Infrared spectrum analysis for 17-iodo-androst-16-ene-derived steroid with good potential to treat breast cancer

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Abstract

This study applies Density Functional Theory (DFT), using the B3LYP functional, and via *ab initio* Restrict Hartree-Fock (RHF) methods, to study the infrared spectrum of steroid 17-Iodo-androst-16-ene. The spectrum was obtained via computational methods ab initio RHF and DFT. Optimization of molecular structure via UFF (Universal Force Field), followed by PM3 (Parametric Method 3), with geometric optimization, obtaining the spectrum of other basis sets of steroid 17-Iodo-androst-16-ene. The study this steroid was chosen because it can could act as aromatase enzyme inhibitors and this phenomenon could be translated as good compounds to treat breast cancer. The B3LYP functional always presents the lowest thermal energy than the RHF in all calculated bases, however the RHF always presents the highest Entropy than the B3LYP, in all the calculated basis sets. The normalized spectrum calculated in the B3LYP/SVP functional/basis set have harmonic frequency with peaks 3,241.83 cm^{-1}, 100% and 3,177.53.5 cm^{-1} at 43.304% absorbance. The study has so far been limited to computational methods compatible with the theory of quantum chemistry.

Keywords: Hartree-Fock method, DFT, B3LYP, UFF, PM3, Infrared spectroscopy, Cancer.

1. Introduction

This study applies Density Functional Theory (DFT), using the B3LYP functional, and via *ab initio* Restrict Hartree-Fock (RHF) methods, [1-13] to study the infrared spectrum of steroid 17-Iodo-androst-16-ene derived [14].

The spectrum was obtained via computational methods *ab initio* RHF and DFT. [1-13] Optimization of molecular structure via UFF (Universal Force Field), followed by PM3[1] (Parametric Method 3) [1-13], with geometric optimization, obtaining the spectrum of other basis sets of steroid 17-Iodo-androst-16-ene [2] derived [14].

A steroid (named after the steroid cholesterol) is a biologically active organic compound with four fused rings arranged in a specific molecular configuration. Steroids have two principal biological functions: as important components of cell membranes that alter membrane fluidity and as signaling molecules. Hundreds of steroids are found in plants, animals and fungi. All steroids are manufactured in cells from the sterols lanosterol (opisthokonts) or cycloartenol (plants). Lanosterol and cycloartenol are derived from the cyclization of the triterpene squalene. [15]

The steroid nucleus (core structure) is called gonane (cyclopentanoperhydrophenanthrene). It is typically composed of seventeen carbon atoms, bonded in four fused rings: three six-member cyclohexane rings (rings A, B and C in the first illustration) and one five-member cyclopentane ring (the D ring). Examples include anabolic steroids, the lipid cholesterol, the sex hormones estradiol and testosterone, and the anti-inflammatory corticosteroid drug dexamethasone. [15]

Some aromatase enzyme inhibitors drugs have been used to treat cancer; however, their interaction with aromatase is not clear. Evaluated the interaction of steroid 17-Iodo-androst-16-ene derivatives with aromatase enzyme surface using 3eqm protein. The results showed differences in the aminoacid residues involved in the interaction of steroid derivatives interact with 3eqm protein surface Arg_{115}; Phe_{134}; Trp_{224}; Ala_{306}; Thr_{310}; Val_{370}; Met_{374}; Leu_{477}. The steroid derivatives could act as aromatase enzyme inhibitors and this phenomenon could be translated as good compounds to treat breast cancer. [17]

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[1] PM3, or Parametric Method 3, is a semi-empirical method for the quantum calculation of molecular electronic structure in computational chemistry. It is based on the Neglect of Differential Diatomic Overlap integral approximation. [1-13]

[2] The steroid [15] 17-Iodo-androst-16-ene derived of testosterone. Testosterone is the primary male sex hormone and anabolic steroid in males [16].

The *ab initio* and DFT [12-18] calculations have been performed to study the equilibrium configuration, and calculation of its Infrared Spectrum (IR), its Entropy (S), Heat capacity (C_V), chemical and molecular structure of steroid derived, via GAMESS[3].

2. Methods

2.1 Hardware and Software

A computer used for was a Desktop AMD Ryzen 7 1800X processor [23], ASUS [24] Prime A320M-K motherboard, 16GB of RAM, with 500GB SSD [16], with SUSE Linux Enterprise Desktop [25],

The *ab initio* and B3LYP [18-22] calculations have been performed to study the equilibrium configuration, for the calculation of chemical and molecular structure, its IR, S, C_V, of the steroid. The set of programs GaussView 5.0.8 [26], GAMESS [21-22], BIOVIA Draw 2017 [27], and CHARMM22 [28, 29] were used.

2.2 Hartree-Fock Methods (HF)

The molecular Hartree-Fock [1-4,7-12] wave function is written as an antisymmetrized product (Slater determinant) of spin-orbitals, each spin-orbital being a product of a spatial orbital ϕ_i and a spin function (either α or β).

The expression for the Hartree-Fock molecular electronic energy E_{HF} is given by the variation theorem as $E_{HF} = \langle D|\hat{\mathrm{H}}_{\mathrm{el}} + \mathrm{V}_{\mathrm{NN}}|D\rangle$ where D is the Slater-determinant Hartree-Fock wave function and $\widehat{\boldsymbol{H}}_{\mathrm{el}}$ and V_{NN} are given by

$$\widehat{\boldsymbol{H}}_{\mathrm{el}} = -\frac{\hbar^2}{2m_e}\sum_i \nabla_i^2 - \sum_\alpha \sum_i \frac{Z_\alpha e'^2}{r_{i\alpha}} + \sum_j \sum_{i>j} \frac{e'^2}{r_{ij}}$$

$$V_{NN} = \sum_\alpha \sum_{\beta>\alpha} \frac{Z_\alpha Z_\beta e'^2}{r_{\alpha\beta}} \tag{1}$$

Since V_{NN} does not involve electronic coordinates and $\boldsymbol{D}$ is normalized, we have $\langle D|V_{NN}|D\rangle = V_{NN}\langle D|D\rangle = V_{NN}$. The operator $\widehat{\boldsymbol{H}}_{\mathrm{el}}$ is the sum of one-electron operators $\hat{f}_i$ and two-electron operators $\hat{g}_{ij}$; we have $\widehat{\boldsymbol{H}}_{\mathrm{el}} = \sum_i \hat{f}_i + \sum_j \sum_{i>j} \hat{g}_{ij}$, where $\hat{f}_i = -\frac{1}{2}\nabla_i^2 \sum_\alpha \sum \alpha / r_{i\alpha}$ and $\hat{g}_{ij} = 1/r_{ij}$. The Hamiltonian $\widehat{\boldsymbol{H}}_{\mathrm{el}}$ is the same as the Hamiltonian $\widehat{\boldsymbol{H}}$ for an atom except that

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[3] Computational chemistry software program and stands for General Atomic and Molecular Electronic Structure System (GAMESS) [21, 22]

$\sum_\alpha \sum_\alpha / r_{i\alpha}$ replaces Z/r_i in $\hat{f}_i$. Hence

$$E = \langle D|\hat{\boldsymbol{H}}|D\rangle = 2\sum_{i}^{n/2}\langle\phi_i(1)|\hat{f}_i|\phi_i(2)\rangle + \sum_{j=1}^{n/2}\sum_{i=1}^{n/2}(2\boldsymbol{J}_{ij} - \boldsymbol{K}_{ij}) \tag{2}$$

where

$$\boldsymbol{J}_{ij} = \langle\phi_i(1)\phi_j(2)|\, e'^2/r_{12}\,|\phi_i(1)\phi_j(2)\rangle$$

and

$$\boldsymbol{K}_{ij} = \langle\phi_i(1)\phi_j(2)|\, e'^2/r_{12}\,|\phi_j(1)\phi_i(2)\rangle$$

$$\hat{f}_i = -(\hbar^2/2m_e)\nabla_i^2 - Z\, e'^2/r_1 \tag{3}$$

can be used to give $\langle D|\hat{\boldsymbol{H}}_{\mathrm{el}}|D\rangle$.

Therefore, the Hartree-Fock energy of a diatomic or polyatomic molecule with only closed shells is

$$\boldsymbol{E}_{HF} = 2\sum_{i=1}^{n/2}\boldsymbol{H}_i^{core} + \sum_{j=1}^{n/2}\sum_{i=1}^{n/2}(2\boldsymbol{J}_{ij} - \boldsymbol{K}_{ij}) + \boldsymbol{V}_{NN} \tag{4}$$

$$\boldsymbol{H}_i^{core} \equiv \langle\phi_i(1)|\hat{\boldsymbol{H}}^{core}(1)|\phi_i(1)\rangle \equiv \left\langle\phi_i(1)\middle|-\frac{1}{2}\nabla_i^2 \sum_{\alpha} Z_\alpha/r_{1\alpha}\middle|\phi_i(1)\right\rangle \tag{5}$$

$$\boldsymbol{J}_{ij} \equiv \langle\phi_i(1)\phi_j(2)|\, 1/r_{12}\,|\phi_i(1)\phi_j(2)\rangle$$

and

$$\boldsymbol{K}_{ij} \equiv \langle\phi_i(1)\phi_j(2)|\, 1/r_{12}\,|\phi_j(1)\phi_i(2)\rangle \tag{6}$$

where the one-electron-operator symbol was changed from $\hat{f}_i$ to $\hat{\boldsymbol{H}}^{core}(1)$. [6]

The vast literature associated with these methods suggests that the following is a plausible hierarchy:

$$HF \ll MP2 < CISD < CCSD < CCSD\,(T) < FCI \tag{7}$$

The extremes of 'best', FCI, and 'worst', HF, are irrefutable, but the intermediate methods are less clear and depend on the type of chemical problem being addressed. The use of HF [1-4, 7-12, 18-22] in the case of FCI was due to the computational cost.

2.3 DFT (Density Functional Theory)

Density Functional Theory (DFT) is a computational quantum mechanical modelling method used in physics, chemistry and materials science to investigate the electronic structure (or nuclear structure) (principally the ground state) of many-body systems, in particular atoms, molecules, and the condensed phases. Using this theory, the properties of a many-electron system can be determined by using functional, i.e. functions of another function. In the case of DFT, these are functional of the spatially dependent electron density. DFT is among the most popular and versatile methods available in condensed-matter physics, computational physics, and computational chemistry. [1-4, 18-22]

As usual in many-body electronic structure calculations, the nuclei of the treated molecules or clusters are seen as fixed (the Born–Oppenheimer approximation), generating a static external potential V, in which the electrons are moving. A stationary electronic state is then described by wavefunction $\Psi(r_1, \ldots, r_n)$ satisfying the many-electron time-independent Schrödinger equation

$$\hat{H}\Psi = \hat{T} + \hat{V} + \hat{U} = E\Psi \tag{8}$$

where, for the N-electron system, $\hat{H}$ is the Hamiltonian, E is the total energy, $\hat{T}$ is the kinetic energy, $\hat{V}$ is the potential energy from the external field due to positively charged nuclei, and $\hat{U}$ is the electron–electron interaction energy. The operators $\hat{T}$ and $\hat{U}$ are called universal operators, as they are the same for any n-electron system, while $\hat{V}$ is system-dependent. This complicated many-particle equation is not separable into simpler single-particle equations because of the interaction of term $\hat{U}$. [1-4, 18-22]

There are many sophisticated methods for solving the many-body Schrödinger equation based on the expansion of the wave function in Slater determinants.

While the simplest one is the Hartree–Fock method, more sophisticated approaches are usually categorized as post-Hartree–Fock methods. However, the problem with these methods is the huge computational effort, which makes it virtually impossible to apply them efficiently to larger, more complex systems. [1-4, 18-22]

The Hybrid functionals are a class of approximations to the exchange–correlation energy functional in density functional theory (DFT) that incorporate a portion of exact exchange from Hartree–Fock theory with the rest of the exchange–correlation energy from other sources (ab initio or empirical). The exact exchange energy functional is expressed in terms of the Kohn–Sham orbitals rather than the density, so is termed an implicit density functional. One of the most commonly used versions is B3LYP, which stands for "Becke, 3-parameter, Lee–Yang–Parr[1-4, 18-22] the B3LYP (exchange-correlation functional is

$$E_{XC}^{B3LYP} = (1-a)\,E_x^{LSDA} + aE_x^{HF} + b\Delta E_x^{B} + (1-c)\,E_c^{LSDA} + cE_c^{LYP}\ , \tag{9}$$

where: a = 0.20, b = 0.72, and c = 0.81. E_x^B is a generalized gradient approximation: the Becke 88 exchange functional and the correlation functional of Lee, Yang and Parr for B3LYP, and E_c^{LSDA} is the VWN local spin density approximation to the correlation functional. [1-4, 18-22]

The three parameters defining B3LYP have been taken without modification from Becke's original fitting of the analogous B3PW91 functional to a set of atomization energies, ionization potentials, proton affinities, and total atomic energies. [1-4, 16, 18-22]

3. Results

3.1 Properties of steroid 17-Iodo-androst-16-ene

Table 3.1: Properties of steroid 17-Iodo-androst-16-ene

Properties	**Results**	**Sources**
IUPAC name	rac-(5R,8S,9R,10S,13S,14S)-17-iodo-10,13-dimethyl-2,3,4,5,6,7,8,9,11,12,14,15-dodecahydro-1H-cyclopenta[a]phenanthrene	[27]
Dipole Moment	1.8778 Debye	[21, 22]
Degree of freedom	141	[21, 22]
Molecular Formula	$C_{19}H_{29}I$	[21, 22]

E(B3LYP)	-7660.80047960 a. u	[21, 22]
Polarizability (α)	218.035129 a. u	[21, 22]
Thermal Energy (E_T)	288.606 KCal/Mol	[21, 22]
Heat Capacity (Cv)	72.217 Cal/Mol-Kelvin	[21, 22]
Entropy (S)	132.406 Cal/Mol-Kelvin	[21, 22]

Source: Authors.

3.2 Analyses, Figures and Tables.

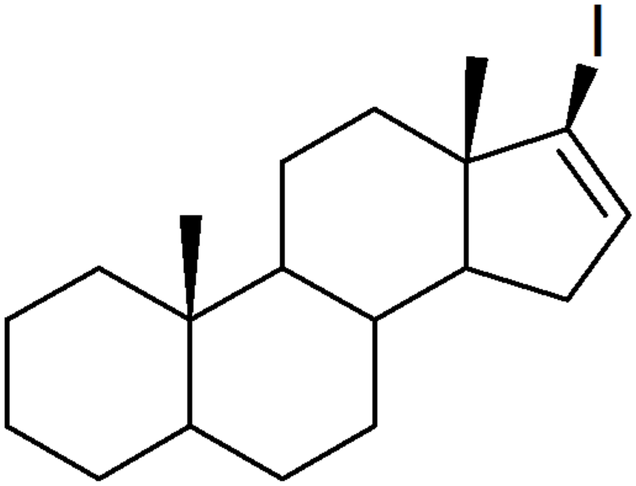
The Figure (1) show Molecular structure of steroid steroid 17-Iodo-androst-16-ene derived.

The Figure (2) show the plot of the normalized spectrum calculated in the B3LYP/SVP functional/basis set, for harmonic frequency peaks 3,241.83 cm^{-1}, 1.0 and 3,177.53.5 cm^{-1} at 0.43304 absorbance.

The Table (1) have the E (Thermal), Heat Capacity (C_V) and Entropy (S) for basis set calculated. This shows the advantages that for a given molecule, the B3LYP functional always presents the lowest thermal energy than the RHF in all calculated bases, but the RHF always presents the highest entropy than the B3LYP, in all the calculated basis sets.

The Table (2) represented the harmonic frequencies (cm^{-1}) for Intensity (km/mol) of the steroid 17-Iodo-androst-16-ene [16] molecule via B3LYP functional [7,15-21] SVP basis set for the infrared spectrum.

Table (2) shows all vibrational harmonics of the infrared spectrum obtained, with their intensities, which were plotted in Figure (2). The biggest peaks obtained that characterize the steroid in question are in the frequency/intensity of 3,241.83 cm^{-1}, 1 and 3,177.53.5 cm^{-1} at 0.43304 absorbance.



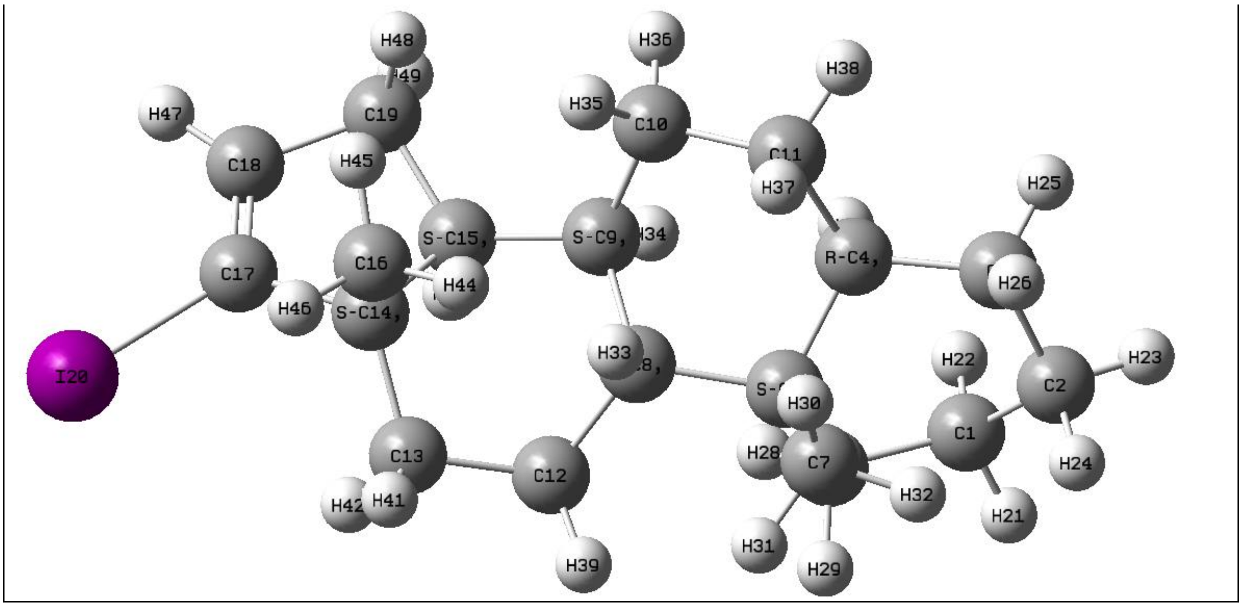
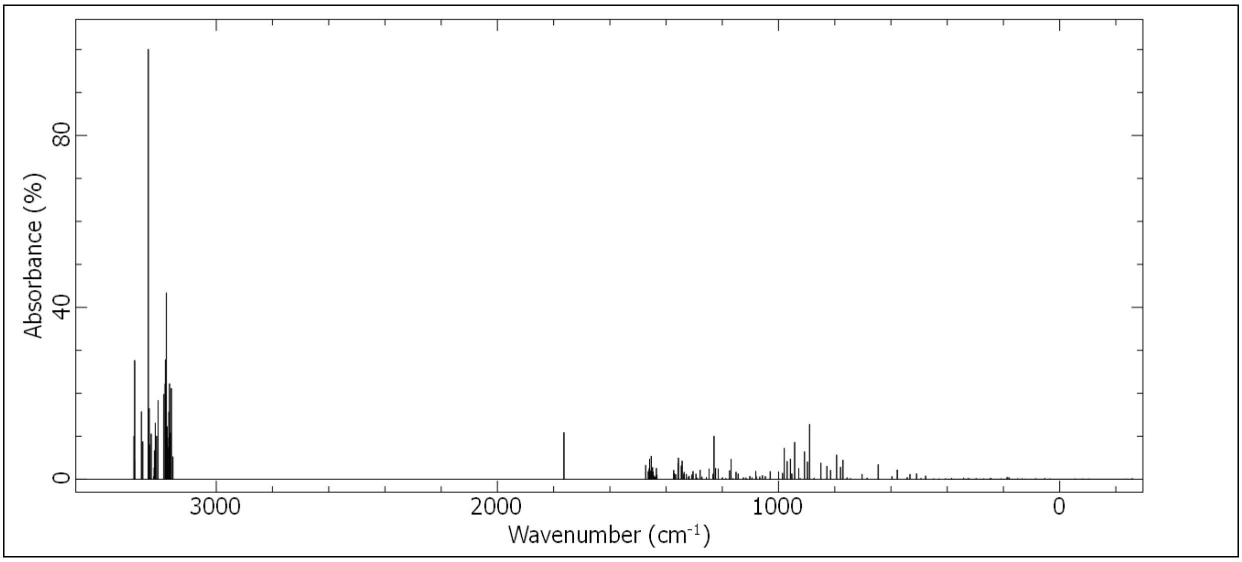


Figure 1: Molecular structure of steroid steroid 17-Iodo-androst-16-ene derived [17], via B3LYP/SVP functional /basis sets, via GAMMES [21, 22], Gaussview [26]. Represented in gray is Carbon, in white is Hydrogen and in purple is Iodine. **Source**: Authors.



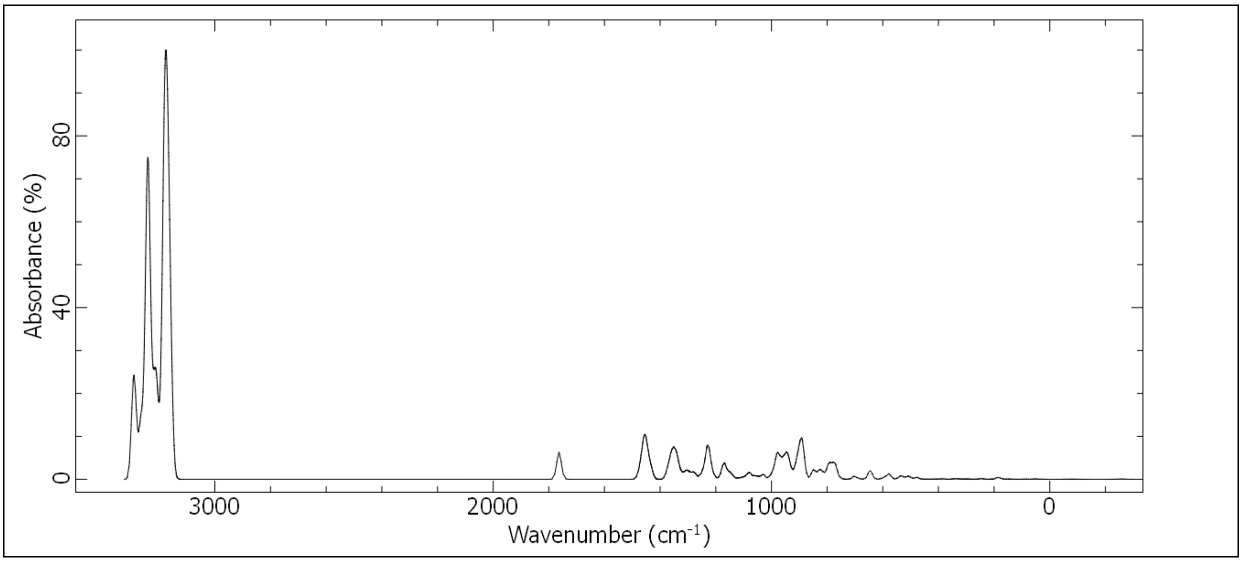


Figure 2: Plot of the normalized spectrum calculated in the B3LYP/SVP functional/basis set. [21, 22] Vibrational frequency peaks 3,241.83 cm^{-1}, 100% and 3,177.53.5 cm^{-1} at 43.304% absorbance. **Source**: Authors.

Table 1: E_T (Thermal Energy) ((KCal/Mol)), Heat Capacity (C_V) (Cal/Mol-Kelvin) and Entropy (S) (Cal/Mol-Kelvin) for basis set calculated. [21, 22]

Methods Functional /Sets	**E_T**	**Cv**	**S**
B3LYP/STO-3G [33, 34]	316.348	59.594	119.201
RHF/STO-3G [33, 34]	344.895	65.810	130.057
B3LYP/3-21G [21, 22]	292.533	69.586	130.041
RHF/3-21G [21, 22]	309.802	71.690	132.448
B3LYP/CEP-4G [30-32]	303.939	54.211	110.839
RHF/CEP-4G [30-32]	326.008	54.260	116.632
B3LYP/CEP-31G [30-32]	290.441	65.369	121.983
RHF/CEP-31G [30-32]	311.292	70.159	133.044
B3LYP/CEP-121G [30-32]	288.725	68.334	129.011
RHF/CEP-121G [30-32]	308.332	71.739	135.093
B3LYP/LanL2MB [33, 34]	316.365	59.658	119.935
RHF/ LanL2MB [33, 34]	344.855	65.923	131.401
B3LYP/SV	290.893	66.858	124.753
RHF/SV	309.770	70.806	137.027
B3LYP/SVP	288.606	72.217	132.406
RHF/SVP	307.899	73.614	135.954
B3LYP/Def2SV [36]	289.118	69.969	128.420
RHF/Def2SV [36]	309.007	73.552	138.035
RB3LYP/SDD [35]	291.647	69.945	131.533
RHF/SDD [35]	310.530	70.939	131.878

Note: Split valence polarization (SVP); Split valence (SV); SDD: D95 up to Ar; Karlsruhe basis sets (def2).
Source: Authors.

Table 2: Table containing the harmonic frequencies (cm^{-1}) for Intensity (km/mol) of the steroid 17-Iodo-androst-16-ene [16] molecule via B3LYP functional, [7,15-21] SVP basis set for the infrared spectrum.

υ(cm^{-1})	I(km/mol)	υ(cm^{-1})	I(km/mol)	υ(cm^{-1})	I(km/mol)	υ(cm^{-1})	I(km/mol)	υ(cm^{-1})	I(km/mol)
33.48	0.0464	685.07	0.2898	1080.87	23.257	1335.94	20.341	3168.65	202.326
53.06	0.1524	702.90	14.162	1094.29	0.3815	1336.64	13.738	3169.84	95.870
84.69	0.0873	744.90	0.1195	1102.08	0.8204	1342.91	54.354	3173.46	124.607
123.50	0.0010	756.25	0.3975	1115.55	0.3262	1345.73	39.468	3174.74	158.114
133.59	0.0282	770.84	57.007	1124.86	0.4039	1356.02	63.424	3177.53	561.518
149.34	0.0909	779.33	35.906	1143.66	15.803	1357.76	46.641	3178.37	241.253
180.22	0.4360	793.53	72.734	1151.17	20.904	1365.56	13.727	3180.55	359.988
186.87	0.5555	814.85	26.389	1162.13	0.1365	1370.11	16.079	3181.93	286.840
208.34	0.0497	827.90	38.593	1168.81	60.287	1372.96	26.183	3186.39	255.467
244.51	0.2453	849.32	48.306	1174.24	25.359	1432.38	11.594	3206.91	237.495
247.75	0.1043	873.37	0.2613	1187.59	0.1919	1434.55	32.322	3212.25	129.553
270.98	0.0411	889.48	165.080	1199.27	0.3966	1434.87	0.5560	3216.76	168.817
296.80	0.1721	897.11	51.766	1214.44	30.657	1438.69	0.5215	3219.44	85.942
323.73	0.1903	907.72	82.487	1223.95	31.939	1441.37	0.9029	3220.83	33.741
329.90	0.0038	922.67	0.1300	1229.54	129.082	1445.90	21.507	3222.15	0.8039
341.65	0.2909	928.03	31.319	1233.00	14.512	1448.04	34.818	3231.53	135.916
384.39	0.2317	942.72	110.899	1247.06	30.392	1452.78	68.980	3237.39	103.298
406.43	0.1051	952.71	15.820	1256.63	0.5116	1454.24	24.984	3238.58	212.661
428.53	0.0474	957.67	60.343	1272.47	0.6238	1458.67	59.623	3241.83	1.296.674
447.92	0.0741	969.44	53.170	1278.90	27.105	1460.12	31.140	3261.61	112.698
476.86	0.9117	979.75	92.767	1288.69	0.1669	1463.31	22.764	3266.21	203.019
493.03	0.1846	985.77	17.521	1291.99	0.3366	1472.39	41.549	3290.24	357.684
509.00	16.175	999.71	22.023	1293.67	15.111	1763.34	140.294	3291.10	55.952
532.51	14.172	1029.66	22.721	1304.18	23.039	3154.39	67.089	3292.53	129.516
542.30	0.4716	1046.99	0.7888	1307.85	12.962	3159.83	273.431		
577.60	27.528	1057.28	10.681	1318.04	0.8485	3163.20	138.985		
596.51	0.7976	1066.75	0.6410	1319.93	0.6160	3166.14	287.559		
645.51	43.702	1079.53	0.7508	1328.04	14.183	3167.11	127.501		

Source: Authors.

The lowest ET (Thermal Energy) calculated is 288.606 KCal/Mol in the B3LYP/SVP functional /basis sets and the highest 344.895 KCal/Mol in the RHF/STO-3G method/basis sets.

The lowest Entropy (S) calculated is 110.839 Cal/Mol-Kelvin in the B3LYP/CEP-4G functional/basis sets and the highest 138.035Cal/Mol-Kelvin in the RHF/def2SV method/basis sets.

The Heat Capacity (Cv) calculated is 54.211 Cal/Mol-Kelvin in the B3LYP/CEP-4G functional/basis sets, and the highest 73.614 Cal/Mol-Kelvin in the RHF/SVP method/basis sets.

The vibrational stability of the molecule is in the lowest state of zero energy and highest entropy, presents better results in B3LYP functional.

The C_V being the amount of heat required to change the physical state of 1 mole of the molecule, presents better results in B3LYP functional.

It can be seen that for the given molecule, the B3LYP functional always presents the lowest thermal energy than the RHF in all calculated bases, however the RHF always presents the highest Entropy than the B3LYP, in all the calculated basis sets. Better bases were not used because they are out of reach for the Iodine atom.

Other calculations were carried out, but the main objective of the work was the characterization of the infrared spectrum of the steroid derivative. Furthermore, what reinforces the research are the results of co-authors L. F. Valverde et al. [17]

As expected, both RHF and B3LYP functional show similar results on the STO-3G and LanL2MB basis sets.

4. Conclusions

The study this steroid was chosen because it can could act as aromatase enzyme inhibitors and this phenomenon could be translated as good compounds to treat breast cancer.

The normalized spectrum calculated in the B3LYP/SVP functional/basis set have harmonic frequency with peaks 3,241.83 cm^{-1}, 100% and 3,177.53.5 cm^{-1} at 43.304% absorbance.

It can be seen that for the given molecule, the B3LYP functional always presents the lowest thermal energy than the RHF in all calculated bases, however the RHF always presents the highest Entropy than the B3LYP, in all the calculated basis sets. Better bases were not used because they are out of reach for the Iodine atom.

The study has so far been limited to computational *ab initio* methods. The results are compatible with the theory of quantum chemistry,

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