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DFT Study of a Series of Nicotinic Acid Benzylidenehydrazide Derivatives: Structure, Stability and Reactivity

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Abstract: Hydrazones especially nicotinic acid benzylidenehydrazide derivatives constitute an important class of compounds that has received much interest in recent years, due to their diverse biological characteristics, such as antimicrobial, anticonvulsant, analgesic, anti-inflammatory, antiplatelet, antituberculous and antitumor activities. These compounds have donor sites such as N and O which have non-bonding doublets which allow them to coordinate with metal ions. For this purpose, ten hydrazones structures were optimized in the DFT method, using the B3LYP functional, with the basis 6-31G** for all atoms, in the gas phase using the Gaussian 09 program. The structural, energetic (energies, EHOMO-LUMO gaps), electronic (dipolar moments, atomic charges) parameters were determined. A study of the stability of the ligands was carried out based on the relative energies to study the chemical reactivity of the optimized structures, we calculated the global reactivity parameters (ionization potential, electronic affinity, electronic chemical potential, absolute hardness, overall softness and overall electrophilicity). The results obtained show that All the systems considered are stabilized by two types of electronic effect. Either; an inductive attractor effect, with a coexistence of mesomeric effects. Analysis of chemical hardness values indicates that the most stable isomers found are the hardest, with larger HOMO/LUMO gaps, and therefore less reactive. As a result, charge transfer will be predominant. The most nucleophilic systems are also determined based on the calculation of the eletrophicity and nucleophilicity indices.

Keywords: Hydrazones, DFT, Reactivity, Stability.

Introduction

Hydrazones were the subject of many interesting studies due to their important applications in much synthetic areas especially in indicators-chemistry. Hydrazones are being used extensively in detection and quantitative determination of several metals, for the preparation of compounds having diverse structures, analytical chemistry for the identification and isolation of carbonyl compounds (Mıtu, 2012). A number of nicotinic acid benzylidenehydrazide derivatives have been synthesized from isoniazid and were found to have potentiated activities against various bacterial and fungal strains (Maccari, 2005) including hydrazones with benzohydrazide and menthone (Al-Khattaf, 2021), Furthermore, metal complexes of isonicotinic hydrazones including, copper, zinc, manganese, nickel showed enhanced activities against microbes, tumor and free radicals (Jabeen, 2018).

- Selection and peer-review under responsibility of the Organizing Committee of the Conference

Nowadays many inorganic chemists have been made citing the successes of different density functional theory (DFT) methods compared to the experimental methods, in computing the molecular structure and reactivity of synthesized compounds, which are very important in order to disclose the relationship between the structure and chemical properties with their biological activity. These compounds coordinate at the metallic ions by oxygen amide (O=C) and the azomethine nitrogen (Ashma,2022). Quantum chemical calculations have been performed in order to compare the structural parameters to that of theoretical data.

Method

Computational Method and Quantum Mechanical Analysis

Full geometry optimization have been made with density functional theory (DFT) using Kohn–Sham's Density Functional Theory subjected to the gradient-corrected hybrid density functional B3LYP. This functional is a is the combinaison of Becke's three parameters hybrid method and the Lee-Yang-Parr correlation functional (B3LYP) (Lee, 1988), and 6-31G (d,p) for all others atoms (H, N, C, O) (Pearson, 1985) in gas phase, as implemented by Gaussian 09 program (Fresch, 2009), without any constraint of symmetry, followed by a calculation of the normal modes of vibration, to make sure that the stationary points were minima. Our complexes are all minima in their potential energy surface. Indeed, the analysis of the frequencies of the normal modes of vibration gives no imaginary frequency. We used the GaussView program to draw the optimized geometries and to visualize the the normal modes vibrations (Fresch, 2009).

We have determined the structure, the electronic parameters, the energies and the gaps E_{HOMO}/E_{LUMO}. Natural bond orbitals (NBO) atomic charges were also reported. The theoretical results obtained are compared with the available experimental data.

In order to study the chemical reactivity of the ligand and its optimized complexes, we calculated the following parameters of several global reactivity descriptors by means of DFT, such as: the ionization potential (I), the electron affinity (A), electronic chemical potential (μ), the absolute hardness (η), the global softness (S) and the global electrophilicity (ω) (Gazquez, 2008). The electronic chemical potential(μ) is defined by Parr and Pearson (Parr, 1983):

$$\mu = -\frac{1}{2}(I + A) = -\chi \qquad (1)$$

Were χ is the electronegativity given by Mulliken.
The global hardness is defined by (Parr, 1991):

$$\eta = \frac{1}{2}(I - A) \qquad (2)$$

The global softness *S* is obtained from:

$$S = \frac{1}{2\eta} \qquad (3)$$

The global electrophilicity (ω) measures the affinity of compounds given by Parr (Parr, 1999) is calculated by:

$$\omega = \frac{\mu^2}{2\eta} \qquad (4)$$

The nucleophilicity index equal to the negative of the ionization potential:

$$Nu= - I \qquad (5)$$

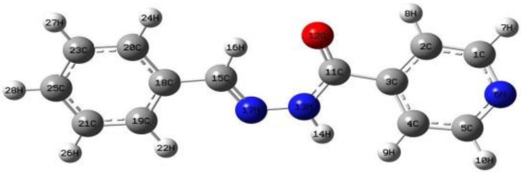
A high value of the nucleophilicity index Nu characterizes a good nucleophile, while a low value indicates a good electrophile.

Results and Discussion

Geometry

Figure 1 shows the optimized structures of a series of nicotinic acid benzylidene hydrazide derivatives (A-J) and all geometric parameters are depicted in Tables 1,2 and 3.

The tables 1,2 and 3 show that in all ligands studied, the 1C-6N and 3C-11C distances are shorter than their 11C-13N and 15C-17N counterparts, respectively, confirming their double bond character. The lengths of the CO double bond are between 1.21 and 1.26 Å. these values are in agreement with the average value for a CO double bond. We notice the absence of the CO single bond. Indeed, there has been an electronic delocalization in the system considered. The analysis of dihedral angles confirms the flatness of the molecules.



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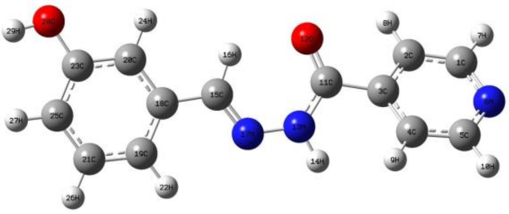

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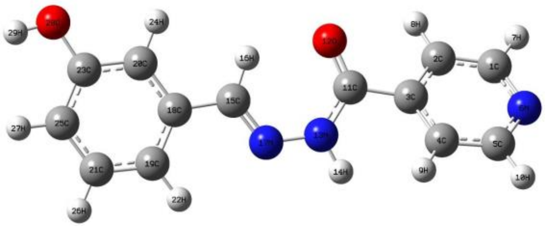

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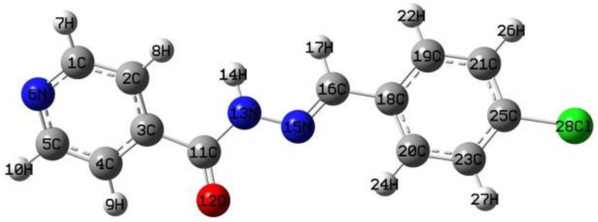

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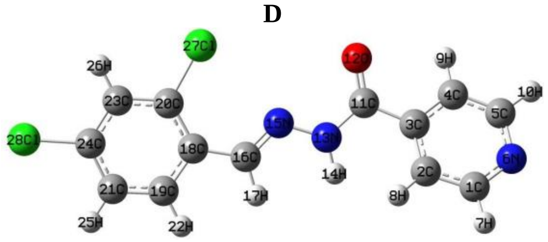

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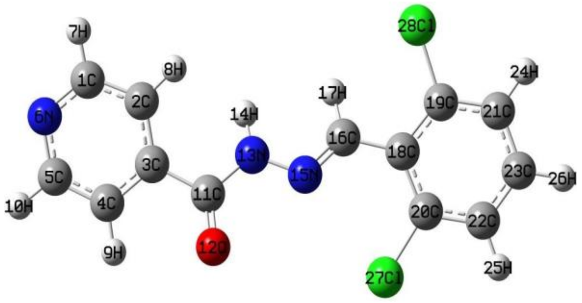

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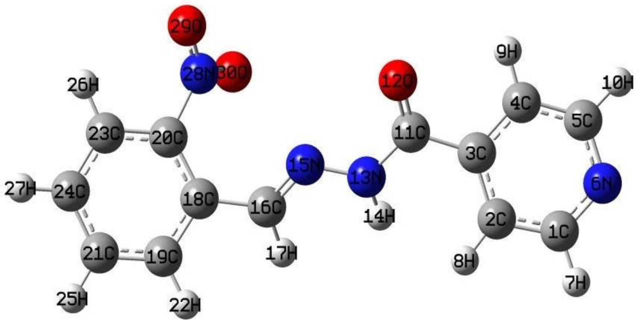

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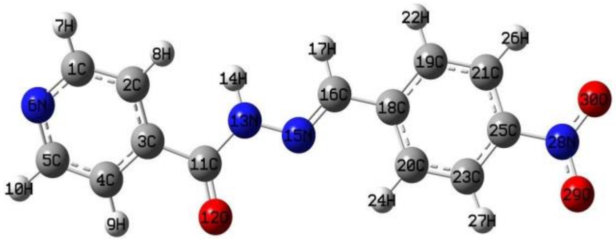

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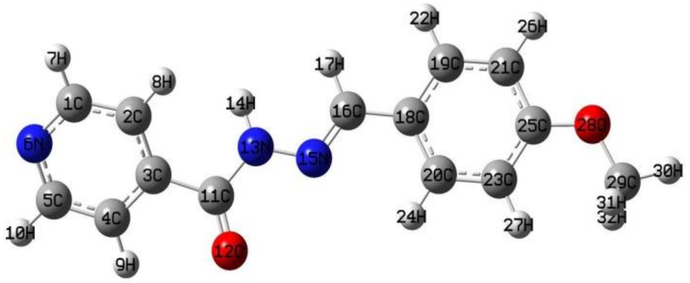

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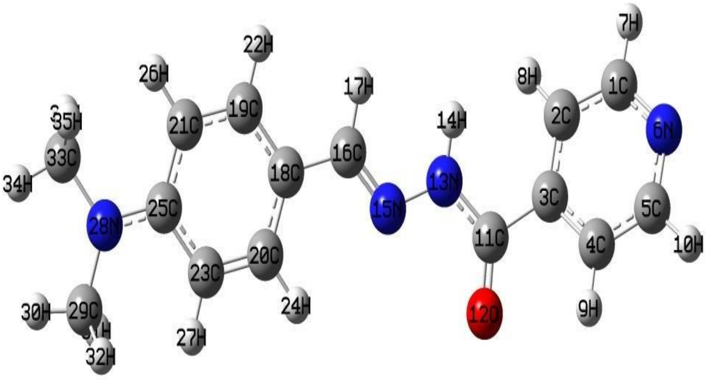


J

Figure 1. The optimized structures of the optimized structures A-J

Table1. Structural parameters (angles) at DFT/B3LYP.

	A	B	C	D	E	F	G	H	I	J
H8C2C3	119.6	119.6	121.8	121.9	121.8	121.8	121.9	121.8	121.7	121.7
C1C2C3	118.7	118.7	118.7	118.7	118.9	118.6	118.6	118.8	118.7	118.7
C2C3C11	117.6	117.6	124.5	124.1	124.2	124.4	124.5	124.1	124.5	124.6
C3C11O12	121.4	121.3	122.0	122.1	121.9	122.2	122.3	122.2	122.0	121.8
N13C11O12	124.2	114.3	123.8	123.6	121.9	123.6	123.5	122.9	123.8	124.1
C11N13H14	117.7	124.2	119.2	119.3	119.5	119.3	119.3	119.6	119.2	119.2
N13N17C15	120.6	119.5	116.8	117.1	120.6	116.3	120.5	118.5	120.8	121.0
N17C15C18	119.7	117.7	116.4	116.6	114.6	123.3	121.3	120.9	122.2	121.1
C18C20H24	119.3	121.2	118.7	119.1	119.9	115.5	118.5	118.6	118.7	118.7
N17C15H16	122.5	111.0	121.3	121.4	120.5	121.0	122.1	121.8	121.3	121.1
C19C21H26	119.7	118.8	120.2	120.7	118.9	119.6	119.7	121.8	121.4	118.8

Table 2. Structural parameters (dihedral angles) at DFT/B3LYP

	A	**B**	**C**	**D**	**E**
C1C2C3C4	1.3	1.3	-0.9	-0.7	-1.0
C1C2C3C11	179.7	179.7	-179.1	-178.8	-179.1
N6C1C2C3	-0.7	-0.7	-0.1	-0.2	-0.0
C5N6C1C2	0.3	0.3	-0.8	-0.8	-0.7
C2C3C11O12	-24.7	-25.0	-27.1	-29.7	-25.5
C2C3C11N13	154.4	154.1	153.5	150.7	155.6
O12C11N13H14	171.7	171.6	169.3	170.2	170.7

Table 3. Optimized structural parameters at DFT

	A	B	C	D	E	F	G	H	I	J
20C=23C	1.394	1.397	1.384	1.390	1.396	1.394	1.391	1.390	1.390	1.383
3C-11C	1.507	1.376	1.507	1.506	1.499	1.506	1.505	1.497	1.507	1.508
15C=17N	1.290	1.289	/	/	/	1.283	1.281	1.295	1.285	1.286
11C-13N	1.376	1.376	1.383	1.385	1.391	1.389	1.391	1.394	1.382	1.380
11C=12O	1.226	1.226	1.218	1.219	1.240	1.215	1.214	1.240	1.218	1.219
1C=6N	1.340	1.340	1.337	1.338	1.350	1.337	1.337	1.350	1.337	1.337
13N-14H	1.008	1.008	1.017	1.017	1.017	1.017	1.017	1.017	1.017	1.017
17N=15C	1.290	1.289	/	/	/	/	/	/	/	/
17N=13N	1.373	1.373	/	/	/	/	/	/	/	/
16C=15N	/	/	1.285	1.284	1.294	1.283	1.286	1.281	1.295	1.285
15N=13N	/	/	1.361	1.358	1.369	1.354	1.363	1.352	1.366	1.361

Energetic Properties

The calculated dipole moment, HOMO, LUMO and gap energy are listed in Table 4

The two isomers B and C are very close in energy. The isomer F is more stable than the isomer E (difference 167.3 Kcal/mole) and the H structure of H is less stable than the G structure . structure of H is less stable than G structure (difference 184.5 Kcal/mole). Compound G is the most polar. Indeed, it has the largest dipole moment (7.20 D), because the polarity of the two carbon-nitrogen bonds adds up.

Table 4. Eenergetic properties of the compounds A-G at DFT.

Compound	Energy (u a)	Related energy kcal/mole	HOMO/LUMO (eV)	Dipole Moment (D)
A	-741.47718727	/	2,721	1.94
B	-816.69699792	0	2,811	3.17
C	-816.69649090	0,31814757	4,048	5.95
D	-1201.09804047	/	2,309	4.16
E	-1660.38218807	167,3192664	2,248	5.47
F	-1660.64882886	0	2,318	4.34
G	-945.95768193	0	2,763	7.20
H	-945.66365691	184,5036278	2,463	6.44
I	-856.00166548	/	2,572	4.18
J	-875.45149019	/	2,185	6.95

Mulliken Charges

The Mulliken charges calculated are listed in Table 5, We notice that oxygen atoms are more negatively charged than nitrogen atoms. Which confirms that they are more reactive with respect to nitrogen. In isomers B and C, the oxygen atoms of the OH group are richer in electrons, which explains the pronounced inductive attracting effect of the oxygen atom. In the E and F isomers, we note that the carbon atoms which are closer to those of chlorine are more negatively charged, compared to those of the D isomer. Indeed, the negative partial charges carried by the carbon atoms close are more important if the two chlorine atoms are involved.

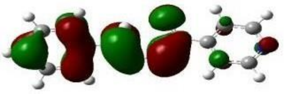
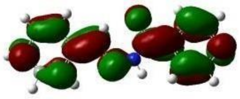
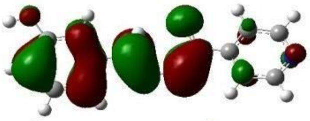
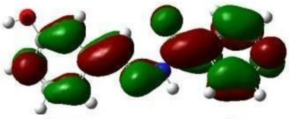
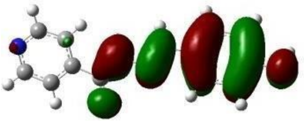
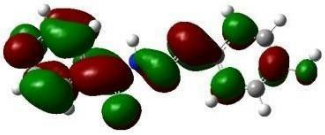
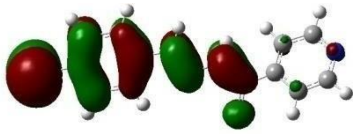
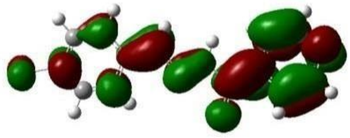
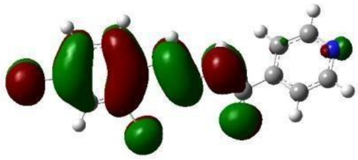
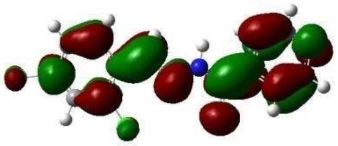
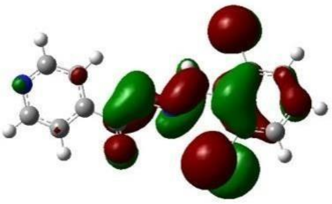
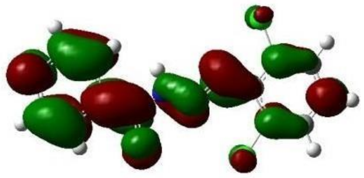
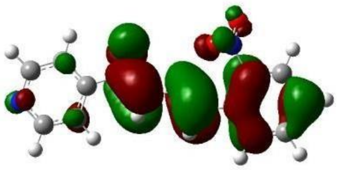
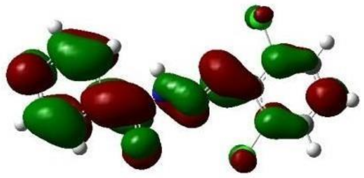
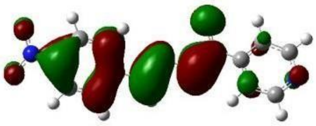
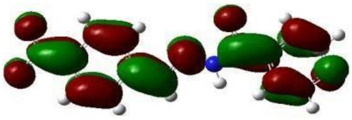
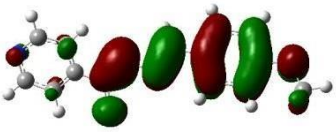
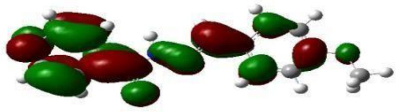
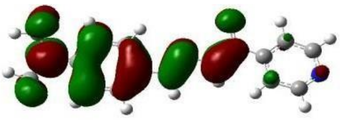
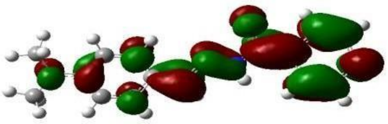
Table 5. Mulliken charges calculated by DFT/B3LYP

	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**
1C	0.090	0.091	0.092	0.584	-0.006	-0.093	0.091	0.093	-0.005	0.092
2C	-0.100	-0.101	-0.133	0.405	-0.124	-0.132	-0.133	-0.132	-0.124	-0.133
3C	0.050	0.051	0.054	0.089	-0.025	-0.053	0.054	0.053	0.026	0.054
4C	-0.131	-0.132	-0.102	0.824	-0.112	-0.101	-0.102	-0.100	-0.111	-0.102
5C	0.091	0.092	0.089	0.443	-0.005	-0.090	0.088	0.090	-0.005	0.089
6N	-0.420	-0.421	-0.422	-0.130	-0.353	-0.421	-0.424	-0.420	-0.351	-0.423
7H	0.107	0.108	0.103	0.150	0.152	0.106	0.102	0.105	0.155	0.103
8H	0.123	0.124	0.090	0.052	0.137	0.093	0.089	0.089	0.138	0.090
9H	0.095	0.096	0.125	0.182	0.181	0.126	0.123	0.129	0.182	0.124
10H	0.107	0.106	0.107	0.149	0.157	0.109	0.105	0.110	0.159	0.107
18C	0.089	0.087	0.091	-0.301	0.156	0.156	0.095	0.132	0.111	0.091
19C	-0.096	-0.102	-0.134	-0.533	-0.174	-0.153	-0.143	-0.141	-0.182	-0.131
20C	-0.126	-0.143	-0.111	0.246	-0.283	-0.137	-0.123	0.199	-0.149	-0.119
12O	-0.509	-0.507	-0.475	-0.397	-0.399	-0.463	-0.481	-0.457	-0.401	-0.477
28O	/	-0.578	-0.549	/	/	/	/	/	/	-0.514
29O	/	/	/	/	/	/	/	-0.369	-0.288	/
30O	/	/	/	/	/	/	/	-0.377	-0.514	/

Frontier Molecular Orbital (FMO)

All the HOMO/LUMO energy gaps obtained for the ligands studied are small, which confirms their good reactivity. The CO fragment mainly contributes to the HOMO, this indicates how electron delocalization can involve the entire system. Although there is some residual pπ contribution from the atoms at its left and right sides. Indeed, this molecular orbital involved has a π character which extends over the molecule. While the LUMO of all systems is located practically on all the atoms constituting the molecules, with an almost homogeneous distribution.

Table 6. FMO for the studied structures.

Molecules	HOMO	LUMO
A		
B		
C		
D		
E		
F		
G		
H		
I		
J		

Reactivity

The parameters μ, η, S, ω and Nu were calculated using the equations 1-5. The results are summarized in the Table 7. Analysis of chemical hardness values indicates that the most stable isomers found are the hardest, with larger HOMO/LUMO gaps, and therefore less reactive. Note that the isomer J is the softest. Therefore, the charge transfer will be predominant. The values of μ and ω indicate that compounds F and G are more electrophilic than the others. While system J is the least electrophilic and the most nucleophilic according to the values of Nu.

Table 7. The parametersμ,η, S, ω and Nu of the studied structures

	EH	**EL**	**I**	**A**	μ	η	**S**	ω
A	-6,1587	-1,9038	6,1587	1,9038	-2,1274	2,1274	0,2350	4,8142
B	-5,9804	-1,8837	5,9804	1,8837	-2,0483	2,0483	0,2441	4,2972
C	-5,8087	-1,7604	5,8087	1,7604	-2,0241	2,0241	0,2470	4,1466
D	-6,5695	-2,4031	6,5695	2,4031	-2,0831	2,0831	0,2400	4,5202
E	-6,6392	-2,3327	6,6392	2,3327	-2,1532	2,1532	0,2322	4,9918
F	-6,5206	-2,0897	6,5206	2,0897	-2,2154	2,2154	0,2256	5,4368
G	-6,6754	-2,3615	6,6754	2,3615	-2,1569	2,1569	0,2318	5,01743
H	-6,9692	-3,1988	6,9692	3,1988	-1,8852	1,8852	0,2652	3,3502
I	-5,7293	-1,7425	5,7293	1,7425	-1,9934	1,9934	0,2508	3,9605
J	-5,1236	-1,5672	5,1236	1,5672	-1,7781	1,7781	0,2811	2,8112

Conclusion

The reactivity of a molecule is linked to its structure and electronic properties. The reactivity indices indicate that all the ligands studied have good chemical reactivity, which will allow their complexation. Quantum chemistry has made it possible to characterize and better understand the electronic properties of these molecules. A chemical group can exert effects of different natures on the distribution of the electronic density of a molecule. There are different types of electronic effects coexistence of both inductive and mesomeric effects. , in the case of isomers containing a single group, the distances are influenced, and the most stable geometry is the one which most allows delocalization under the control of the mesomeric effect.

In the case of a single grouping, the inductive effect prevails by favoring the structure with free rotation. The reactivity of a molecule is linked to its structure and electronic properties. The reactivity indices indicate that all the ligands studied have good chemical reactivity, which will allow their complexation.

Scientific Ethics Declaration

The authors declare that the scientific ethical and legal responsibility of this article published in EPSTEM journal belongs to the authors.

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