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Quantum chemical treatment of nivalenol and its tautomers

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Abstract

Nivalenol, a highly poisonous mycotoxin, and its possible tautomers have been considered theoretically by RHF/6-31G/d,p) and B3LYP/6-31G(d,p) calculations together with a semi-empirical PM3 method. The calculations revealed that some of the tautomers are more stable and exothermic than nivalenol. The calculated IR spectra as well as some geometrical and physicochemical properties of the structures considered have been presented.

Keywords: Nivalenol; Tautomerism; Molecular orbital calculations; RHF; B3LYP; PM3; Mycotoxin

1. Introduction

Nivalenol (3α, 4β, 7α,15-tetrahydroxy-12,13-epotrichotec-9-en-9-one) is a mycotoxin produced by fungi of *Fusarium* genus, i.e., *Fusarium cerealis* (*F. crookwellence*) *Fusarium poae* and also *Fusarium culmorum* and *Fusarium graminearum*. Nivalenol was first isolated from *F. Nivale Fn2B* [1]; a typical strain of *F. sporotrichioides*. The fungi which produce trichothecenes are soil fungi and are important plant pathogens that affect the crop (wheat, maize, barley, oat, and rye) in the field. They also contaminate processed grains (malt, beer and bread).

Chemically, nivalenol belongs to trichothecenes of type B [2]. The structure was reported in ref. [3] and its toxicology in ref. [4]. The trichothecenes are in general very stable compounds, both during storage/milling and the processing/cooking of food and they do not degrade at high temperatures [2].

Nivalenol was implicated as a chemical warfare agent in Southeast Asia with T-2 toxin. It is a strong hemorragenic agent, causes blisters, necrosis of tissues, nausea, vomiting, diarrhea and eventually death [5]. It was reported that nivalenol inhibits protein synthesis in rabbit reticulocytes in vitro [6] and synthesis of nucleic acids in vitro [7,8]. Effective detection methods of nivalenol and other trichothecenes have been described in refs. [9–12].

The immunosuppressive and carcinogenic character of *Fusarium* mycotoxins (they may possibly appear in some domestic food products) led the scientists to investigate the immunological effects of them on human peripheral blood mononuclear cells [13]. Among the *Fusarium* mycotoxins (including nivalenol) tested, nivalenol exerted one of the highest immunosuppressing effects on human peripheral blood mononuclear cells in vitro [13].

Different toxic properties have been associated to trichothecenes. In particular a series of studies with experimental animals demonstrated effects on the immune system, including impaired delayed-type hypersensitivity responses, phagocyte activity [14–16] and modulation of host response to enteric infections [17]. In particular, nivalenol inhibited total and antigen specific IgE production in ovoalbumin specific T-cell receptor ab transgenic mice [18]. In vitro analyses showed that trichothecenes can both suppress and stimulate immune functions [19]. Nivalenol inhibits blastogenesis in cultured human lymphocytes producing 50% inhibition of thymidine incorporation in mitogen-stimulated human peripheral lymphocytes [20]. Thuvander et al. [12] found that nivalenol inhibited

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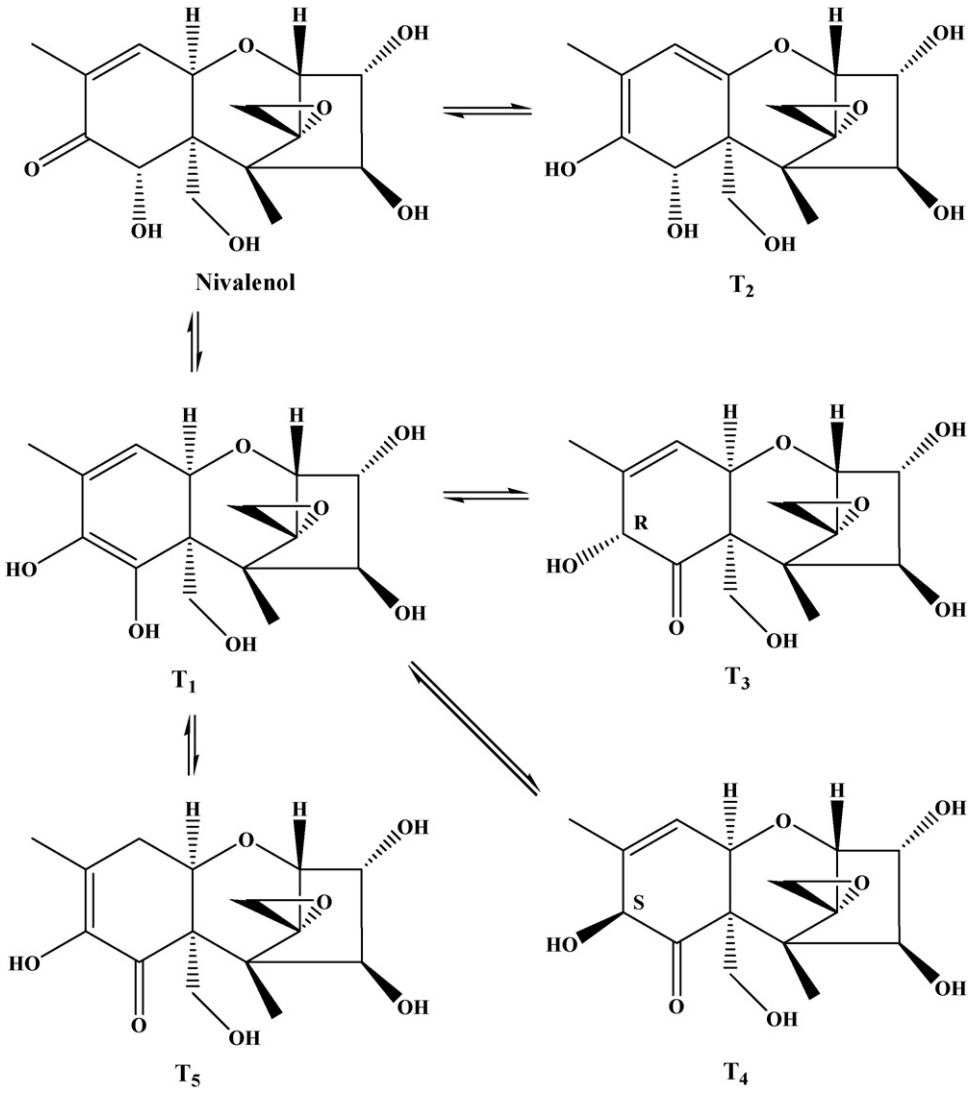

Fig. 1. Nivalenol and its tautomers.

Table 1
Some calculated energies of the present systems (RHF/6-31G(d,p))

System	Total energy (Hartrees)	ZPE (kJ/mol)	Enthalpy (kJ/mol)	Entropy (J/mol K)	C_v (J/mol K)
Nivalenol	−1103.639621	982.1839	1034.0388	567.5518	316.4308
T_1	−1103.614572	978.7054	1031.9664	573.8812	324.6086
T_2	−1103.500245	974.4611	1028.1907	594.8455	326.0882
T_3	−1103.632995	979.2415	1031.6503	572.3678	318.7911
T_4	−1103.631327	977.7521	1030.9154	574.4181	321.6055
T_5	−1103.648001	979.7272	1032.3182	573.2363	319.3047

Table 2
Some calculated energies of the present systems (B3LYP/6-31G(d,p))

System	Total energy (Hartrees)	ZPE (kJ/mol)	Enthalpy (kJ/mol)	Entropy (J/mol K)	C_v (J/mol K)	Total energy (aq) (Hartrees)
Nivalenol	−1110.122550	908.7585	963.7733	585.2894	339.9270	−1110.14504
T_1	−1110.102457	904.6777	961.5571	597.2993	348.8910	−1110.12583
T_2	−1110.008599	900.1905	957.4343	607.7419	351.3741	−1110.03930
T_3	−1110.114007	904.3957	960.3727	593.4350	343.8909	−1110.13764
T_4	−1110.108345	902.2276	959.2912	598.4800	347.6360	−1110.13648
T_5	−1110.134421	907.1631	962.8028	591.5853	341.8650	−1110.15909

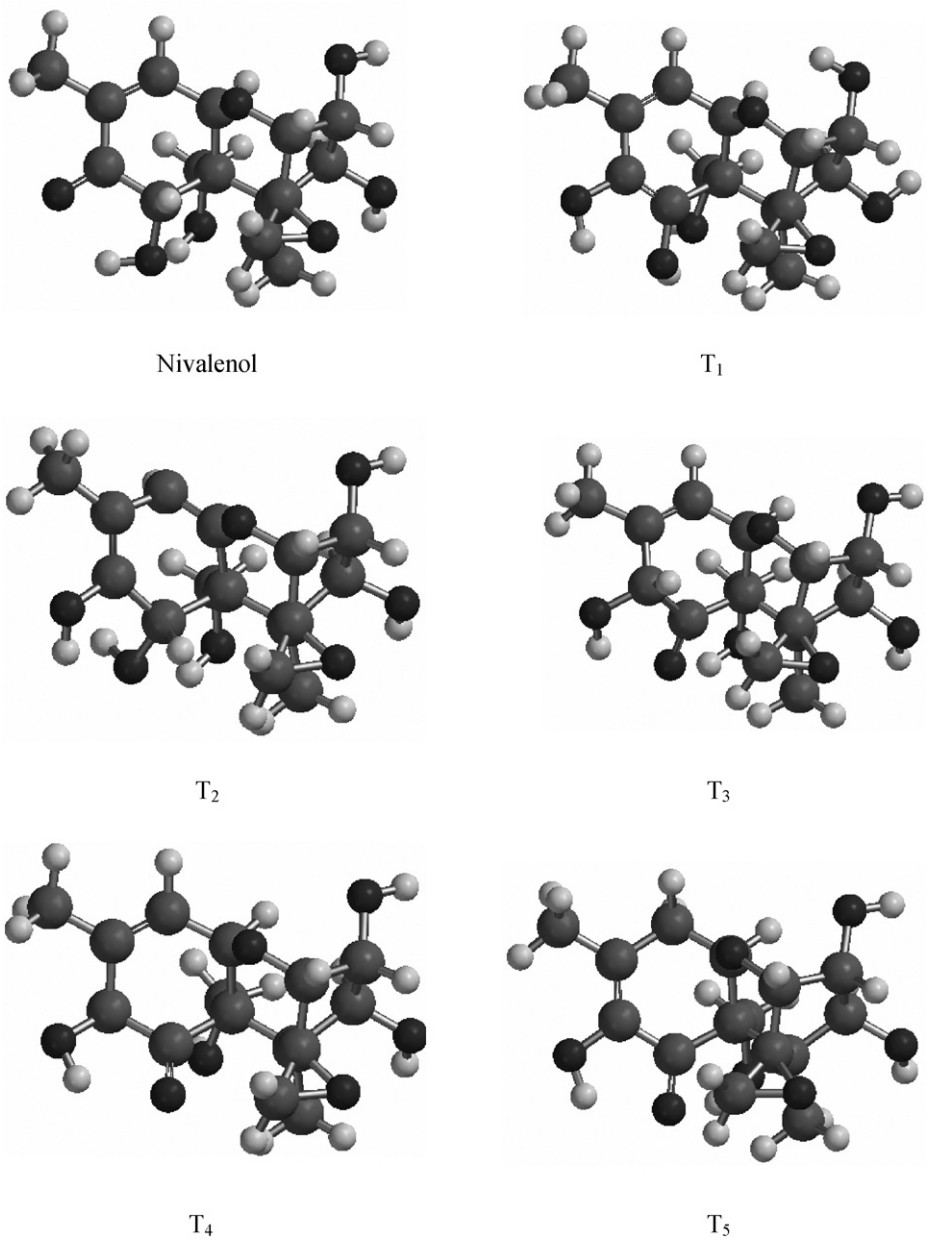

Fig. 2. The geometry optimized structures of the present systems (B3LYP/6-31G(d,p)).

proliferation of human male and female mitogen-stimulated lymphocytes.

The findings of Rossi and co-workers [21] highlight the potential immunomodulatory effects of nivalenol and deoxynivalenol at different concentrations on a model of human lymphocyte. The assessment of mRNA transcription showed different effects of nivalenol and deoxynivalenol in modulating Th1-type cytokines, depending on the dose whereas trichothecenes were found to interact and inhibit lymphocyte proliferation through apoptosis.

Table 3
Some calculated energies of the present systems (PM3) (energies in kJ/mol)

Energy	Nivalenol	T_1	T_2	T_3	T_4	T_5
Total energy	−399433.26	−399412.62	−399416.63	−399435.30	−399430.78	−399454.76
Heat of formation	−967.64	−946.99	−951.01	−969.68	−965.16	−989.14
Binding energy	−17796.96	−17776.31	−17780.33	−17798.99	−17794.48	−17818.46
Isolated atomic energy	−381636.30	−381636.30	−381636.30	−381636.30	−381636.30	−381636.3
Electronic energy	−3160965.00	−3155456.30	−3151674.20	−3166073.60	−3148813.40	−3163283.60
Core–core interaction	2761531.79	2756043.60	2752257.56	2766638.30	2749382.70	2763828.80

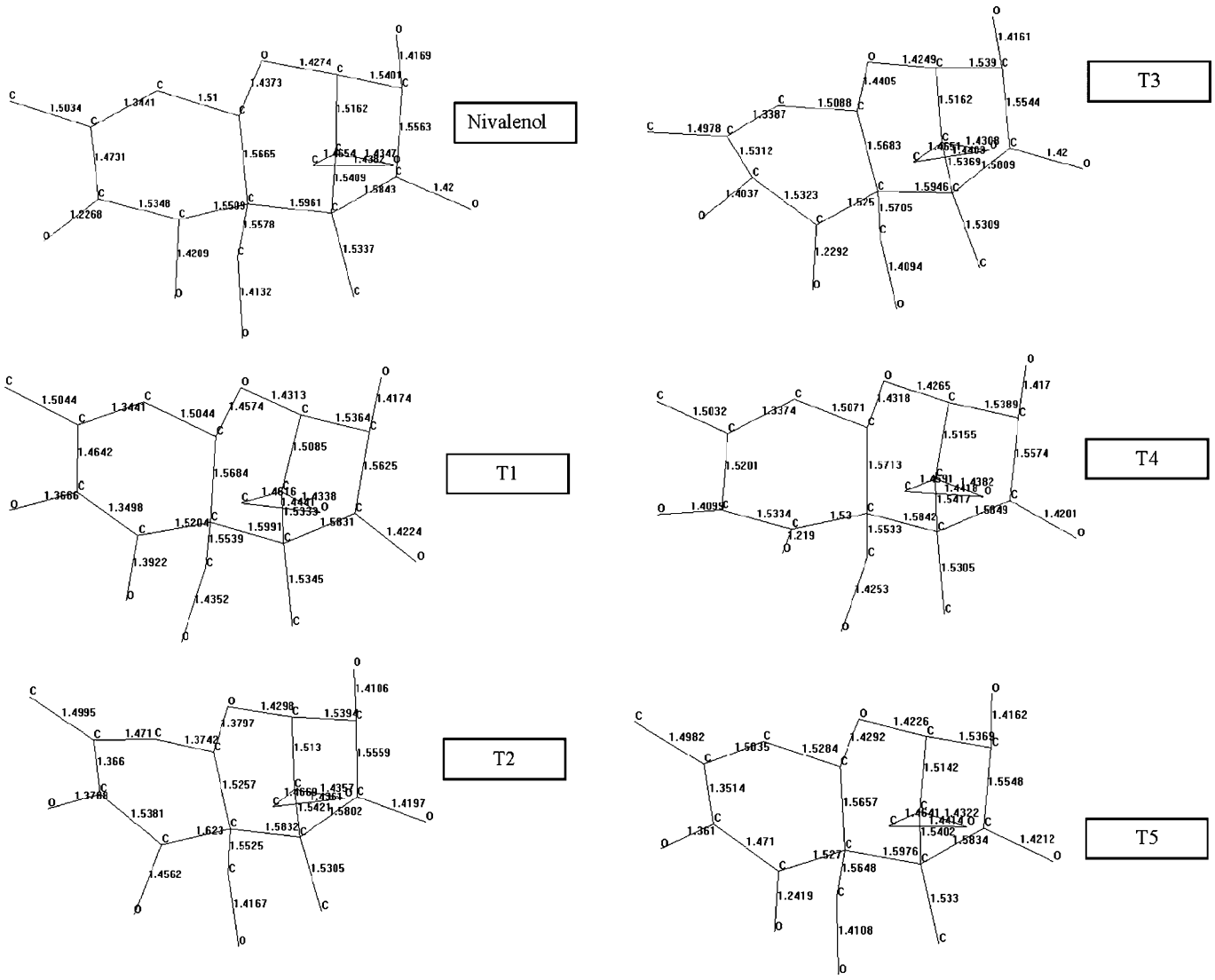

Fig. 3. The geometry optimized bond lengths of nivalenol and its tautomers (B3LYP/6-31G(d,p)).

Table 4
Some geometrical and physicochemical properties of the systems considered presently (area, volume, polarizability, refractivity, hydration energy values and dipole moments are in the order of 10^{-20} m^2, 10^{-30} m^3, 10^{-30} m^3, 10^{-30} m^3, kJ/mol and Debye, respectively)

	Nivalenol	T_1	T_2	T_3	T_4	T_5
Area	447.8	447.37	444.66	446.23	451.41	448.62
Volume	776.14	777.71	775.57	776.87	779.14	779.74
Polarizability	28.92	29.28	29.28	28.92	28.92	28.92
Refractivity	72.83	75.12	75.14	72.83	72.83	73.3
log P	−0.8	−2.29	−2.54	−0.80	−0.80	−1.08
Hydration energy	−56.73	−79.83	−76.06	−65.35	−64.81	66.32
Dipole moment	2.25	4.26	2.47	1.61	4.93	2.47

Table 5
RHF/6-31G(d,p) calculated LUMO, HOMO, $\Delta\varepsilon$ values for the structures presently considered (energies in eV) ($\Delta\varepsilon = \varepsilon_{LUMO} - \varepsilon_{HOMO}$)

Energy	Nivalenol	T_1	T_2	T_3	T_4	T_5
LUMO	2.43	3.56	3.14	3.42	4.06	2.40
HOMO	−10.5	−8.01	−7.65	−9.80	−9.79	−9.21
$\Delta\varepsilon$	12.88	11.57	10.79	13.22	13.85	11.61

Table 6
B3LYP/6-31G(d,p) calculated LUMO, HOMO, $\Delta\varepsilon$ values for the structures presently considered (energies in eV) ($\Delta\varepsilon = \varepsilon_{LUMO} - \varepsilon_{HOMO}$)

Energy	Nivalenol	T_1	T_2	T_3	T_4	T_5
LUMO	−2.07	−0.67	−1.11	−1.42	−0.85	−1.88
HOMO	−6.79	−5.26	−4.81	−6.77	−6.59	−6.27
$\Delta\varepsilon$	4.72	4.59	3.70	5.35	5.74	4.39

Table 7
PM3 calculated LUMO, HOMO, $\Delta\varepsilon$ values for the structures presently considered (energies in eV) ($\Delta\varepsilon = \varepsilon_{LUMO} - \varepsilon_{HOMO}$)

Energy	Nivalenol	T_1	T_2	T_3	T_4	T_5
LUMO	−0.44	−0.08	−0.35	0.20	0.32	−0.48
HOMO	−10.33	−8.78	−8.85	−10.08	−10.01	−9.38
$\Delta\varepsilon$	9.89	8.70	8.49	10.28	10.33	8.90

There is considerable evidence that mycothoxins produced by microorganisms in our foodstuffs constitute a serious threat to human health through likely reactions of their enols and epoxides. Nivalenol being one of the trichothecenes has the capacity for enol tautomerism. Moreover, the epoxide group present makes it capable of reacting directly with thiol forms of the vitaletheine modulators [13].

In this study, nivalenol and its possible tautomers have been subjected to quantum chemical calculations with ab initio, DFT and semi-empirical methods.

2. Method

The initial geometry optimizations of all the structures leading to energy minima were achieved by using MM2 method followed by semi-empirical PM3 self-consistent fields molecular orbital (SCF MO) method [22,23] at the restricted level [24]. Then, further geometry optimizations were achieved within the framework of ab initio Hartree-Fock (HF), and density functional theory (DFT, B3LYP) [25,26] at the level of 6-31G(d,p) (restricted closed-shell) [24]. The exchange term of

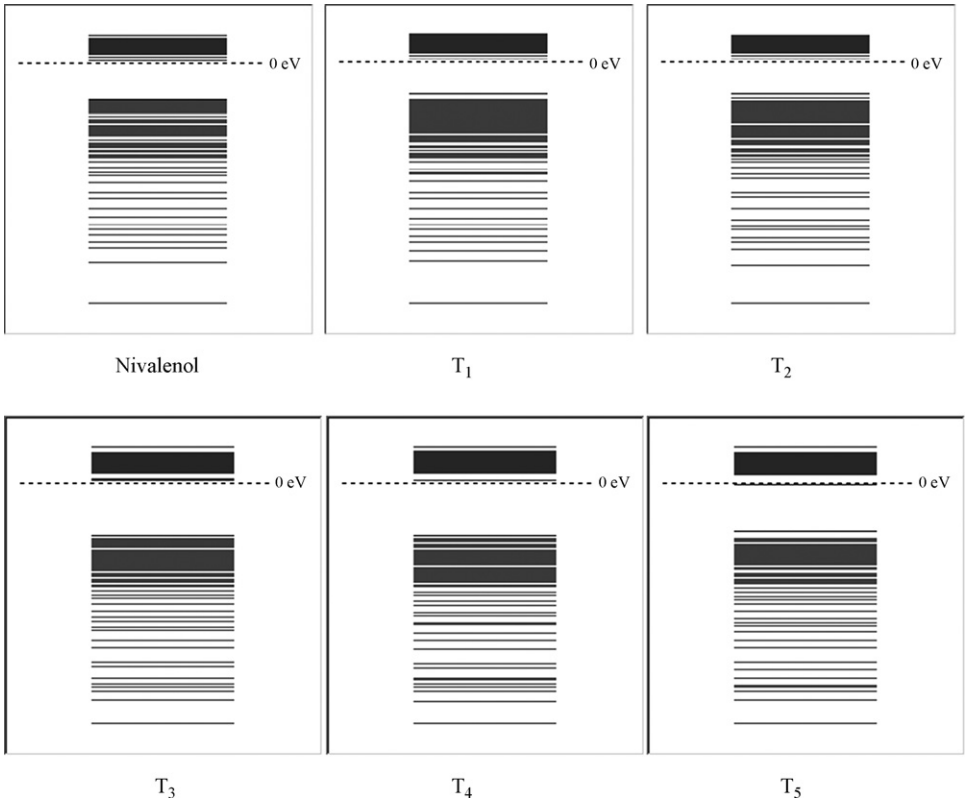

Fig. 4. Molecular orbital energy spectra of the systems under consideration (PM3).

B3LYP consists of hybrid Hartree-Fock and local spin density (LSD) exchange functions with Becke's gradient correlation to LSD exchange [27]. The correlation term of B3LYP consists of the Vosko, Wilk, Nusair (VWN3) local correlation functional [28] and Lee, Yang, Parr (LYP) correlation correction functional [29]. The normal mode analysis for each structure resulted in no imaginary frequencies for all the three methods of calculations.

All these computations were performed by using Gaussian 03 [30] and Spartan 04 [31] package programs, and some geometrical and QSAR properties were calculated using Hyperchem (release 7.5) package program [32].

3. Results and discussion

In the present work, the structural and electronic properties of nivalenol (a mycotoxin) and its tautomers (see Fig. 1 for the structures) have been investigated by the application of PM3 (RHF), RHF/6-31G(d,p) and B3LYP/6-31G(d,p) type quantum chemical calculations. The interesting features (see Section 1) of nivalenol and the possibility of presence of various tautomeric forms make this study worthwhile. As far as the literature survey suggests, there is no theoretical investigation either on nivalenol or its tautomers. Even none of the tautomeric forms of nivalenol appear in the experimental literature.

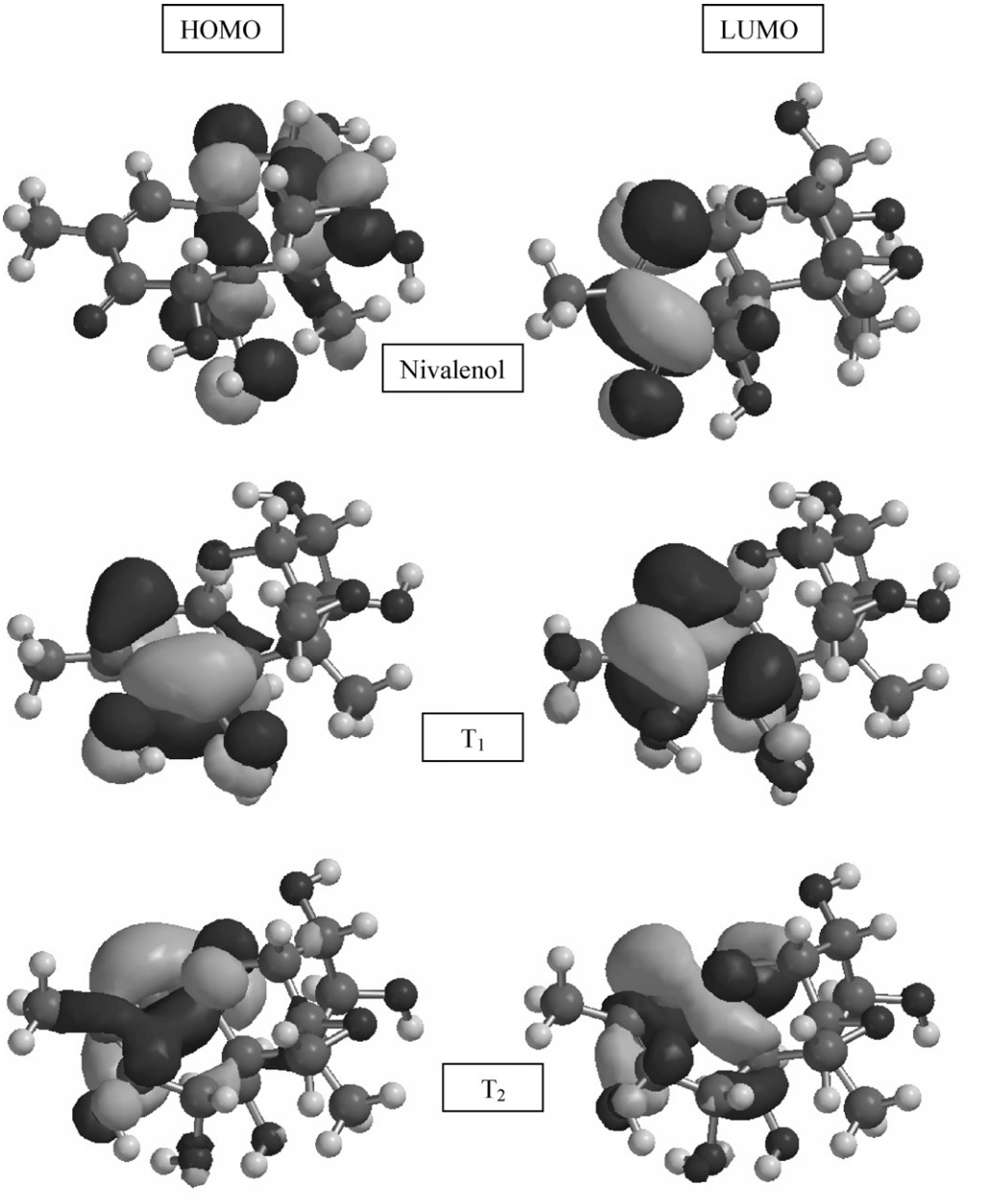

Fig. 5. Frontier molecular orbital schemes of the present systems (B3LYP/6-31G(d,p)).

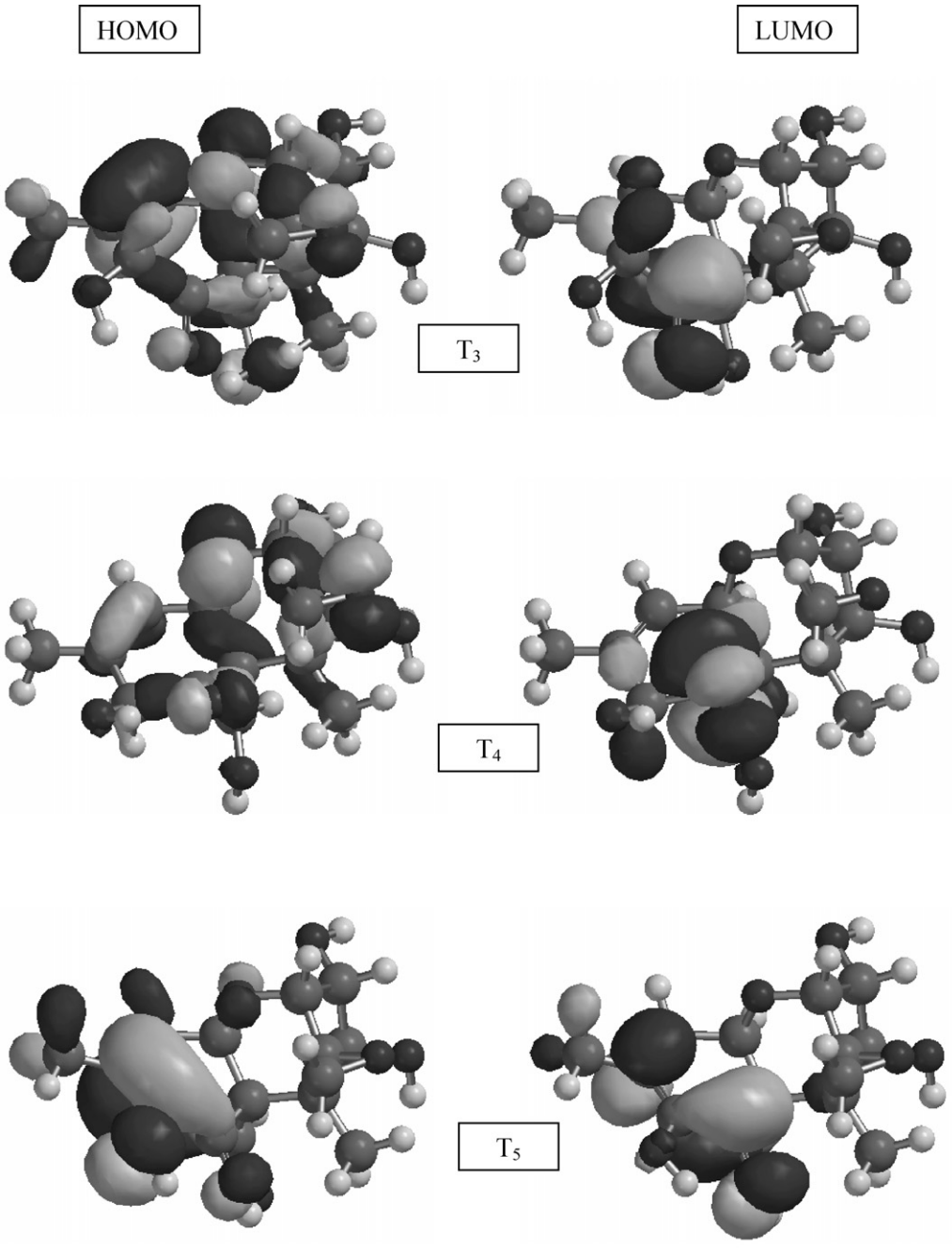

Fig. 5. (*Continued*).

Fig. 2 shows the geometry optimized (B3LYP/6-31G(d,p)) structures of the presently considered systems. The tautomer T_1 is obtained by 1,3-(keto-enol tautomerism), while T_2 is obtained by 1,5-tautomerism of the parent compound nivalenol. T_3 and T_4 are tautomeric forms of T_1. They have opposite absolute configurations on the carbon that is in the neighborhood of the carbonyl group. T_3 and T_4 are enantiomeric pairs and possess *R* and *S* configurations on the carbon considered, respectively. The keto-enol tautomerism of T_1 should result in enantiomeric pairs, T_3 and T_4. On the other hand, T_5 derived from T_1 is a 1,5-tautomer. In the structure of nivalenol, α-hydrogen atom in theory can easily undergo tautomerism because it is (due to the presence of adjacent –OH group) more acidic and better enolizable than any other α-methylenic or α-methine hydrogens. Therefore, at first glance T_1 seems to be a quite likely structure accompanying nivalenol, especially in polar solvents. On the other hand, in nivalenol the hydrogen on the bridgehead position, flanked by etheric oxygen should undergo tautomerism to yield T_2. In this case, the geometry of the six-membered ring allows double bond formation at the bridgehead position, contrary to the Bredt's rule [33]. T_5 is also derived from T_1 (a dienol) by a shift of proton from alcoholic group to the

opposite end of the diene π-system. In Fig. 3, the geometry optimized bond lengths (in Å) of the present systems have been given.

Tables 1–3 tabulate the total energies obtained by the application of RHF/6-31G(d,p), B3LYP/6-31G(d,p) and PM3 (RHF) type quantum chemical calculations, respectively. Moreover, some calculated energies have also been given in these tables. All the structures are found to be stable, as the total (Tables 1–3) and binding energies (Table 3) indicate. Indeed, all the structures possess negative formation enthalpies (Table 3). According to the results obtained by all the methods, T_5 has been found to be the most stable and the most exothermic one among all. The predicted stability order is as follows: $T_5 > \text{nivalenol} > T_3 > T_4 > T_1 > T_2$ for Hartree-Fock and DFT calculations (Tables 1 and 2) however, $T_5 > T_3 > \text{nivalenol} > T_4 > T_2 > T_1$ order is obtained by PM3 method. The same order (PM3) holds for the heat of formation values (Table 3). In all cases B3LYP method predicted more negative values of the total energies as expected. In addition to the calculations in the gas phase, the stabilities of the present sys-

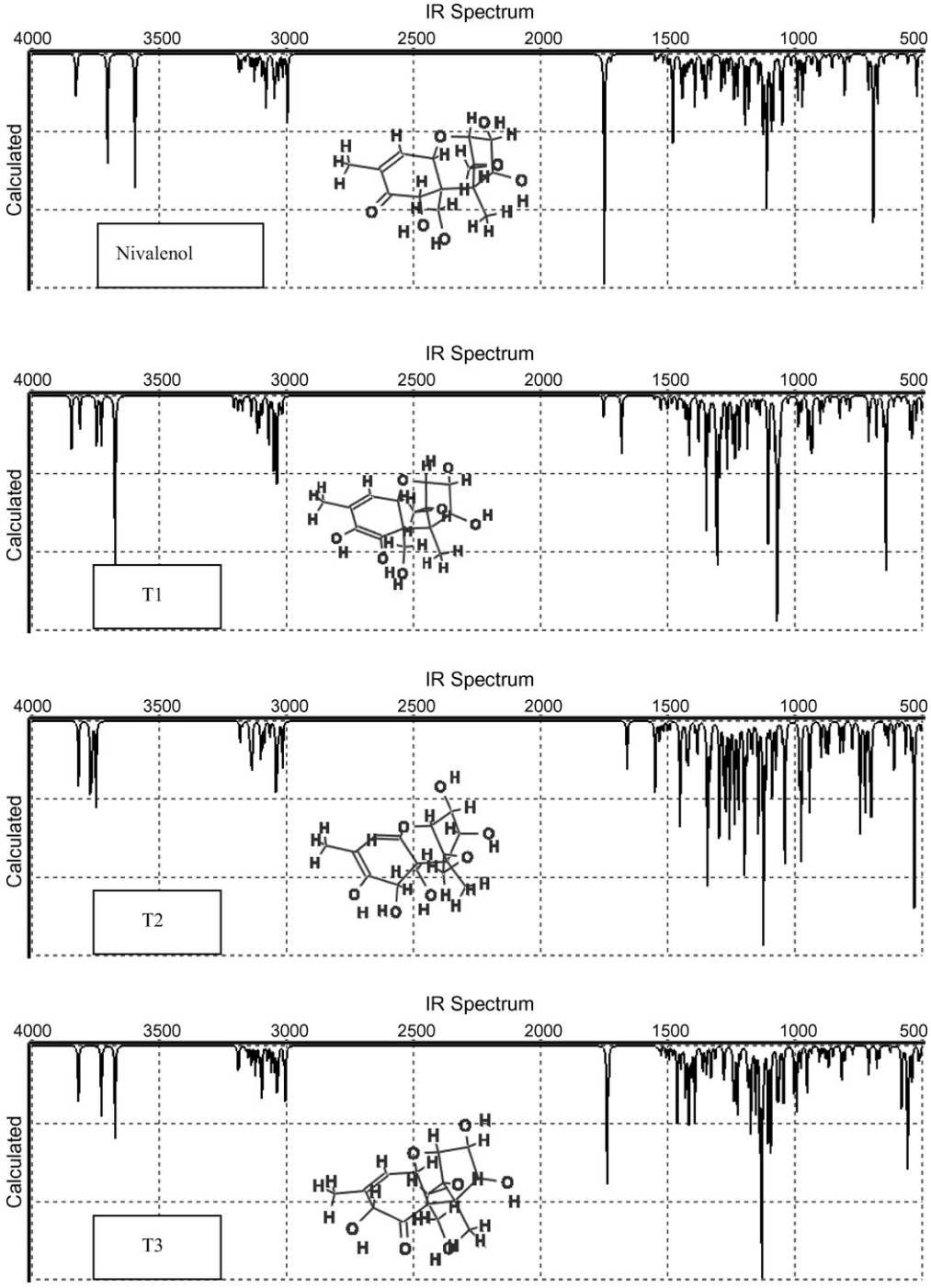

Fig. 6. Calculated IR spectra of nivalenol and its tautomers (B3LYP/6-31G(d,p)).

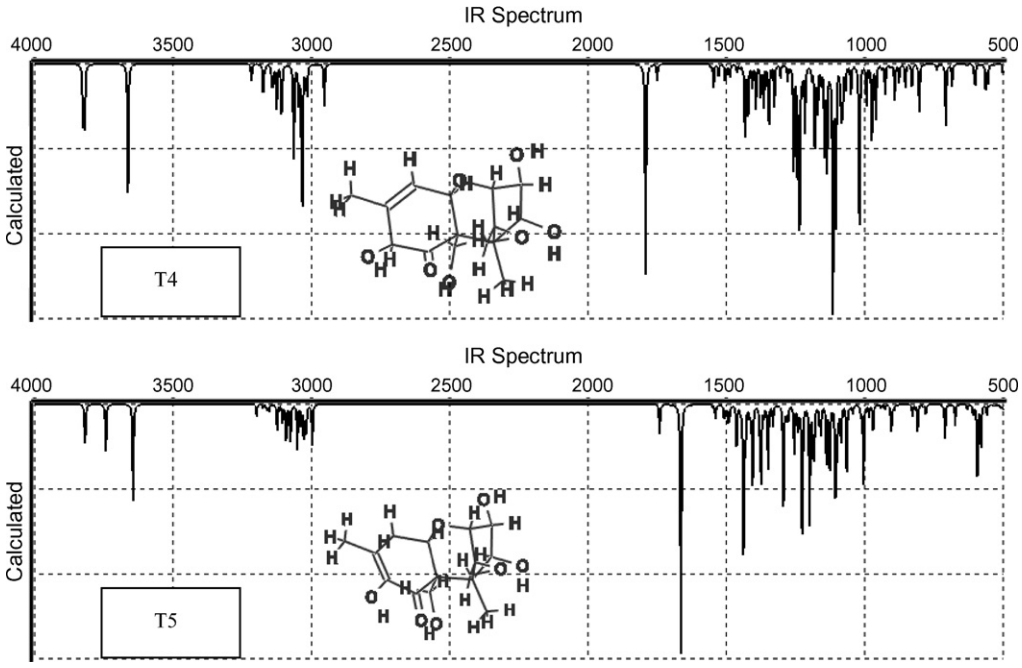

Fig. 6. (*Continued*).

tems in aqueous media have also been considered (see Table 2). The results of the aqueous system are in parallel with that of the calculations in the gas phase.

In Table 4 various geometrical and physicochemical properties of the nivalenol systems, based on RHF PM3 type geometry optimizations, are given. However, some data in the table are obtained based on group additivities and independent of the geometry optimizations (such as refractivities and polarizabilities). On the other hand, log *P*-values and hydration energies are to be considered on the relative basis, within the group but not to be taken as absolute values. The polarizabilities are due to atomic contributions whereas the refractivities are based on group contributions. Hence, some structures considered have identical values for these properties.

Tables 5 (RHF) 6 (B3LYP) and 7 (PM3) tabulate the frontier molecular orbital energies (HOMO and LUMO), as well as the interfrontier energy gaps ($\Delta\varepsilon$). Tables 5–7 reveal that the enol form of nivalenol, T_1, is characterized with narrowing of the interfrontier energy gap ($\Delta\varepsilon$ value) [34] as compared to the parent compound. This is due to the extended conjugation present in T_1, because the lone-pair electrons of –OH group may undergo conjugation with the diene π-system. T_2 has the smallest interfrontier energy gap within the group, whereas T_3 and T_4 possess the highest and the next highest values. It is all because of no π-delocalization is possible in their structures.

Within the group, nivalenol and T_2 possess the deepest and the highest lying HOMO levels, respectively (see Tables 5 and 6). Hence, T_2 is to be more susceptible to oxidations than the others. Although, nivalenol is practically quite stable, if its degradation occurs by atmospheric oxidation, it is probably via T_2 tautomer. The calculations indicate that the enantiomers, T_3 and T_4 have to be more or less like nivalenol in oxidation reactions.

On the other hand, T_5 and nivalenol have the lowest and the next lowest LUMO energies, respectively. Whereas, the enentiomers T_3 and T_4 possess quite highly lying (within the group) LUMO energy levels which result in comparatively unfavorable reduction potentials.

As seen in Fig. 4, all the structures considered have similar molecular orbital energy spectra. The density of states for inner lying occupied molecular orbitals is low but increases as the orbital number increases (the upper energy states) and band-like appearance for the unoccupied molecular orbitals emerges. The interfrontier molecular orbital energy gap ($\Delta\varepsilon$) in each case is distinctly apparent. Tables 5–7 shows also the $\Delta\varepsilon$ values where T_2 and T_4 are characterized with the smallest and the largest energy gaps, respectively. In the same table, also the lowest occupied and highest unoccupied molecular orbital (LOMO and HUMO, respectively) energies are given.

Fig. 5 shows the HOMO and LUMO of nivalenol and its tautomers considered. As it is seen there the frontier molecular orbitals (HOMO and LUMO) in almost each case are constituted by the contribution of atomic orbitals of the six-membered hydrocarbon ring system (cyclohexenone or cyclohexadienol moiety depending on the structure). Of these structures, the nivalenol is exceptional because the cyclohexanone moiety does not contribute to the HOMO. In the case of T_3 and T_4 all the ring systems contribute the HOMO, thus they are exceptional cases too. Generally, the frontier molecular orbitals of the structures possess π-type (either π or π^*) symmetry. However, exceptional ones exist.

Fig. 6 shows the calculated (B3LYP/6-31G(d,p)) infrared spectra of the nivalenol and its tautomers considered. All these

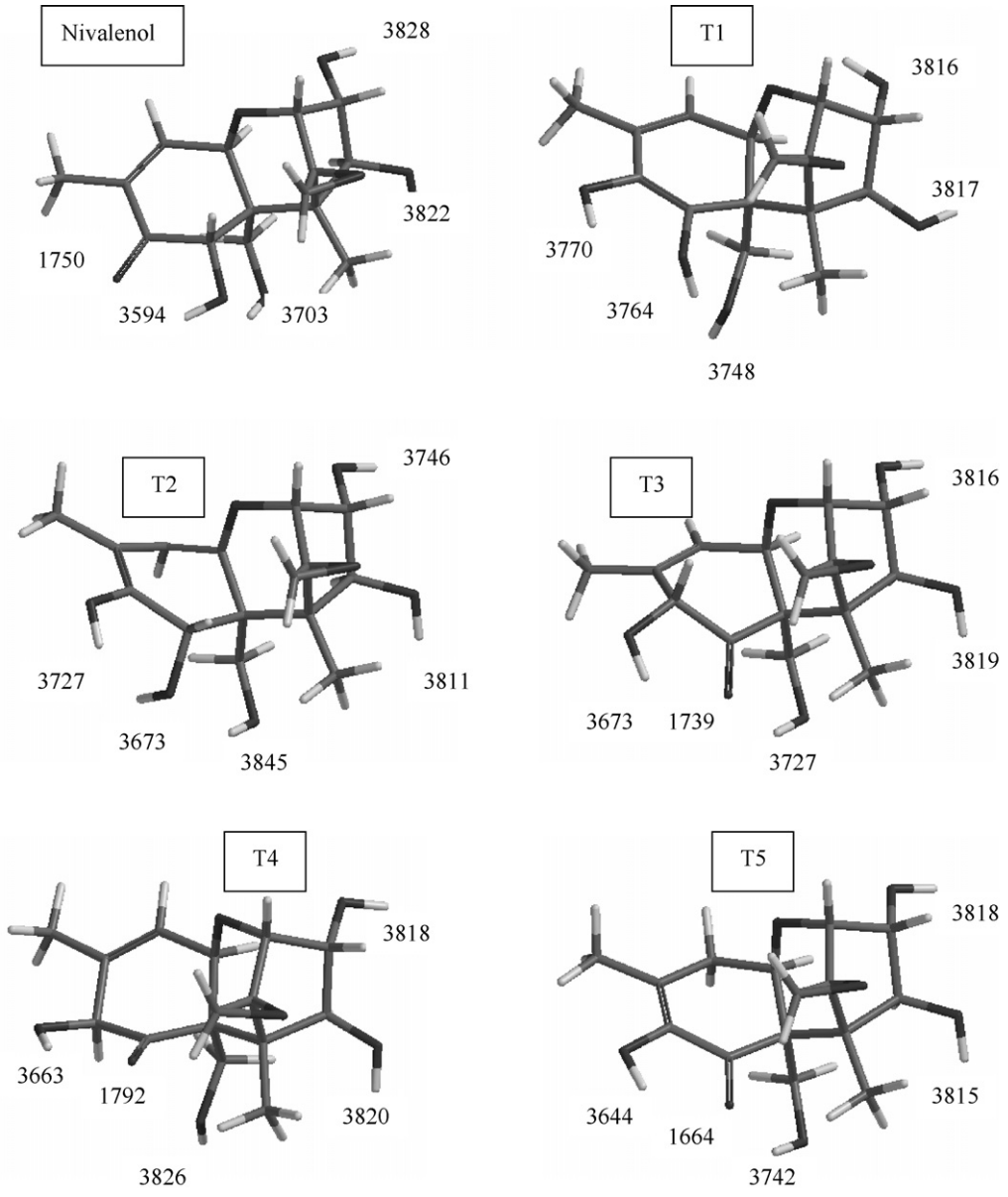

Fig. 7. The O–H and C=O stretchings of the structures considered (B3LYP/6-31G(d,p)).

structures possess many OH groups. Nivalenol and T_5 contain a conjugated enone group. T_3 and T_4 have carbonyl group unconjugated with an olefinic bond. Fig. 7 shows the O–H and C=O stretchings of the structures considered. Although, the calculated spectra give rather meaningful values for O–H stretchings, C=O stretching of nivalenol was produced as rather high for an α,β-unsaturated ketone (experimental value 1700 cm^{-1} [35]), but it occurred at 1664 cm^{-1} for T_5 which is a suitable estimate. The calculated carbonyl stretching for T_3 is acceptable but T_4 is somewhat high for a keto group. However, in the literature there are no spectral data for the tautomers of nivalenol to compare. Thus, those unexpected frequencies might be due to the ring strains of the systems. In the spectra, the peaks at 3200–3000 cm^{-1} are to be due to various symmetric and asymmetric C–H stretchings and C=C stretchings mostly occur at 1500–1450 cm^{-1} (somewhat low) however, in the spectra of T_1 and T_2 bands between 1600 and 1500 cm^{-1} are attributable to C=C stretchings. Actually, one should keep in mind that the positions of bands in calculated spectra are useful for relative comparison rather than absolute.

4. Conclusion

Nivalenol, a highly poisonous chemical can contaminate various crops, hence dangerous for human health. Not much information exists in the literature about nivalenol and nothing about its possible tautomers, molecular orbital properties and electronic structure of them. The present detailed theoretical investigation might be a pioneering work enlightening various quantum chemical and physicochemical properties of these structures.

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