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Conformational study of (*E*)-4-{1-[2-(carbamothioyl) hydrazin-1-ylidene] ethyl}-phenyl-4-methylbenzoate ($C_{17}H_{17}N_3O_2S$)

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Abstract

The (E)-4-{1-[2-(carbamothioyl) hydrazin-1-ylidene] ethyl}-phenyl 4-methylbenzoate is a thiosemicarbazone of $C_{17}H_{17}N_3O_2S$ formula. As several thiosemicarbazones, it has some pharmacological properties. By HF and DFT/B3LYP methods as implemented in the gaussian 09, in the 6-31G, 6-311G, 6-31G (d, p) and 6-311G (d, p) basis set, the structural study of this molecule was performed. Among the molecule conformers modelled, the calculated values of geometrical parameters of two are very close to crystallographic data. Besides, the trypanocide activity of both conformers has been evaluated with a predicting model established by DFT/B3LYP/6-31G (d, p) calculations.

Keywords: Hartree Fock (HF), density functional theory (DFT), thiosemicarbazone, conformers, trypanocide.

Introduction

In recent decades there has been a growing interest in the pharmacological properties of thiosemicarbazones and their complexes with transition metals because of their ability to act as antiviral[1,2], antibacterial[3,4], antifungal[5,6] and anticancer[7,8] agents. Studies to date show that these activities are related to the molecular stability[9]. Thiosemicarbazones (RR'C = N-NH-C (S) -NH_2) are then a class of compounds with a broad spectrum of biological or therapeutic applications.

Several methods were thus proposed to investigate molecular geometries. These are essentially methods using molecular identification spectroscopy: IR, NMR, UV-VIS and XRD. Of all these methods, XRD remains the leading source of information on the structure of three-dimensional molecules. This method, however, has a major handicap which consists in obtaining the single crystals of the complex. Since the experimental conditions are not always exploitable, predictive methods of conformation have been developed. The best known are those based on empirical computation methods such as molecular mechanics, semi-empirical such as PM3 or non-empirical such as DFT[10]. Theoretical study of transition metal complexes plays an important role in the description of the stereochemistry of these compounds. The theoretical results are actually considered as a complement of the experimental results. Molecular modeling calculations make it possible to determine both the optimal geometry and the essential parameters such as bond lengths, torsion angles, atomic charges and coordinates, or steric energy characteristic parameter of the stability of the complexes. Knowledge of all these parameters will facilitate the understanding of the different biological activities of these complexes. We present in this work the results of the structural study of (E)-4-{1-[2-(carbamothioyl) hydrazin-1-ylidene]ethyl}-phenyl-4-methylbenzoate ($C_{17}H_{17}N_3O_2S$). This study was carried out in order to calculate the geometrical, energetic and electronic parameters of the two most stable conformers which are helpful in their relative stability study and in their trypanocidal activity estimation.

Methodology

Computational details: Scanning (variation of a dihedral within the molecule before optimization) of the structure of (E)-4-{1-[2-(carbamothioyl) hydrazin-1-ylidene]ethyl}-phenyl-4-methylbenzoate was carried out in B3LYP / 6-31G (d, p). This allowed us to identify two conformers having relative higher stability. These aforementioned conformers have been optimized with HF and DFT methods and in 6-31G, 6-311G, 6-31G (d, p) and 6-311G (d, p) bases. Geometric, energetic and electronic parameters were calculated. Using the optimized conformers. As far as local indices of reactivity are concerned, they have been calculated from the log file of the single point thanks to the D-Cent-QSAR software with a correction of the population of Mulliken[11,12]. All calculations were carried out using Gaussian software in its 03 and 09 versions. The different representations were made with Gaussview 5.0 and ChemDraw ultra 8 software. The work was performed at a temperature of 25°C and at a pressure of 1atm. Statistica software was used to perform multiple linear regression analysis[13]. For the calculation of the IC_{50} we used a prediction model (equation-1), previously established on the basis of DFT/B3LYP/6-31G (d, p)[14] calculations.

$$\log(IC_{50}) = -8.89 - 2.52F_2(HOMO)^* + 0.41\mu_4 - 10.25s_5 - 1.93S_4^E - 0.59\eta_9 - 0.43F_{10}(LUMO+1)^* - 0.66F_1(HOMO-1)^* \qquad (1)$$

Here $F_2(HOMO)^*$ is the electron population (Fukui index) of the highest occupied MO localized on atom 2, μ_4 is the local atomic electronic chemical potential of atom 4, ς_5 is the local atomic softness of atom 5, S_4^E is the total atomic electrophilic super delocalizability of atom 4, η_9 is the local atomic hardness of atom 9, $F_{10}(LUMO+1)^*$ is the Fukui index of the second lowest vacant MO localized on atom 10 and $F_1(HOMO-1)^*$ is the Fukui index of the second highest occupied MO localized on atom 1.

The index of electronic parameters of the equation, are atoms numbers in the basic skeleton of thiosemicarbazones.

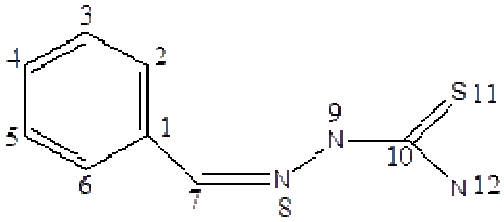

Figure-1: Skeleton numbering.

Results and discussion

Figure-2 represents the potential energy surface obtained by varying the dihedral angle $\alpha = C^{33}O^{13}C^4C^3$ from 0 to 180° in steps of 10° and Figure-3 shows the structure of the molecule showing the dihedral having undergone variation.

The illustration of the potential energy surface took into account only two of the degrees of freedom, represents the energy above the plane that they defined and thus creating a surface. Each point corresponds to a precise molecular structure, and the height of the surface at each point represents the energy of this structure. Five extrema (α = 0°, 40°, 90°, 140° and 180°) were observed on potential energy surface, including two minima (α = 40° and 140°). The corresponding geometries of these five extrema are represented on Figure-4 to Figure-8. The structure relative to α = 40 ° seems the most stable. The relative stability of these conformers is in ascending order of 40°, 140°, 0 ° 180° and 90°.

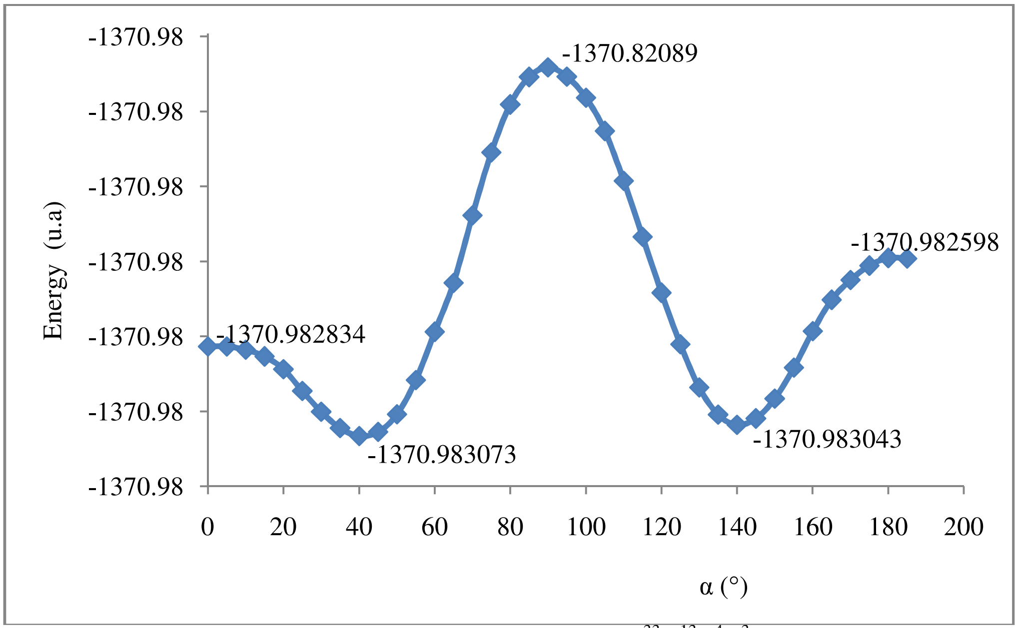

Figure-2: Potential energy surface around the dihedral $\alpha = C^{33}O^{13}C^4C^3$ to B3LYP / 6-31G (d, p).

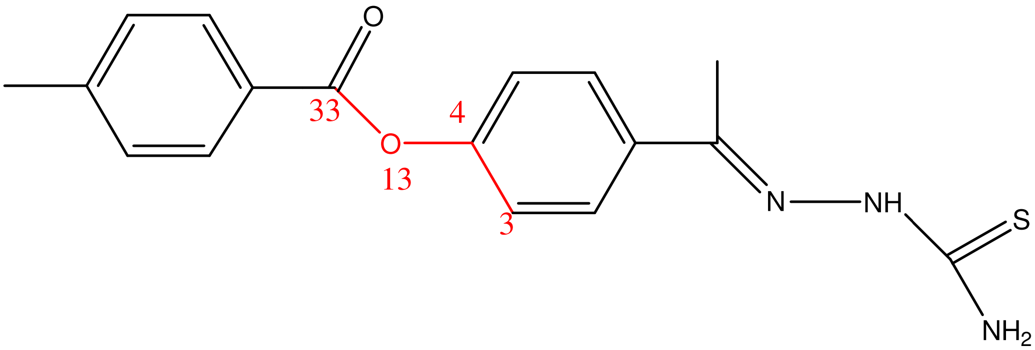

Figure-3: Structure of the molecule showing the dihedral having undergone variation.

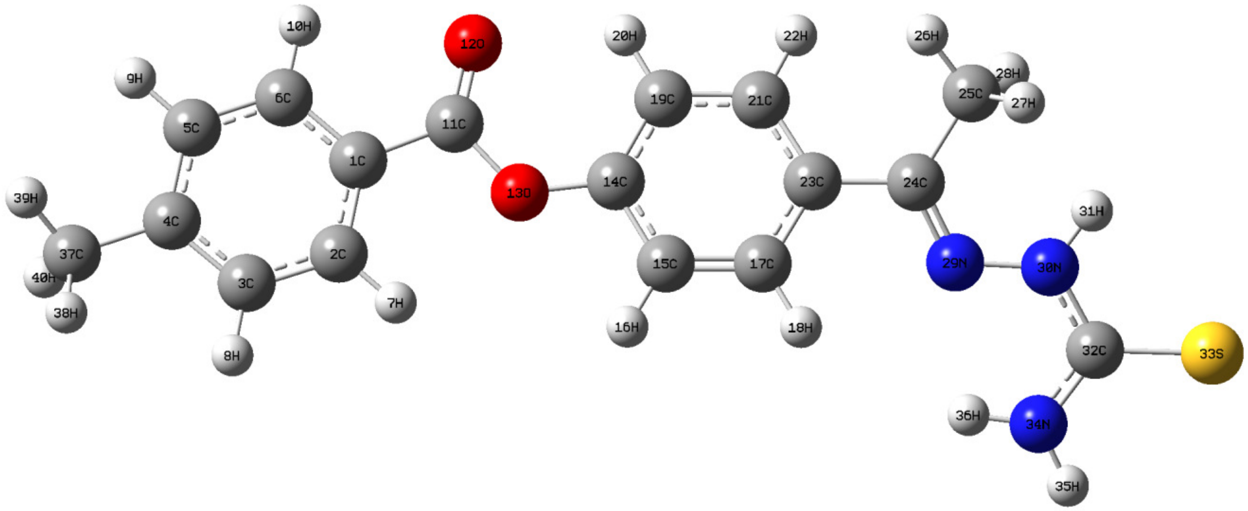

Figure-4: Structure for α =0°.

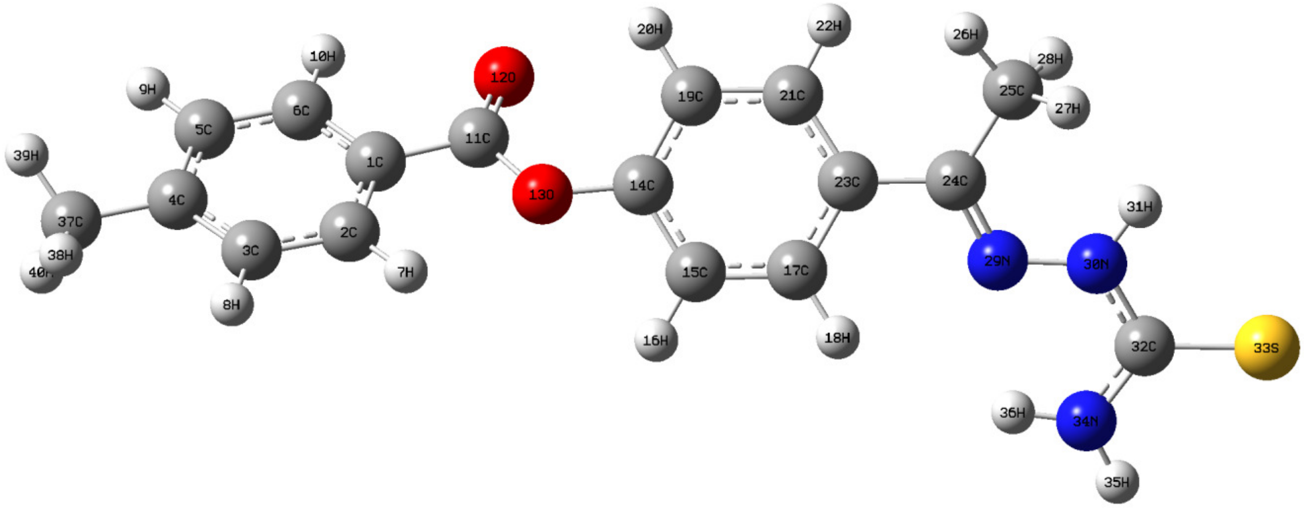

Figure-5: Structure for α =40°.

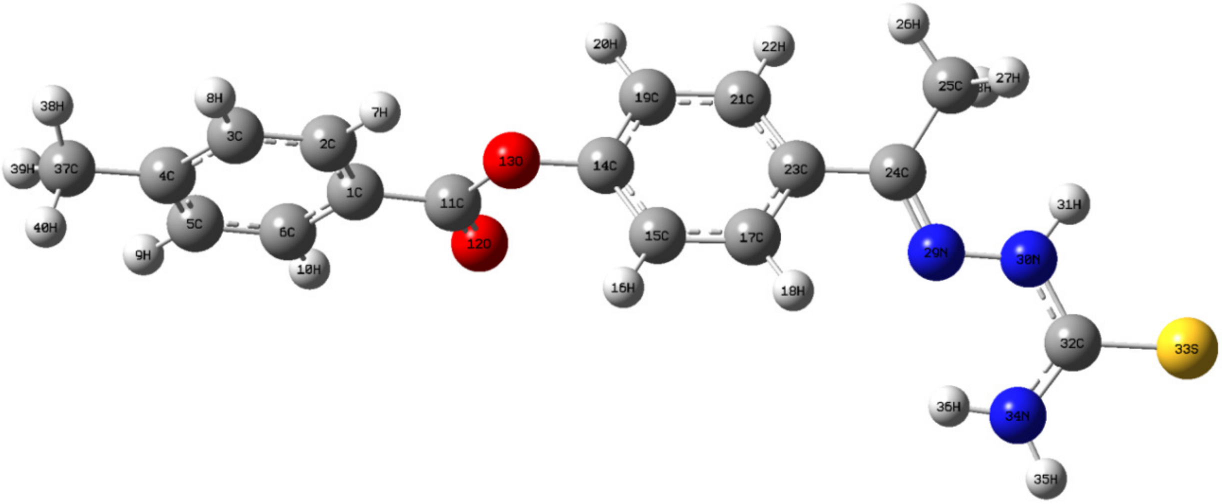

Figure-6: Structure for α =90°.

The IR frequencies calculated for these structures revealed no imaginary frequency meaning that structures are really stationary states. The global minimum is the structure corresponding to 40° whereas 140° corresponds to a local minimum. To ensure that the geometries of the two more stable conformers are close to the really structure, the geometrical parameters obtained with each couple method/basis are compared with the crystallographic data.

Conformer A: The calculated geometric parameters of the conformer A are gathered in Tables-2, 3 and 4.

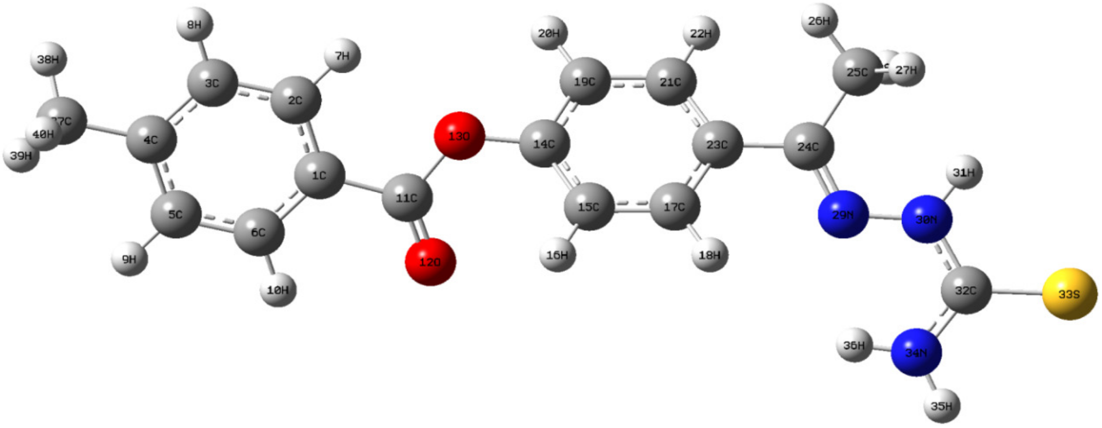

Figure-7: Structure for α =140°.

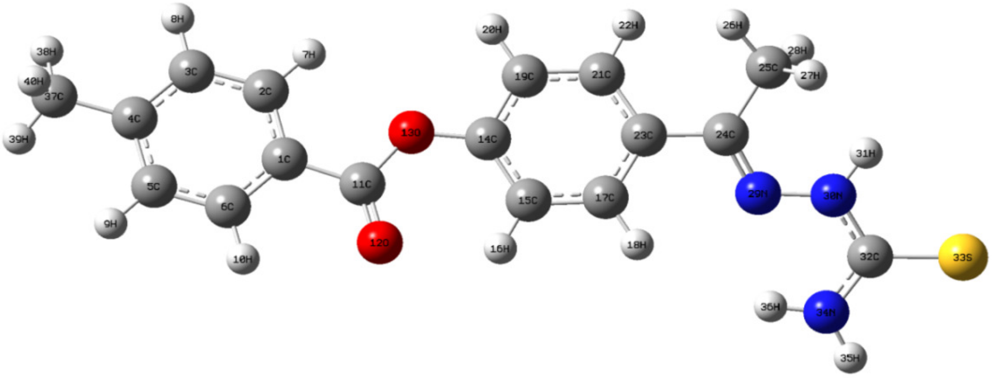

Figure-8: Structure for α =180°.

Table-1: The bond lengths of the A conformer.

Basis	6-31G		6-311G		6-31G (d,p)		6-311G (d,p)		RX (exp)
Methods	HF	DFT/B3LYP	HF	DFT/B3LYP	HF	DFT/B3LYP	HF	DFT/B3LYP	
C^{37}-C^{14}	1.508	1.511	1.507	1.510	1.509	1.509	1.509	1.508	1.511
C^{37}-H^{38}	1.083	1.096	1.082	1.092	1.085	1.094	1.086	1.093	0.960
C^{17}-H^{32}	1.070	1.082	1.068	1.079	1.073	1.084	1.073	1.082	0.930
C^{23}-C^{33}	1.471	1.476	1.469	1.474	1.485	1.484	1.485	1.484	1.476
C^{21}-C^{19}	1.382	1.392	1.380	1.390	1.379	1.389	1.378	1.387	1.383
C^{33}-O^{34}	1.214	1.238	1.210	1.235	1.186	1.211	1.179	1.203	1.195
C^{33}-O^{13}	1.359	1.392	1.361	1.393	1.343	1.375	1.343	1.375	1.362

The results from these methods and bases of computation, with regard to the interatomic distances are not only all very close to each other but also close to the experimental values. This indicates that both used methods in the entire four bases reproduce well the structure of the studied molecule.

In view of the values obtained, all the angles vary very little from one base to another whatever the method. But compared to the crystallographic values, the highest gap is around one degree. This allows us to conclude that all the four basis and calculations methods used are significant when studying the angles of conformers and conformer A can be assumed to be in agreement with the experimental values.

Dihedral also have been analyzed. Very little change of the calculated values with the crystallographic data is observed with all the methods and basis used. Indeed, the gap is 3° at the maximum. So all these angles are in line with reality. The negative value of some dihedral is due to the position of the molecule with respect to a given plane and therefore does not change the structure of the molecule.

Table-2: The angles in the A conformer.

Basis	6-31G		6-311G		6-31G (d,p)		6-311G (d,p)		RX (exp)
Methods	HF	DFT/B3LYP	HF	DFT/B3LYP	HF	DFT/B3LYP	HF	DFT/B3LYP	
C^{19}-C^{14}-C^{37}	120.56	120.63	120.46	120.57	120.33	120.74	120.27	120.66	120.7
C^{21}-C^{23}-C^{17}	119.48	119.35	119.44	119.25	119.40	119.31	119.37	119.25	118.99
C^{17}-C^{23}-C^{33}	122.30	122.80	122.25	122.85	122.63	123.01	122.63	123.01	122.88
O^{34}-C^{33}-O^{13}	122.47	123.32	122.07	123.30	123.09	123.70	123.08	123.62	122.2
O^{34}-C^{33}-C^{23}	124.90	125.04	125.23	125.03	124.72	125.00	124.83	125.15	125.62
O^{13}-C^{33}-C^{23}	112.62	111.64	112.70	111.67	112.19	111.30	112.09	111.23	112.18

Table-3: The dihedral in the A conformer.

Basis	6-31G		6-311G		6-31G (d,p)		6-311G (d,p)		RX(exp)
Methods	HF	DFT/B3LYP	HF	DFT/B3LYP	HF	DFT/B3LYP	HF	DFT/B3LYP	
C^{37}-C^{14}-C^{15}-C^{17}	178.87	178.98	178.81	178.65	179.01	178.66	179.43	178.62	179.79
C^{15}-C^{17}-Cb^{23}-C^{33}	-180.00	179.91	179.82	179.88	179.83	179.70	179.89	179.69	177.90
C^{33}-C^{23}-C^{21}-C^{19}	-179.95	-179.90	-179.87	-179.89	-179.87	-179.77	-179.93	-179.79	-179.26
C^{21}-C^{23}-C^{33}-O^{34}	-1.28	-0.30	1.31	-0.04	0.66	0.51	0.66	1.35	-3.70
C^{17}-C^{23}-C^{33}-O^{34}	178.74	179.84	-178.48	-179.87	-179.17	-179.18	-179.23	-178.31	177.00

Table-4: Bond lengths of B conformer.

Basis	6-31G		6-311G		6-31G (d,p)		6-311G (d,p)		RX (exp)
Methods	HF	DFT/B3LYP	HF	DFT/B3LYP	HF	DFT/B3LYP	HF	DFT/B3LYP	
C^{37}-C^{14}	1.508	1.511	1.507	1.510	1.509	1.509	1.509	1.508	1.518
C^{37}-H^{38}	1.082	1.096	1.080	1.090	1.085	1.094	1.086	1.093	0.960
C^{17}-H^{32}	1.072	1.082	1.069	1.081	1.073	1.084	1.073	1.082	0.930
C^{23}-C^{33}	1.471	1.476	1.469	1.474	1.485	1.484	1.485	1.484	1.480
C^{21}-C^{19}	1.384	1.392	1.384	1.393	1.379	1.389	1.378	1.387	1.379
C^{33}-O^{34}	1.214	1.238	1.210	1.235	1.186	1.211	1.179	1.203	1.195
C^{33}-O^{13}	1.359	1.392	1.361	1.393	1.343	1.375	1.343	1.375	1.357

Conformer B: As for conformer A, the calculated geometric parameters of the conformer B are gathered in Tables-5, 6 and 7.

As observed for conformer A, all the geometric parameters calculated are in one hand close to each other passing from one basis set to another for both methods and in the second hand really close to the crystallographic data. This means that the conformer B modeled would be of the same stability with the real molecule and can be used to theoretically determine the electronic properties of our studied molecule counting in great part in its trypanocide activity assessment.

Though the proximity of conformers A and B geometries, the thermodynamic analysis in both methods and all the basis has shown that conformer A is slightly more stable than B. Indeed, the conformer A energy is smaller in all the cases (Table-7).

In order to predict the trypanocide activity of the two conformers, their electronic parameters have been calculated at the same level of theory. These are the HOMO-LUMO gap, chemical potential, hardness, softness and electrophilicity which values are in Table-8.

Table-5: The angles in the B conformer.

Basis	6-31G		6-311G		6-31G (d,p)		6-311G (d,p)		RX (exp)
Methods	HF	DFT/B3LYP	HF	DFT/B3LYP	HF	DFT/B3LYP	HF	DFT/B3LYP	
$C^{19}-C^{14}-C^{37}$	120.90	120.85	120.93	120.93	120.33	120.74	120.27	120.66	121.20
$C^{21}-C^{23}-C^{17}$	119.48	119.35	119.44	119.25	119.40	119.31	119.37	119.25	119.00
$C^{17}-C^{23}-C^{33}$	118.23	117.86	118.32	117.93	122.63	123.01	122.63	123.01	123.52
$O^{34}-C^{33}-O^{13}$	122.47	123.32	122.07	123.30	123.09	123.70	123.08	123.62	122.65
$O^{34}-C^{33}-C^{23}$	124.91	125.04	125.24	125.05	124.72	125.00	124.83	125.15	125.32
$O^{13}-C^{33}-C^{23}$	112.62	111.64	112.70	111.65	112.19	111.30	112.09	111.23	112.02

Table-6: The dihedra in B conformer.

Basis	6-31G		6-311G		6-31G (d,p)		6-311G (d,p)		RX (exp)
Methods	HF	DFT/B3LYP	HF	DFT/B3LYP	HF	DFT/B3LYP	HF	DFT/B3LYP	
$C^{37}-C^{14}-C^{15}-C^{17}$	178.89	178.63	178.90	178.73	179.16	178.58	-179.92	178.67	178.70
$C^{15}-C^{17}-C^{23}-C^{33}$	-179.98	179.86	-179.99	179.83	-179.99	179.95	-179.91	-180.00	-178.80
$C^{33}-C^{23}-C^{21}-C^{19}$	-178.84	-179.88	-179.96	-179.85	-179.96	-179.92	179.96	-180 .00	177.90
$C^{21}-C^{23}-C^{33}-O^{34}$	-1.39	-0.04	-1.46	0.23	-0.86	-0.72	-0.85	-1.39	9.90
$C^{17}-C^{23}-C^{33}-O^{34}$	178.61	-179.86	178.57	-179.54	179.16	179.41	179.07	178.69	-171.80

Table-7: Energies of conformers A and B in ua.

Methode/Basis	Conformer A	Conformer B
B3LYP/6-31G	-1370.667	-1370.667
B3LYP/6-31G(d,p)	-1370.983	-1370.983
B3LYP/6-311G	-1370.920	-1370.920
B3LYP/6-311G(d,p)	-1371.229	-1371.229
HF/6-31G	-1363.842	-1363.842
HF/6-31G(d,p)	-1364.294	-1364.294
HF/6-311G	-1364.057	-1364.057
HF/6-311G(d,p)	-1364.502	-1364.502

Table-8: Electronic Parameters of Conformers.

	6-31G			6-31G (d,p)			6-311G			6-311G (d,p)		
	$Conf^A$	$Conf^B$	ΔX/X*	$Conf^A$	$Conf^B$	ΔX/X	$Conf^A$	$Conf^B$	ΔX/X	$Conf^A$	$Conf^B$	ΔX/X
$\Delta E_{HOMO-LUMO}$	3.657	3.652	0.001	3.895	3.883	0.003	3.672	3.667	0.001	3.897	3.895	0.0005
μ	-3.742	-3.731	0.002	-3.620	-3.617	0.0008	-3.967	-3.955	0.003	-3.847	-3.836	0.002
η	-1.828	-1.826	0.001	-1.947	-1.941	0.003	-1.836	-1.833	0.001	-1.948	-1.947	0.0005
ς	-0.546	-0.547	0.001	-0.513	-0.515	0.003	-0.544	-0.545	0.001	-0.513	-0.513	0.000
ω	3.828	3.811	0.004	3.375	3.359	0.004	4.285	4.266	0.004	3.798	3.778	0.005

*With ΔX / X = [X (B) -X (A)) / X (A)]; $Conf^A$ and $Conf^B$ are respectively the A and B conformers.

It can be seen that the two conformers do not have the same values of the electronic parameters. The calculated relative uncertainty is significant only in the base 6-31G (d, p) which could justify the choice of the prediction equation obtained in the base 6-31G (d, p) of the previous works. It is noted that the hardnesses of the two conformers are weak and almost equal, which would mean that it is easy for these molecules to let their electronic density be modified by their environment. The Gap (HOMO-LUMO) of the A conformer is greater than that of the B conformer regardless to the basis set, so the A conformer is more stable relatively to B. The electrophily of the A conformer is greater than that of B regardless of the basis set, so the conformer A has a higher capacity to capture electron.

After this step, the meaningful calculated electronic parameters were introduced in equation 1 above-mentioned with the aim to assess predictive values of the IC50 of conformers. The obtained values are indicated in Table below.

Table-9: Electronic parameters and IC_{50} of the two conformers and the values of IC_{50} by using equation 1

B3LYP/6-31G (d,p)	Conformer A	Conformer B
F_2 (HOMO)	0.0433	0.0404
μ_4	-3.6237	-3.5828
S_5	0.2116	0.2053
s^{E}_{4}	-8.0677	-8.1003
η_9	3.8809	3.9856
F_{10} (LUMO+1)	0.1047	0.0731
F_1 (HOMO-1)	0.2235	0.2148
Log (IC_{50})	0.4347	0.5439
IC_{50} (μM)	2.72	3.50

The median inhibitory concentration (IC_{50}) of both conformers is inferior to 10 showing that they all have interesting tripanocide activity. Given that the IC_{50} of Conformer A (2.72) is smaller than that of B (3.50), one can conclude that the structure allowing a greater trypanocide activity is the one of conformer A.

Conclusion

The conformational analysis of (E) -4- {1- [2- (carbamothioyl) hydrazin-1-ylidene] ethyl} -phenyl 4-methylbenzoate have been conducted in this work with two methods and many basis. It resort that two conformers are more stable and all the used methods in all the basis reproduce well the crystallographic data. The conformer called A obtained at α = 40° is slightly more stable than the second called B obtained at α = 140°. They all have geometric parameters suiting well with crystallographic data to allow efficient theoretical assessment of biological activities. The electronic properties calculated are slightly different for conformers and show that conformer A has higher stability and electron capture capacity given its higher electrophily and HOMO-LUMO gap. The median inhibitory concentrations (IC_{50}) calculated with our predictive equation showed that both conformers have interesting tripanocide activity but conformer A is the most active.

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