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Phellandrenes and Some Species from Them - A DFT Treatment

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Abstract

Phellandrenes are naturally occurring cyclic dienes belonging to cyclic monoterpene class and have many medicinal applications. In the present study, some resonance stabilized radicals from α- and β-phellandrene and also some closed shell structures from those radicals have been investigated within the constraints of density functional theory and basis set employed. For structure optimizations of the closed-shell and open-shell structures, B3LYP/6-311++G(d,p) and UB3LYP/6-311++G(d,p) level of theories have been adopted, respectively. All the systems considered have been found to be thermo chemically favorable and electronically stable. Various structural, quantum chemical and spectral properties of them have been obtained and discussed.

1. Introduction

In pharmacy plant-based medicines play a vivid role in health care [1]. Among them, essential oils (EOs) from plants have been reported to have wide spread antimicrobial activity against various bacterial and fungal pathogens, and those active substances include phellandrenes especially α-phellandrene (α-Phe), nonanal and other volatile substances [2,3].

Alpha-phellandrene (5-Isopropyl-2-methyl-1,3-cyclohexadiene) is a very common cyclic monoterpene found in several essential oils, which shows extensive biological activities. Alpha-phellandrene, isolated for the first time from *Eucalyptus phellandra* (also called *E. radiata*) and its name originates from it. Alpha-phellandrene is one of a pair of phellandrene cyclic monoterpene and double-bond isomers. It can be extracted from the essential oils of the turmeric leaf (54%), *Boswellia sacra* (42%), *Eucalyptus*

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elata (35%), dill weed (30%) and *Eucalyptus dives* (17%) [4,5]. However, it is also found in several different plant species, including *Cryptomeria japonica, Heracleum antasiaticum, E. camaldulensis, Gossypium hisutum, Cistus ladanifer*, and *Cannabis sativa*, among others [6].

α-Phellandrene is a natural plant-derived compound with various medicinal properties, found useful in the pharmaceutical, food, cosmetic and perfume industries [7,8]. Phellandrene (PHE) compounds are prevalently used in fragrances [9]. It is known that α-phellandrene enhances the immune response and resistance against *Vibrio alginolyticus* in white shrimp [10]. On the other hand, *α*-phellandrene was found to be significantly toxic to L3 of *L. cuprina*. That is why it could be considered as a good ecofriendly product to control this pest [11].

The anti-microbial activities of phellandrenes or other terpenes were more effective against Gram-positive bacteria. The anti-fungal activity of α-phe involves alteration in the mycelial morphology, disturbed membrane stability, and increased ions and other cell materials leakage [12]. Also it has been reported that α-phe can induce changes in lipid and fatty acid contents of the cells and thus causes K^+ leakage, increase in extracellular pH. Furthermore it destroys fungal or microbial cells [2]. α-Phe might exert anti-inflammation activity by preventing NF-kB activity, reducing the production of TNF-α and IL-6 from LPS-stimulated macrophages [13,14], pro-inflammatory enzymes [15] and through inhibition of neutrophil infiltration and mast cell degranulation [13].

It has been found that the possible analgesic effect of α-phe could involve glutamatergic, opioid, nitrergic, cholinergic and adrenergic systems [16]. It is a known fact that the nociceptive receptors, such as the transient receptor potential (TRP) family, including TRPM8 and TRPA1, mediate the analgesic effect [17,18]. α-Phe might have antihyperalgesic activity against cold sensitivity, SNI-induced hyperalgesia, and depression-like behavior in rats. Because of all these α-phe could be used in treating pain resulting from neuropathy and infections and is clinically involved in developing new antinociceptive drugs [19]. Researchers have observed that the antinociceptive effect of α-phe was reverted by an opioid receptor antagonist, naloxone, which clearly indicates that antinociceptive activities depend on the opioid system [20].

α-Phe also exhibits wound-healing efficiency because the terpenes possess an adhesive effect on the skin, which initiates the healing effect [21,22]. Terpenes, such as α-phe and α-pinene, act as primary agents in repairing wounds by providing good tensile strength for scar and accelerating wound closure [23]. α-Phe favors wound-healing

activities by inducing the proliferation and migration of fibroblasts, which stimulate wound closure. It is also known that α-Phe decreases intracellular NO levels and superoxide anion, thereby inhibiting oxidative stress and boosting cutaneous wound healing [22].

Gonçalves et al., have established that α-Phellandrene attenuates tissular damage, oxidative stress, and TNF-α levels on acute model ifosfamide-induced hemorrhagic cystitis in mice [24].

Baldwin and Krueger, investigated stereoselective photochemical electrocyclic valence isomerizations of alpha-phellandrene conformational isomers [25]. Also some mechanistic studies have appeared in the literature. Formighieri and Melis studied carbon partitioning to the terpenoid biosynthetic pathway which enables heterologous β phellandrene production in *Escherichia coli* cultures [26]. Lafever and Croteau, reported hydride shifts in the biosynthesis of the p-menthane monoterpenes α-terpinene, γ terpinene, and β-phellandrene [27]. Whereas, Miller and Borden considered β phellandrene ((6S)-3-methylidene-6-propan-2-ylcyclohexene) in their studies [28].

2. Method of Calculations

In the present study, all the initial structure optimizations of the closed-shell structures leading to energy minima have been achieved by using MM2 method then followed by semi empirical PM3 selfconsistent fields molecular orbital (SCF MO) method [29,30] at the restricted level [31]. Afterwards, the structure optimizations have been managed within the framework of Hartree-Fock (HF) and finally by using density functional theory (DFT) at the level of B3LYP/6-311++G(d,p) [32,33]. The radical species (in the doublet state) are treated at the unrestricted level of calculations and finally at UB3LYP/6-311++G(d,p) level. It is worth mentioning that 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 [34]. Also note that the correlation term of B3LYP consists of the Vosko, Wilk, Nusair (VWN3) local correlation functional [35] and Lee, Yang, Parr (LYP) correlation correction functional [36]. In the present study, the normal mode analysis for each structure yielded no imaginary frequencies for the 3*N*–6 vibrational degrees of freedom, where *N* is the number of atoms in the system. This search has indicated that the structure of each molecule corresponds to at least a local minimum on the potential energy surface. Furthermore, all the bond lengths have been thoroughly searched in order to find out whether any bond cleavage

occurred or not during the geometry optimization process. All these computations were performed by using SPARTAN 06 [37].

3. Results and Discussion

Phellandrenes are cyclic dienes. In α-phellandrene, both double bonds are endocyclic and in β-phellandrene, one of them is exocyclic. The α-phellandrene isomer can form hazardous and explosive peroxides on contact with air at elevated temperatures. Figure 1 shows α- and β-phellandrenes and some species derived from them. The radicals considered presently (I, II and V) are conjugated with the diene system (resonance stabilized) embedded in phellandrenes. Structures III and IV contain an extra double bond. Structures-III and IV can be theoretically obtained from the radicals-II and I, respectively by the removal of α-hydrogen atom in order to get a closed-shell system. Alternatively, structure-IV can be engendered from structure-III by a hydrogen shift to exocyclic double bond or resonance assisted proton tautomerism to get a phenyl ring.

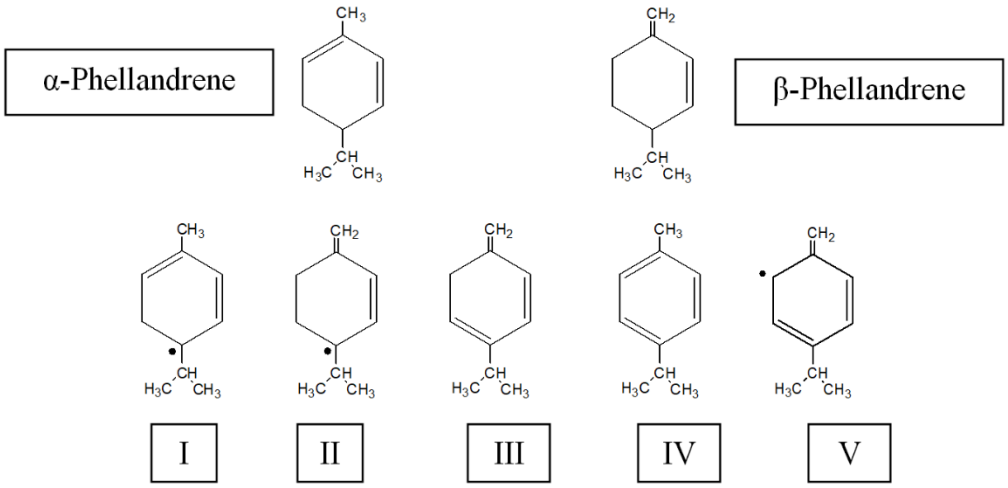
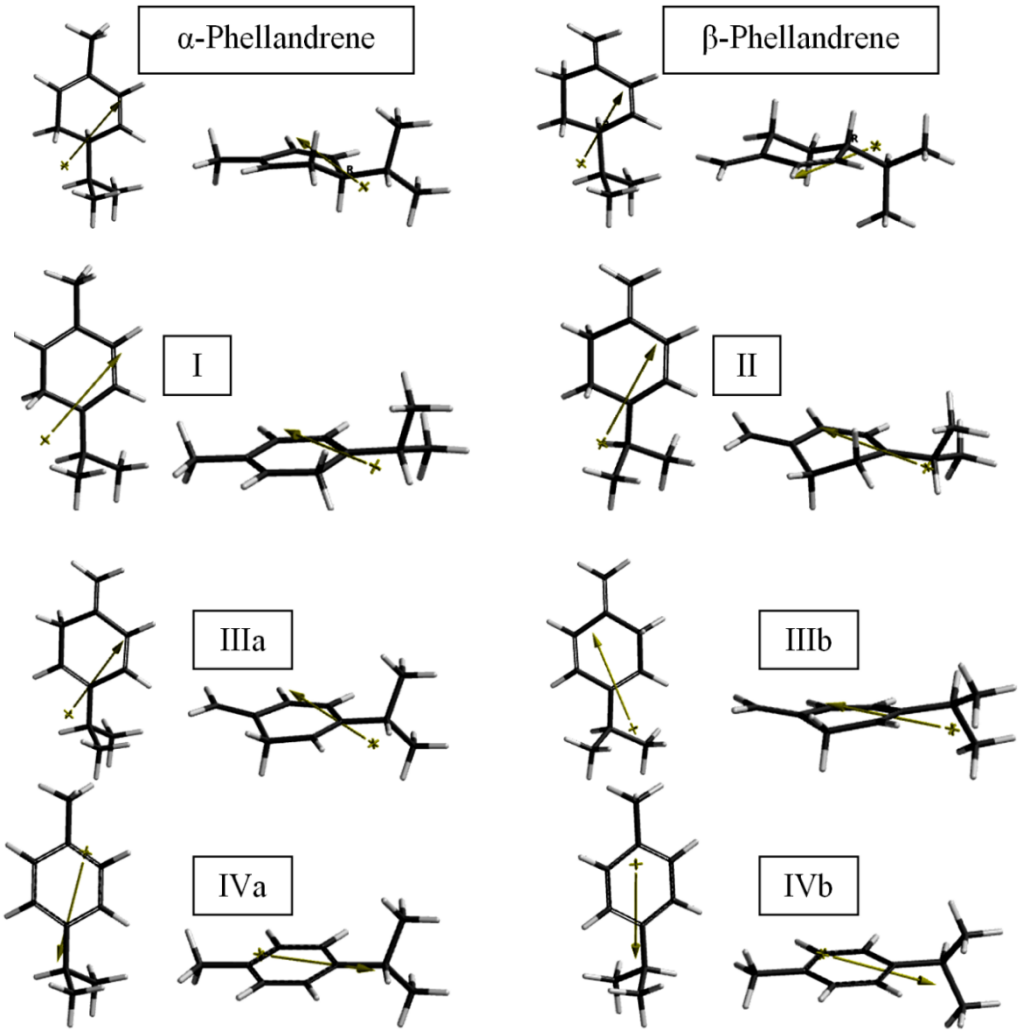


Figure 1. α- and β-Phellandrenes and some species derived from them.

Optimized structures of the species concerned are shown in Figure 2 which also displays the direction of the dipole moment vectors of the structures. Note that the direction of dipole moment vector in IV is different from the others and its head directs to isopropyl moiety. In the cases of structures III and IV, conformers "a" and "b" possessing very comparable energy values have been detected by the program. Table 1 shows some properties of the species concerned as well as their Boltzmann distributions. As seen in

the table, the dipole moments of phellandrenes follow the order of β-phellandrene > α-phellandrene. Although they are small in magnitude, the moment of β-phellandrene is far greater than the α-isomer. The out come should arise from positions of the double bonds. The polarizabilities of α- and β-phellandrenes are quite comparable with each other. The logP values are all positive for the closed-shell structures listed in the table. LogP is a critical measure that not only determines how well a drug will be absorbed, transported, and distributed in the body but also dictates how a drug should be formulated and dosed. A positive value for logP denotes a higher concentration in the lipid phase.



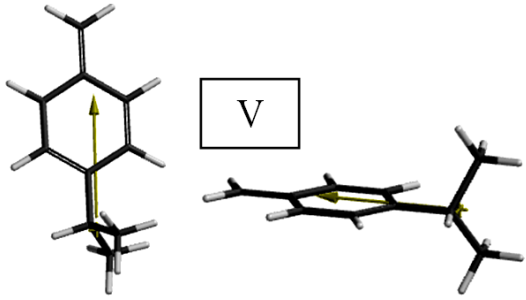


Figure 2. Optimized structures (top and side views) of the species concerned.

Table 1. Some properties of the species concerned.

	Formula	Boltzmann distribution	Dipole moment	Polarizability	logP
α-Phellandrene	$C_{10}H_{16}$	1.000	0.29	54.53	3.12
β-Phellandrene	$C_{10}H_{16}$	1.000	0.91	54.45	3.17
I	$C_{10}H_{15}$	1.000	0.54		
II	$C_{10}H_{15}$	1.000	1.15		
IIIa	$C_{10}H_{14}$	0.653	0.68	54.41	2.69
IIIb	$C_{10}H_{14}$	0.347	0.67	54.38	2.69
IVa	$C_{10}H_{14}$	0.483	0.04	53.90	3.76
IVb	$C_{10}H_{14}$	0.517	0.05	53.90	3.76
V	$C_{10}H_{13}$	1.000	0.70		

Dipole moments in debye units. Structures I, II and V are radicals.

Some thermo chemical values of the structures considered are tabulated in Table 2. As seen in the table, all the structures have exothermic heat of formation and favorable Gibb's free energy of formation values at the standard state. The orders of H^o and G^o values are β-phellandrene < α-phellandrene and α-phellandrene < β-phellandrene, respectively. Whereas for the radicals derived from phellandrenes the order is I < II for

both of H^o and G^o. As for the isomeric structures, III and IV, the orders for H^o and G^o values are the same that is IVb < IVa < IIIa < IIIb. Note that structure-IV (conformers a and b) is an aromatic compound but III is just an alicyclic unsaturated isomer of IV.

Table 3 shows some energies of the structures considered where E, ZPE and E_C stand for the total electronic energy, zero point vibrational energy and the corrected total electronic energy, respectively. The data reveal that all the structures considered are electronically stable. The algebraic order of E_C values of phellandrenes is α-phellandrene < β-phellandrene. Thus, the former one is electronically more stable than the later one. It is the effect of presence of endocyclic/ exocyclic double bond on the optimized geometries of the phellandrenes.

As for the isomeric radicals I and II, the data reveal that the former one is electronically more stable than the second one. Although both of them are radicals conjugated with a 4π-system, in the case of radical-I 4π-system of it is endocyclic. As for the isomeric closed-shell structures III and IV, the order of E_C values is IVb < IVa < IIIa < IIIb. So the aromatic character of isomer-IV dictates the order. Note that radical-V does not have any isomers among the species considered presently. Radicals I and II may play some role in the process of auto oxidation of phellandrenes.

Table 2. Some thermo chemical properties of the species concerned.

	H^o	S^o (J/mol^o)	G^o
α-Phellandrene	-1025371.432	398.57	-1025490.269
β-Phellandrene	-1025371.918	392.18	-1025488.846
I	-1023772.085	396.65	-1023890.347
II	-1023754.301	389.07	-1023870.540
IIIa	-1022222.907	389.07	-1022338.910
IIIb	-1022220.833	386.46	-1022336.056
IVa	-1022358.996	388.09	-1022474.705
IVb	-1022359.647	389.47	-1022475.766
V	-1020685.071	384.01	-1020799.564

Energies in kJ/mol.

Table 3. Some energies of the species concerned.

	E	ZPE	E_C
α-Phellandrene	-1026003.35	612.96	-1025390.39
β-Phellandrene	-1026005.04	615.05	-1025389.99
I	-1024368.57	577.75	-1023790.82
II	-1024352.63	580.38	-1023772.25
IIIa	-1022792.88	552.36	-1022240.52
IIIb	-1022791.31	553.10	-1022238.21
IVa	-1022931.34	554.92	-1022376.42
IVb	-1022931.51	554.35	-1022377.16
V	-1021222.33	520.22	-1020702.11

Energies in kJ/mol.

Bond dissociation energy calculations indicate that β-phellandrene relatively requires 18.17 kJ/mol more energy to break the C-H bond homolytically compared to α-phellandrene.

Table 4 shows the aqueous energies of the closed-shell species considered. α-Phe is better solvated than the beta isomer. As for the others, order of better solvation is IVb > IVa > IIIa > IIIb.

Table 4. Aqueous energies of the closed -shell species considered.

α-Phe	β-Phe	IIIa	IIIb	IVa	IVb
-1025999.58	-1025997.86	-1022789.35	-1022787.91	-1022931.03	-1022931.21

Energies in kJ/mol.

Figure 3 illustrates the electrostatic potential maps of the phellandrene isomers considered. The red/orange regions stand for negative whereas the blue regions for positive charge/potential development. Figure 4 illustrates the electrostatic potential maps of the species from phellandrenes considered.

In phellandrenes negative potential region of the map is over the 4π-system, whereas in the others it mainly coincides with the hexagonal ring (Figure 4).

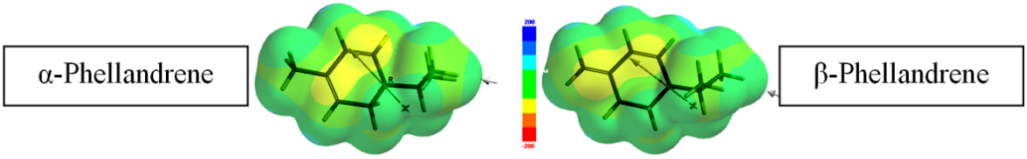


Figure 3. Electrostatic potential maps of α- and β-phellandrenes.

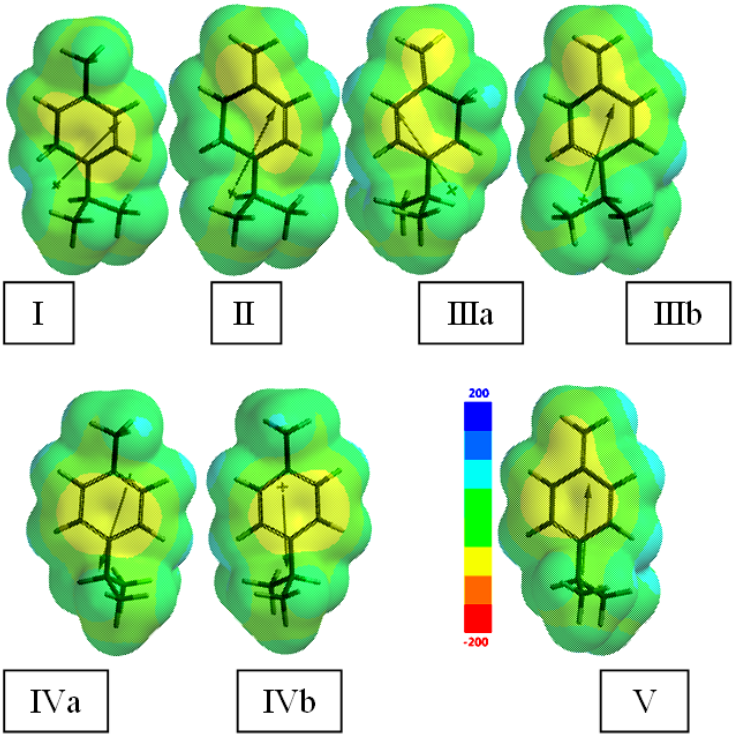


Figure 4. Electrostatic potential maps of the species from phellandrenes considered.

Figure 5 is the local ionization potential maps of the phellandrenes and the other closed- shell systems considered, where conventionally red/reddish regions (if any exists) on the density surface indicate areas from which electron removal is relatively easy, meaning that they are subject to electrophilic attack.

Figure 6 shows the LUMO maps of the phellandrenes and the other closed shell systems considered. Note that a LUMO map displays the absolute value of the LUMO on the electron density surface. The blue color (if any exists) stands for the maximum value of the LUMO and the red-colored region, associates with the minimum value.

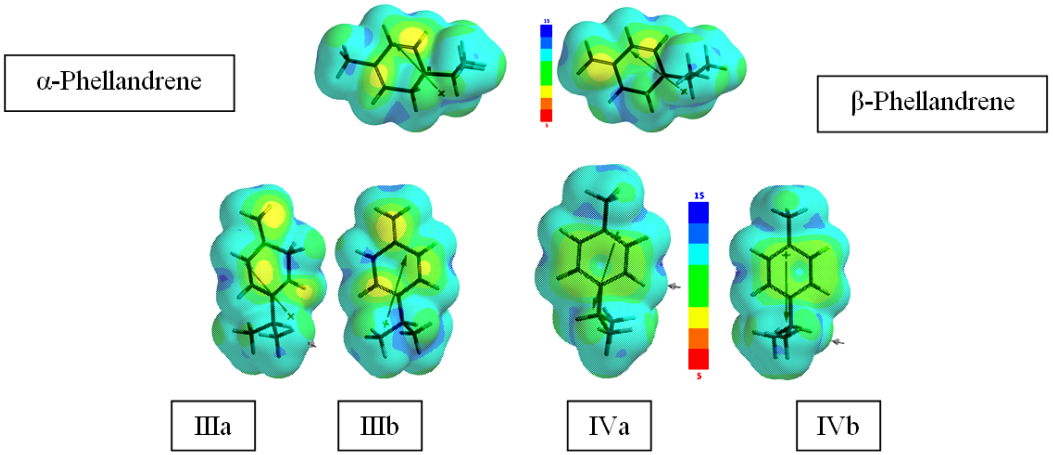


Figure 5. Local ionization potential maps of α- and β-phellandrenes and the other closed shell systems considered.

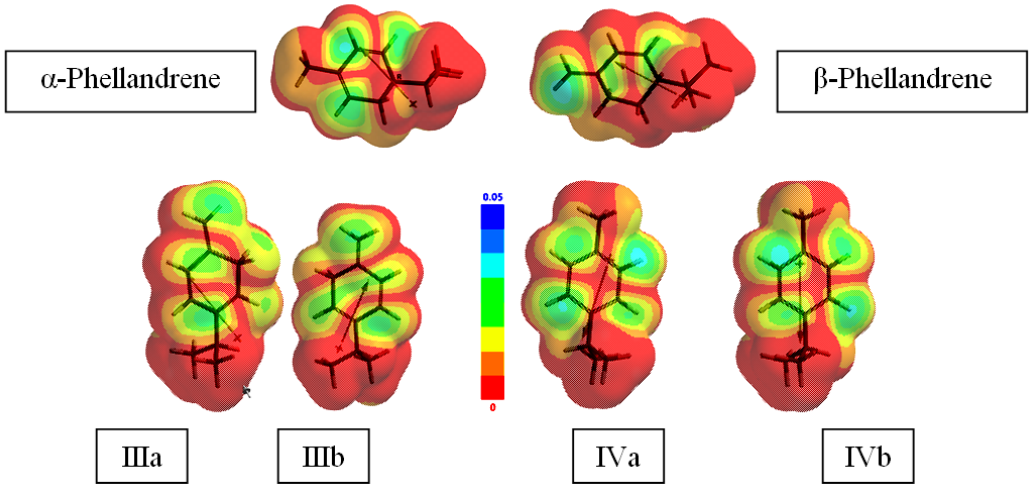


Figure 6. The LUMO maps of α- and β-phellandrenes and the other closed shell systems considered.

The electrostatic potential (ESP) charges on atoms of the structure considered are depicted in Figure 7. 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 [37]. As mentioned above, radical-I is electronically is more

stable and thermally more favorable than radical-II, both of which are on α-carbon to the π-systems present. Note that in radical-II, two like charges are side by side on the radical and the adjacent carbon of the π-system. Also, like charges happen on the carbon atoms of the endocyclic π-system in radical-II. This fact might be the reasons for preferable stability and thermal favorability of radical-I over radical-II.

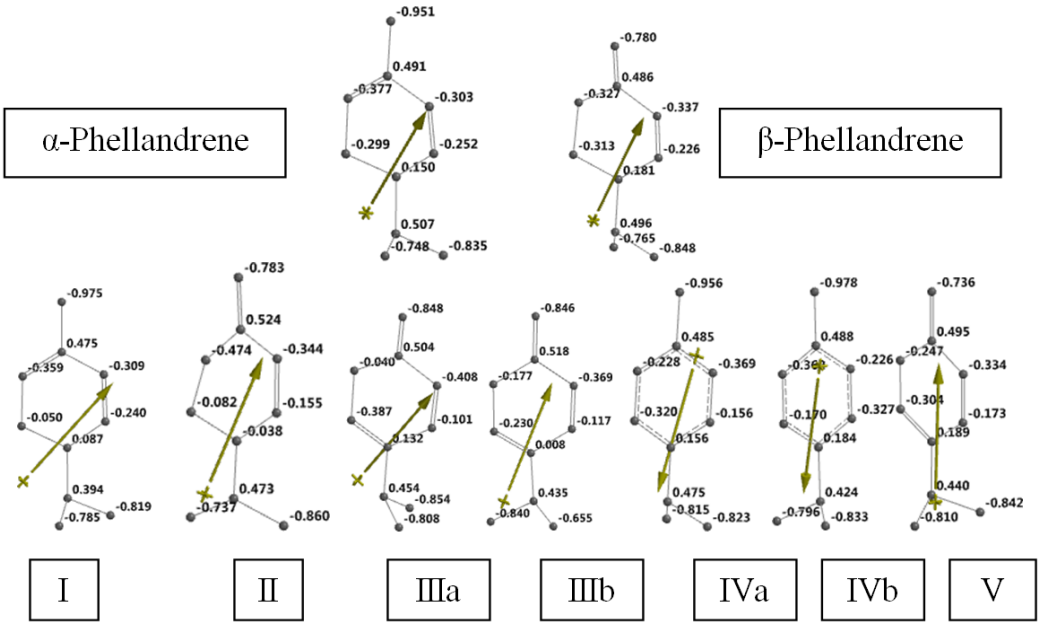


Figure 7. The ESP charges on the atoms of the species of present concern (Hydrogens omitted).

Figure 8 shows the spin densities and spin density maps of the open-shell systems considered as well as the numbering of the positions. The blue regions stand for high spin density possessing sites which indicates that in radicals I and II, spin density mainly accumulates at positions C2 and C6 and C6 and C7, respectively. Whereas in radical-V spin density resides on C7.

The HOMO, LUMO energies and intermolecular orbital energy gap ($\Delta\varepsilon=\varepsilon_{LUMO}-\varepsilon_{HOMO}$) values of the species considered are shown in Table 5.

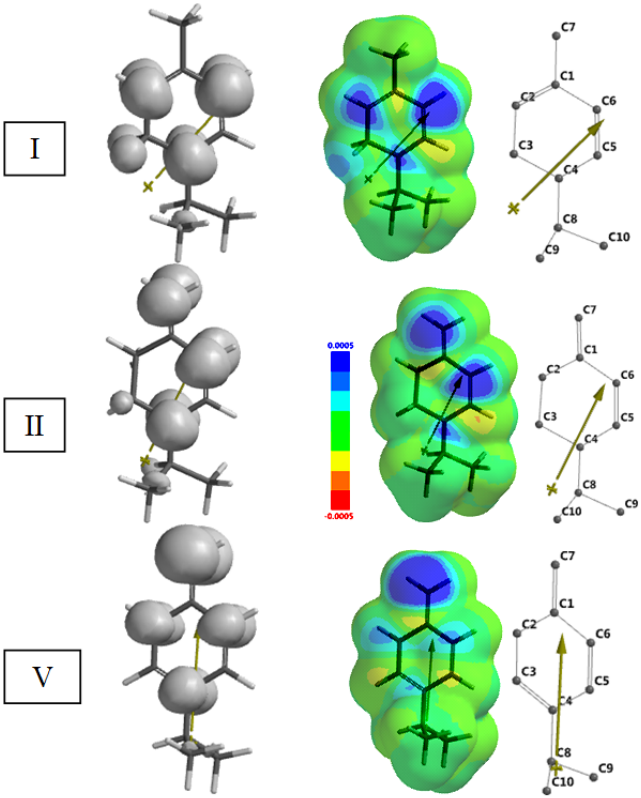


Figure 8. The spin densities and spin density maps (colored) of the radicals considered.

Table 5. The HOMO, LUMO energies and Δε values of the species concerned.

	HOMO	LUMO	Δε
α-Phellandrene	-559.58	-78.02	481.56
β-Phellandrene	-592.53	-82.39	510.14
I	-427.76	-27.97	399.78
II	-455.65	-38.58	417.07
IIIa	-538.78	-141.12	397.66
IIIb	-539.30	-138.39	400.91
IVa	-622.99	-35.86	587.13
IVb	-623.09	-35.79	587.30
V	-483.27	-47.07	436.20

Energies in kJ/mol.

The order of HOMO energies are β-phellandrene < α-phellandrene, II < I and IVb < Iva < IIIb < IIIa. Whereas the LUMO energies follow the order of β-phellandrene < α-phellandrene, II < I and IIIa < IIIb < IVa < IVb. Consequently, order of Δε values are α-phellandrene < β-phellandrene, I < II and IIIa < IIIb < IVa < IVb.

Table 6 lists λ_{max} values of the species considered. The phellandrenes considered absorb in the UV region of the spectrum. Since, the interfrontier molecular orbital energy gap for (Δε) for α-phellandrene is less it absorbs at higher λ_{max} value compared to the β-isomer. The isomeric radicals I and II possess some absorption also in the visible region but less intense. Radical-V absorbs in the UV-region but partly skirt of the absorption curve occurs in the visible region. The isomeric closed-shell structures, III and IV absorb in the UV region. However, the spectrum of III spreads over a much larger area than IV. Note that Δε value of III is much smaller than the respective value of IV. It is worth mentioning that structure IV is an aromatic compound having a ring current of 6π-electrons.

Table 6. λ_{max} values of the species considered.

α-Phellandrene	β-Phellandrene	I	II	III	IV	V
259.12	225.22	318.06	305.79	301.00	209.01	318.57
		439.00	433.07			

λ_{max} values in nm. The first entry in each row stands for the main absorption value.

4. Conclusion

Within the limitations of the theory and basis set used, the present DFT treatment has indicated that in vacuum and aqueous conditions, the species presently considered are electronically stable and have thermo chemically favorable formation values. The effects of structural and conjugative factors on some properties of phellandrenes and the related species from them have been obtained. The radicals are resonance stabilized and may play some role in the auto oxidation of phellandrenes. Phellandrenes exert many biological activities. However, more studies are needed to investigate more of their bio-properties and the adverse effects of them. The present study puts some light on phellandrenes at the molecular level.

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