -266.74 | 361.02              |
| VT        | -621.08 | -276.16 | 344.92              |

Energies in kJ/mol.
Figure 11 shows the UV-VIS spectrum of the valence tautomer VT.

**Thermochemistry**

Table 5 displays some thermochemical data about the species considered. The order of $H^\circ$ values is lactam<VT<lactim<TR2<TR1. Whereas, the order of entropy value is TR2>VT> TR1>lactim>lactam. So the lactam form is more favored over the lactim form both by enthalpy and entropy contributions. Moreover, TR2 is less energy demanding than TR1 and also entropically favored. Consequently, the $G^\circ$ order becomes lactam<VT<lactim<TR2<TR1. Therefore, the lactam-lactim equilibrium favors the lactam side. A similar argument holds for lactam-VT tautomerism that is VT formation is not favored over the lactam although the valence tautomer entropically is more favored than the lactam. On the other hand, the standard free energy of activation values for TR1 and TR2 are 77.613 kJ/mol and 43.812 kJ/mol, respectively. Since, standard free energy of activation for TR2 is less energy demanding, formation of the valence tautomer is expected to be through TR2.

**Table 5.** Some thermochemical data of the species considered.

| Species | $H^\circ$ (kJ/mol) | $S^\circ$ (J/molº) | $G^\circ$ (kJ/mol) |
|---------|-------------------|-------------------|-------------------|
| Lactam  | -1959924.35       | 451.28            | -1960058.90       |
| Lactim  | -1959899.58       | 450.72            | -1960033.97       |
| TR1     | -1959843.63       | 461.71            | -1959981.29       |
| TR2     | -1959876.56       | 464.62            | -1960015.09       |
| VT      | -1959916.38       | 464.56            | -1960054.89       |

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4. Conclusion

The present DFT treatise within the limitations of the level of calculations employed predicts the lactam form to be more stable than the other tautomers considered in vacuum conditions. The valence tautomer is electronically less stable than the lactam but more stable than the lactim form. Formation of the valence tautomer should be expected through the second type of transition state (TR2) and accompanied by a considerable bathochromic effect that is a shift into the visible region.

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