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Theoretical Study on the Conformational Equilibrium of 1’, 2' and 3'-Nitro-4-hydroxy-3-methoxy Chalcone Isomers

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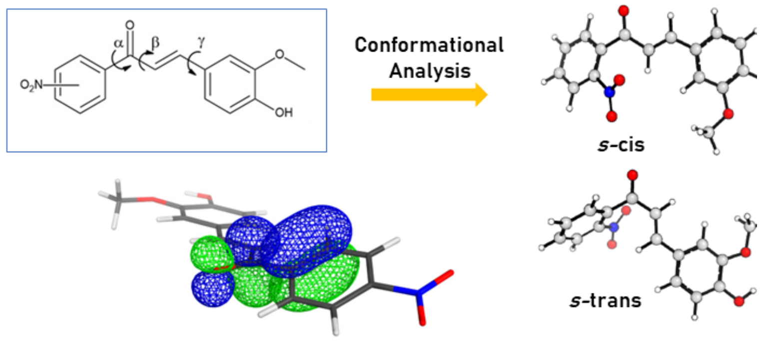
This paper presents the conformational analysis of three chalcone compounds, 1'-nitro-4-hydroxy-3-metoxychalcone (*o*-CHAL), 2'-nitro-4-hydroxy-3-metoxychalcone (*m*-CHAL) and 3'-nitro-4-hydroxy-3-metoxychalcone (*p*-CHAL). By employing theoretical calculations, the most stable conformers of each compound were obtained. The natural bond orbital (NBO) analyses were carried out with all compounds using the Density Functional Theory (DFT) and the M06-2X method combined with the basis set 6-311++G (2d,dp) in isolated phase and indicated greater electron delocalization in *s-cis* conformers. The theoretical calculations provided the parameters that led to more stable *s-cis* in conformational equilibrium for all the isomers under investigation. However, the *s-trans* conformer population was influenced by the position of the nitro group in the ring A, for mainly *o*-Chal.

Graphical abstract



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1. Introduction

Chalcones are a class of natural origin compounds belonging to the flavonoid family [1]. Their structure comprises two aromatic rings joined by a three-carbon α,ß-unsaturated carbonyl system [2]. The possibility of obtaining chalcone derivatives by reactions between different acetones and benzaldehydes has raised interest in the production of these compounds and the investigation of their biological activities such as antimicrobial [3], antimalarial, anti-inflammatory and antioxidant, among others [4].

The antioxidant property of flavonoids and chalcones might present an expressive increase in the presence of

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hydroxyl groups in its structure aromatic rings. Such antioxidant potential is associated to a reduction in the oxidative stress related to several diseases, including cancer, atherosclerosis, hypertension and heart diseases [5]. In addition to the hydroxyl group, since some nitroaromatic compounds present cytotoxic, antibacterial and antifungal activities, the nitro group is very often added to the chalcone chemical structure aiming at a bioactive compound [6].

Organic compounds can have their chemical and physical properties simulated by using computational chemistry [7]. In this area, the density functional theory (DFT) is recognized by enabling theoretical tests on chemical reactivity in relation to the biological activity of compounds [8]. Therefore, DFT calculations have been employed to evaluate the structure-activity relationship in several biological properties of pharmacological relevance such as the antioxidant activity in flavonoids [9].

Based on these facts, this study aims to carry out the conformational analysis of some chalcone derivatives containing the nitro, hydroxyl and methoxy groups in isolated phase. Theoretical calculations were performed and the chalcones selected were 1’, 2' and 3'-nitro-4-hydroxy-3-methoxy chalcones. The three chalcones investigated are shown in Figure 1 and denoted ***o*-Chal, *m*-Chal** and ***p*-Chal**.

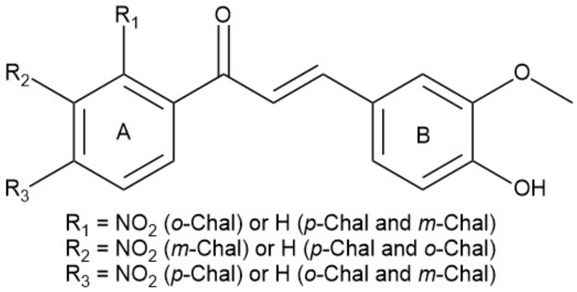


Fig. 1. Structure of the studied chalcones.

2. Results and Discussion

Conformational Analysis

The investigation started from the conformational preference of all compounds (***o*-Chal, *m*-Chal** and ***p*-Chal**) in equilibrium, by performing potential energy surface (PES) calculations. Three dihedral angles were investigated, as shown in Figure 2: dihedral α (angle between the carbonyl and ring A), dihedral β (angle between the carbonyl and the vinylic unsaturation) and dihedral γ (angle between the vinylic unsaturation and the ring B).

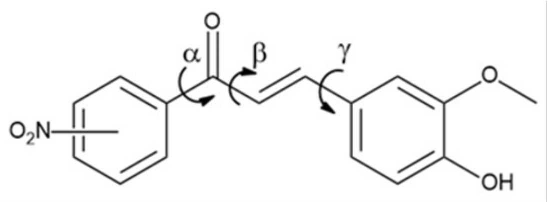


Fig. 2. Dihedral angles analyzed for ***o*-Chal, *m*-Chal** and ***p*-Chal**.

After investigating the three dihedral angles, points of minimum were obtained and the PES results enabled the verification of the presence of different conformations, later on submitted to optimization calculations to obtain the most stable geometries for each conformation. Frequency calculations were also carried out to obtain the zero-point energy, as well as to characterize each geometry obtained as a “real” point of minimum for the inexistence of imaginary frequencies.

Table 1 shows the values of the dihedral angles obtained as the population at equilibrium for each conformation of each of the isomers under study, obtained by the Boltzmann equation using the energy difference between conformations. The first compound to be analyzed was ***o*-Chal**. The conformational analysis data revealed five preferential conformations, from which three were *s-cis* (***o*-Chal-1–3**) and two were *s-trans* (***o*-Chal-4–5**), in relation to the carbonyl position and the vinylic bond (Figure 3).

In this isomer, the *s-cis* ***o*-Chal-2** conformer was the most stable of all, corresponding to 41.5% at equilibrium, followed by the *s-trans* ***o*-Chal-4** and **5** conformers, with 21.9 and 28.2% at equilibrium, respectively.

Regarding **m-Chal,** two *s-cis* (**m-Chal-1–2**) conformations and two *s-trans* (**m-Chal-3–4**) were observed (Figure 4), in which the two *s-cis* conformations were more stable, corresponding to 86.2% at equilibrium.

When ***p*-Chal** was investigated, four preferential **conformations** were observed (Figure 5), from which two were *s-cis* (***p*-Chal-1** and **2**) and two were *s-trans* (***p*-Chal-3** and **4**), again the *s-cis* conformations were seen to be more stable (36.0 and 40.0% at equilibrium).

In conjugated systems, such as the chalcones in this study, resonance is favored when the π orbitals are the most parallel possible. The dihedral angles α, β and γ are relevant to minimize this effect and, the closer they are to 180° or 0°, the greater the alignment between the π orbitals in the conformer.

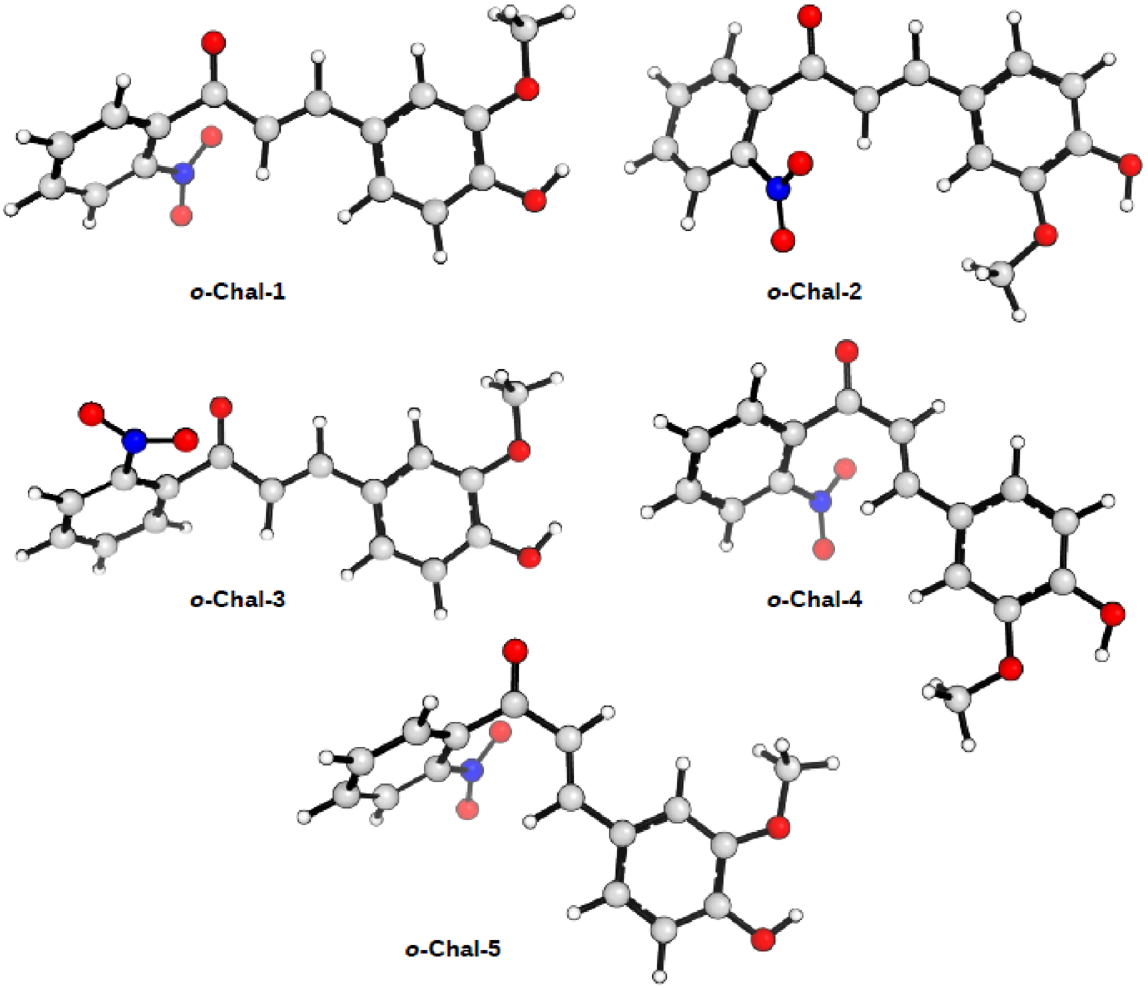
In general, when evaluating the data in Table 1, where the values of these dihedral angles are presented for all conformers of the three isomers under study, the *s-cis* conformers were observed to present smaller deviation in relation to the ideal angles. Regarding the dihedral angle α (carbonyl double bond and ring A), except for the ***o*-Chal-3** conformer, all the remaining *s-cis* conformers present a smaller deviation in the favorable dihedral angle than that of the *s-trans* conformers, that is, this region of the *s-cis* conformers is more planar than that of *s-trans* conformers. As for the dihedral β (carbonyl double bond and carbon double bond), the deviations of *s-cis* conformations are considerably smaller than those of the *s-trans* conformations in all cases. However, for both conformers, the deviations of the dihedral angle β are smaller than those observed for the dihedral angle α. The dihedral angle γ (carbon double bond and ring B) presents small deviation in relation to the angles of the largest planarity possible, except for the ***o*-Chal-2** and ***o*-Chal-4** conformers. No other conformation showed this deviation over 10°.

The region of the molecules where the planarity is smaller is that involving the carbonyl and the ring A (dihedral angle α), which is the ring that contains the substituted nitro group and is interesting to observe how the variation of position of this substituent in the ring influences the conformational equilibrium of each of the three isomers under study.

The ortho isomer presents the most interesting equilibrium due to the position the nitro group occupies in ring A. This isomer presented the greatest contribution of *s-trans* conformers at equilibrium. When analyzing its conformations, the *s-cis* conformations, ***o*-Chal-1** and ***o*-Chal-2** were seen to approach the nitro group with three atoms that do not belong to ring A (C1, C2 and H2), and the greatest proximities involve the H2 vinylic hydrogen, which is the smallest atom among those involved.

Table 1. Dihedral angles, relative energy, population at equilibrium and dipole moment of the conformers of ***o*-Chal, *m*-Chal** and ***p*-Chal** calculated at M06-2X/6-311++G(2d,dp) level.

Conformers	**Dihedral angles (°)**			**ΔE (kcal/mol)**	**Population (%)**	**Dipole**
	α	**β**	**γ**			
***o*-Chal-1**	44.1	1.5	1.5	1.04	7.2	3.30
***o*-Chal-2**	37.6	0.2	13.6	0.00	41.5	4.49
***o*-Chal-3**	60.3	2.5	2.7	2.09	1.2	4.54
***o*-Chal-4**	50.2	14.5	17.4	0.38	21.9	6.45
***o*-Chal-5**	54.8	14.8	2.0	0.23	28.2	3.22
***m*-Chal-1**	20.8	8.0	4.5	1.05	12.5	8.44
***m*-Chal-2**	17.2	6.9	0.2	0.00	73.7	1.80
***m*-Chal-3**	35.0	23.3	3.7	1.72	4.1	7.60
***m*-Chal-4**	37.7	22.0	2.5	1.20	9.7	4.22
***p*-Chal-1**	21.7	6.6	2.4	0.05	36.0	5.75
***p*-Chal-2**	20.1	7.3	2.9	0.00	40.0	7.05
***p*-Chal-3**	40.4	21.6	2.1	0.45	19.0	6.65
***p*-Chal-4**	39.4	23.9	9.9	1.24	5.0	5.44



***o*-Chal-1**

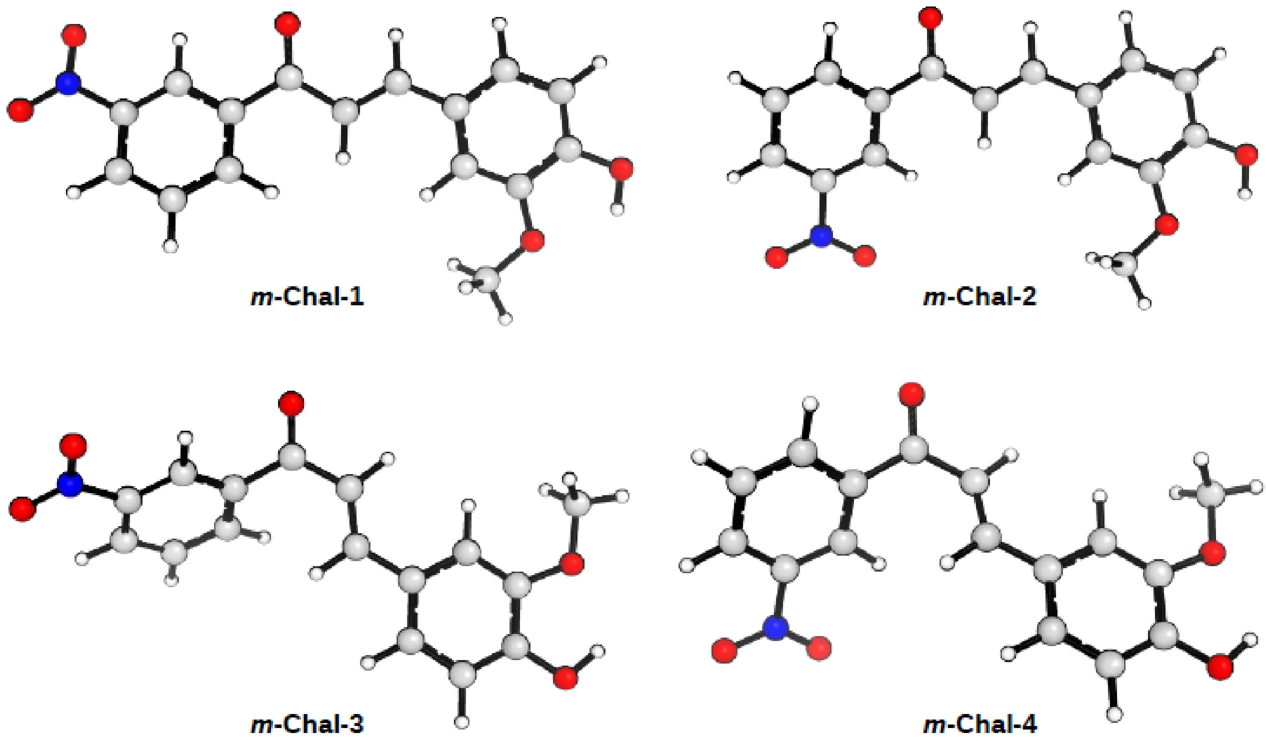
***o*-Chal-2**

***o*-Chal-3**

***o*-Chal-4**

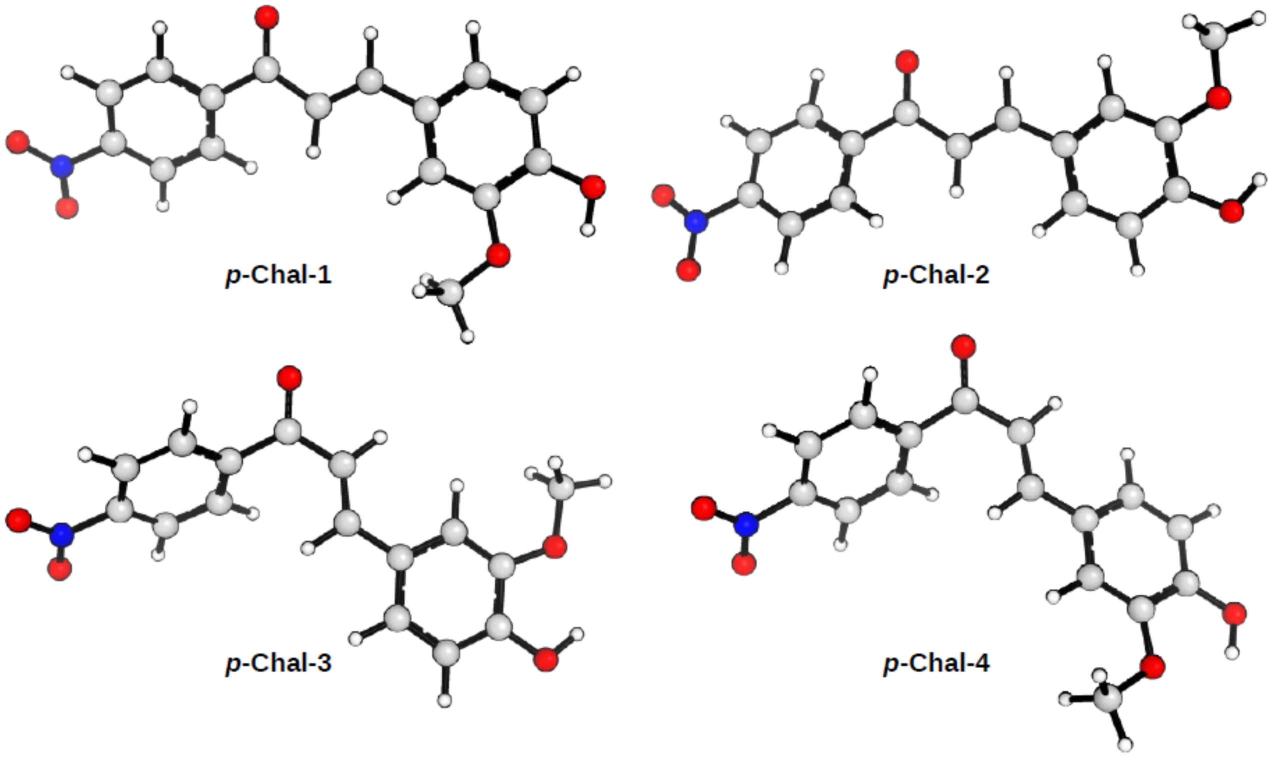
***o*-Chal-5**

Fig. 3. Conformers at equilibrium obtained at M06-2X/6-311++G(2d,2p) level for ***o*-Chal**.



***m*-Chal-1** ***m*-Chal-2** ***m*-Chal-3** ***m*-Chal-4**

Fig. 4. Conformers at equilibrium obtained at M06-2X/6-311++G(2d,2p) level for ***m*-Chal.**



***p*-Chal-1** ***p*-Chal-2** ***p*-Chal-3** ***p*-Chal-4**

Fig. 5. Conformers at equilibrium obtained at M06-2X/6-311++G(2d,2p) level for ***p*-Chal.**

The *s-trans* conformations ***o*-Chal-4** and ***o*-Chal-5** approached the nitro group of four atoms (C1, C2, C3 and H3) that do not belong to ring A. In these conformations, smaller distances involving the atoms in the nitro group are from the atoms C1 and C2. The distance from the closest vinylic hydrogen (H3 for *s-trans* conformers) is larger than that of the *s-cis* conformers ***o*-Chal-1** and ***o*-Chal-2** (in these cases, H2).

The *s-cis* conformation ***o*-Chal-3** shows great proximity of the carbonyl oxygen with one of the oxygens in the nitro group. This is the only conformation that presented a nitro group turned towards the carbonyl oxygen, which results in greater steric and electrostatic repulsion, influencing the greater relative energy of this conformation. A more detailed analysis of the interactions of the ortho isomer conformations is still necessary to completely understand the conformational equilibrium observed and is presented in the next section.

In relation to the geometry of the meta isomer conformations, both s-cis conformations (***m*-Chal-1** and ***m*-Chal-2**) are more planar than the s-trans conformations (***m*-Chal-3** and ***m*-Chal-4**), in which the ***m*-Chal-2** conformation is the most planar with all.

In the *meta* position, the nitro group no longer present significant interactions with the carbonyl or the vinylic double bond, being positioned far from these groups. The main repulsion source appears then between the vinylic hydrogens and the hydrogens in the ortho position of the aromatic rings.

In *s-cis* conformations, the geometry adopted by the vinylic double bond and the carbonyl does not cause great proximity between the H2 vinylic hydrogen and the hydrogen in the *ortho* position of ring A, so that the dihedral α is closer to 0° or 180°, leading to a greater planarity of molecules in these two conformations. However, regarding the *s-trans* conformations, the spatial arrangement in these conformations approximates the H3 vinylic hydrogen a lot to the ortho hydrogen in ring A, preventing the dihedral angle from getting closer to the values that would lead to the molecule greater planarity.

In the case of the para isomer, the behavior of the conformations is similar to that observed for the *meta* isomer. Since the nitro substituent in ring A is the farthest possible from the remaining molecule in this position, the geometry of the conformers also tends to be influenced by the steric repulsion between the vinylic hydrogens and those in the *ortho* position of ring A.

NBO Analysis

The NBO analysis indicated greater electron delocalization in *s-cis* conformers. This results from the greater planarity of these conformations, which allows a better alignment between the adjacent orbitals π and π*, contributing to a greater relative stability of these conformations in general.

The most relevant orbital interactions in this sense are those involving the carbonyl π orbitals and ring A, the carbonyl and the vinylic double bond, and the vinylic double bond and ring B. These orbital interactions are directly influenced by the dihedral angles α, β and γ, respectively. When the dihedral angles are closer to 0° or 180° the overlapping integral between the donor orbital and the acceptor orbital is larger and the electron delocalization effect is greater between these orbitals.

The analysis of the energies involved in these orbital interactions helps to explain the conformational preference observed at equilibrium for the compounds investigated (Table 2), and the orbital interaction showing the most significant difference between the *s-cis* and *s-trans* conformers is that involving the carbonyl π orbitals and ring A ($\pi_{C1=O}\rightarrow\pi^*_{C2=C3}$ and $\pi_{C2=C3}\rightarrow\pi^*_{C1=O}$), related to the dihedral angle α.

Table 2. Selected orbital interaction energies for the ***o*-Chal, *m*-CHAL** and ***p*-CHAL** conformers calculated at the M06-2X/6-311++G(2d,dp) level.

Orbital Interaction	*o*-Chal-*1*	*o*-Chal-*2*	*o*-Chal-*3*	*o*-Chal-*4*	*o*-Chal-*5*	*m*-Chal-*1*	*m*-Chal-*2*	*m*-Chal-*3*	*m*-Chal-*4*	*p*-Chal-*1*	*p*-Chal-*2*	*p*-Chal-*3*	*p*-Chal-*4*
C=O – C=C	30.14	30.76	31.04	30.02	30.36	29.75	30.54	28.35	29.21	30.13	29.95	29.08	27.92
C=O – Ring A	**11.73**	**13.79**	**6.49**	**9.16**	**7.50**	**20.92**	**22.22**	**15.75**	**16.20**	**20.15**	**20.67**	**14.77**	**15.12**
C=C – Ring B	28.08	31.80	29.12	25.71	32.41	34.24	34.52	32.46	32.51	34.51	29.11	32.63	27.26
Ring B	160.64	154.99	160.95	159.42	154.44	154.62	154.41	154.19	154.37	154.56	160.89	154.24	159.93
Ring A	173.58	173.50	171.99	174.18	173.91	168.15	169.66	169.79	170.27	169.61	169.34	170.66	170.80
Ring A – NO_2	24.40	23.52	23.18	22.23	23.92	25.25	25.63	25.29	25.27	27.46	27.45	27.60	27.63
NO_2 – C=C	0.60	0.66	-	-	-	-	-	-	-	-	-	-	-
NO_2 – Ring A	4.87	4.32	4.89	4.35	4.81	4.34	4.43	4.34	4.43	5.55	5.55	5.54	5.53
NO_2	21.93	21.91	22.23	20.61	21.22	21.13	21.14	21.18	21.29	21.26	21.27	21.28	21.28
LP O17	52.51	52.33	54.41	51.00	51.17	51.68	51.23	49.86	49.26	51.44	51.23	49.56	49.54
LP O18	58.96	59.80	59.15	59.28	59.99	60.17	60.25	60.32	60.25	60.17	59.36	60.32	59.48
LP O19	41.42	42.15	41.75	41.42	42.32	42.72	42.78	42.72	42.70	42.83	42.01	42.80	41.89
LP O20	263.98	48.63	49.46	250.68	260.68	268.32	47.65	269.37	47.58	271.15	271.92	47.78	47.81
LP O21	48.69	260.00	268.27	49.75	50.08	48.27	267.72	48.15	271.70	47.80	47.79	271.81	271.56
Sum	921.53	918.16	922.93	897.81	912.81	929.56	932.18	921.77	925.04	936.62	936.54	928.07	925.75

The conformational equilibrium of *meta* and *para* isomers might be explained in a satisfactory way by the energy data of the orbital interactions presented. However, regarding *ortho* isomers, the orbital interactions alone do not explain the greater contribution of *s-trans* isomers to the equilibrium when compared to the conformational equilibrium of the remaining compounds.

This occurs because the nitro group position in this isomer allows its interaction with the carbonyl and the vinylic double bond, mainly from the steric repulsion and electrostatic interaction standpoint.

The ***o*-Chal-3** conformer, for example, showed the greatest values in the sum of orbital interactions presented in that Table, but it is the least stable conformer, since it presents noticeable electrostatic repulsion between one of the oxygen atoms in the nitro group with the carbonyl oxygen atom.

The *ortho* isomer is the one presenting the greatest deviations in the dihedral angles more favorable for dihedral α in both conformers *s-cis* and *s-trans*, leading to the lowest orbital interaction energies between the carbonyl and ring A. This is interesting because the s-cis conformers are not much more stable than the *s-trans* isomers as in other isomers, in addition to the existence of a greater steric and electrostatic repulsion contribution in *s-cis* isomers than in the same conformers of the *meta* and *para* isomers. Thus, the energy difference between the *s-cis* most stable conformer (***o*-Chal-2**) and the two *s-trans* isomers (***o*-Chal-4** and ***o*-Chal-5**) is the smallest among the isomers studied and the population of *s-trans* conformers is larger in the *ortho* isomer.

3. Material and Methods

In the computational procedures, all the compounds were submitted to theoretical calculations using the programs

GAUSSIAN 09 [10] and NBO 5.9 [11] for calculations involving the natural bond orbitals theory. The selection of the most stable conformers was carried out through scan calculations employing the M06-2X/6-31G level of theory, combining the 10° rotations in 36 steps. All the structures of energy minimum obtained from the previous calculations were optimized with the M06-2X/6-311++G(2d,dp) level of theory [12].

Frequency calculations, with the same level of theory, were carried out to characterize the structures as a minimum and to correct the point-zero energy.

4. Conclusions

Through theoretical calculations it was possible to determine the geometries involved in the equilibrium of these chalcones. The *s-cis* conformations were observed to the more stable at equilibrium for all isomers studied. However, the population of *s-trans* conformers was influenced by the position of the nitro group in ring A, mainly for *o*-Chal. These investigations are important, mainly because we have selected groups on aromatic rings that are potentially known to have pronounced biological activity. Thus, the more we learn about the behavior of these groups, the more we can contribute to research in other areas.

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Author Contributions

Both B.C. Fiorin and T.C. Rozada contributed in conceptualization, project administration, supervision and writing (original draft). H.V. Emiliano especially was responsible for formal analysis and writing (original draft). R.P. Guaringue contributed in formal analysis and writing (review & editing).

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