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Synthesis, Characterization, Antioxidant Activity and Conformational Study of 4-Hydroxychalcone

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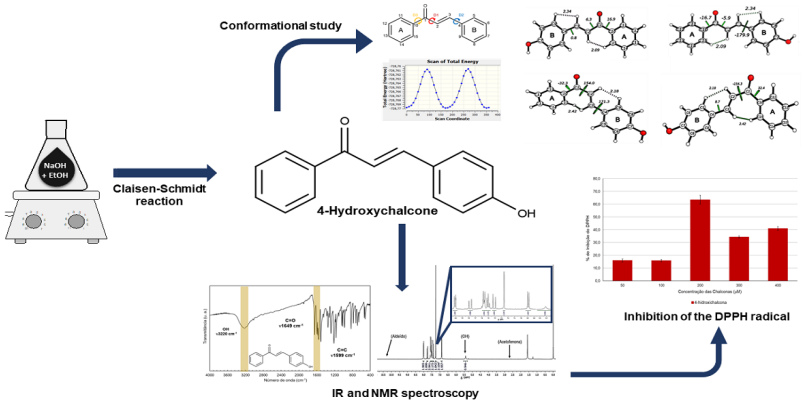
The objective of this work was to develop a synthesis, characterization, and conformational study of 4-hydroxychalcone. The chalcone was obtained using Claisen-Schmidt reaction. The product was characterized by FTIR and NMR spectroscopy. The latter technique was extremely important to verify the presence of the vinyl double bond formed in the reaction and to determine its *trans* configuration. The antioxidant activity of 4-hydroxychalcone showed a satisfactory result when compared to antioxidants already reported in the literature, with 63.4% inhibition of the DPPH radical. Also, theoretical calculations were performed to determine conformational preference. The *s-cis* (b) (52.0%) and the *s-cis* (a) (35.0%) conformers showed less energy when compared to *s-trans* conformers, due to the higher stabilizing effect of electron delocalization involving the π orbitals resulting from the higher planarity of *s-cis* conformers. However, the *s-cis* (a) conformer showed greater stabilization energy (510.37 kcal mol^{-1}) in relation to the *s-cis* (b) conformer (505.32 kcal mol^{-1}), this fact might be explained by the hydroxyl group interaction with the aromatic ring B, as observed by the NBO calculations.

Graphical abstract



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1. Introduction

Chalcones, with a general structure 1,3-diphenyl-2 propen-1-one [1] are α,β-unsaturated ketones that are found in the main plant structures, such as roots, leaves and flowers, being a natural precursors of flavonoids. There are different methods to obtain chalcones via synthetic routes with the purpose to produce compounds with interesting pharmacological properties [2]. The most common method is Claisen-Schmidt condensation with acid or basic catalysis [2, 3]. After synthesized, the products are characterized by Fourier transformed infrared (FTIR) and nuclear magnetic resonance (NMR) spectroscopy. Also, analysis to verify possible pharmacological activity, such as antioxidant, antibacterial, antifungal, anticancer, among others are performed [4]. The conformational behavior of chalcones is

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also investigated by theoretical calculations with the density functional theory (DFT), which provides data to explain electronic and structural properties, such as relative energy of conformers, dipole moment, molecular vibrations, among others. These data can be correlated with the results obtained experimentally [5]. Therefore, the aim of this work was to synthesize, characterize, investigate antioxidant activity, and develop a conformational study of 4-hydroxychalcone.

2. Results and Discussion

To characterize the chalcone obtained, IR and ^{1}H NMR were performed. By FTIR, bands were found at 1650 and 1611 cm^{-1}, related to C=O and C=C bonds, respectively, besides the band near 3200 cm^{-1}, which refers to the hydroxyl group linked to the aromatic ring, as shown in Fig. 1 (A). Through the ^{1}H NMR spectrum, it was possible to analyze the stereochemistry of 4-hydroxychalcone with respect to vinyl double bonding. A doublet signal at 7.80 ppm from α-carbonyl vinyl hydrogen and with coupling constant $J_{H\alpha H\beta}$ of 15.66 Hz and a doublet signal at 7.44 ppm which corresponds to β-carbonyl vinyl hydrogen and with the coupling constant $J_{H\beta H\alpha}$ of 15.65 Hz, characterizing the formation of the chalcone *trans* isomer, according to the data presented in the literature [6]. Fig. 1 shows the FTIR (A) and ^{1}H NMR (B) spectra of 4-hydroxychalcone.

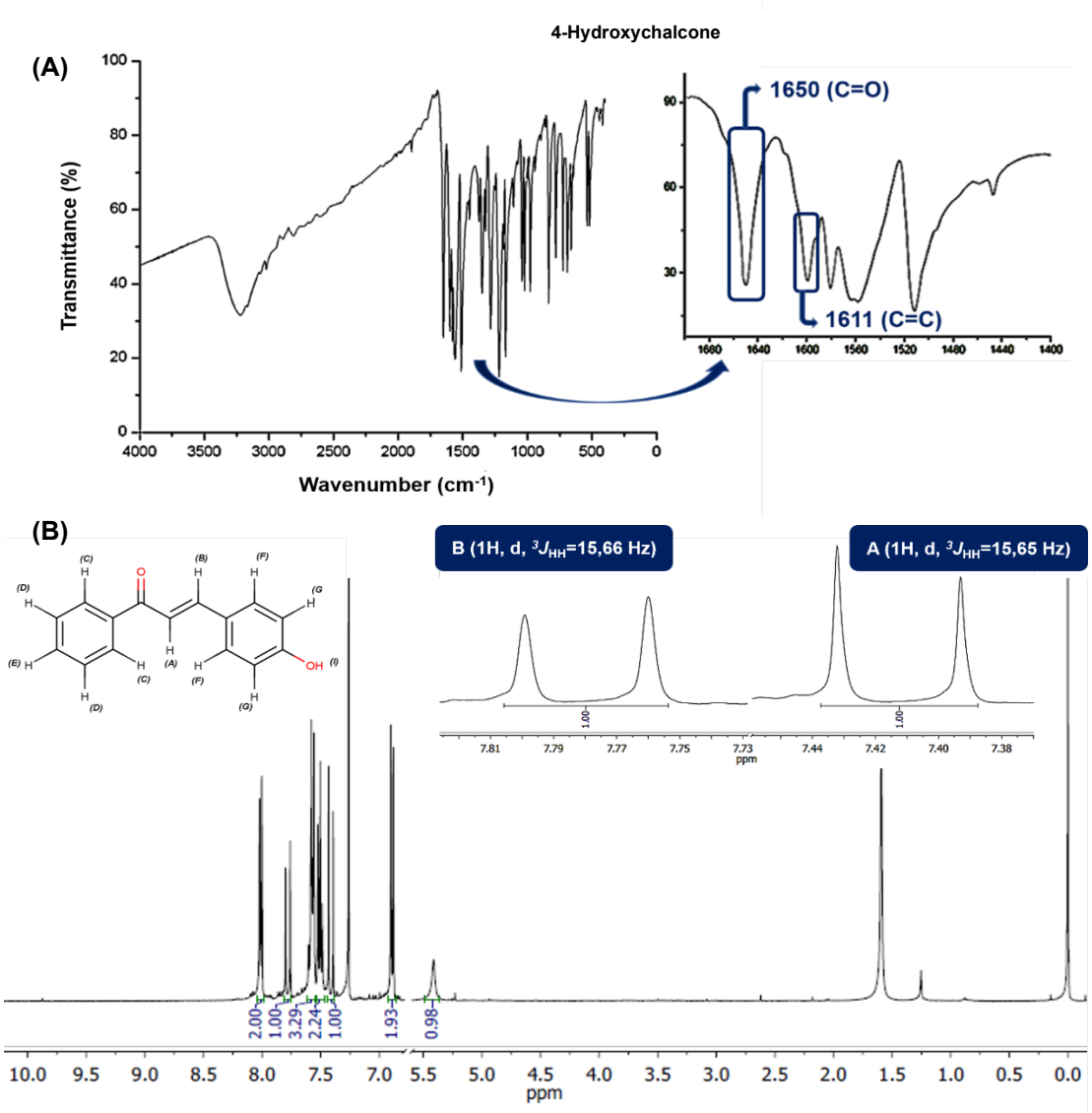

Fig. 1. FTIR with 64 scans, 4 cm^{-1} resolution and 400-4000 cm^{-1} range (A) and ^{1}H NMR in 400 MHz with $CDCl_3$ as a solvent (B) of 4-hydroxychalcone spectra.

Regarding the antioxidant activity, the method of inhibiting the radical 2,2-diphenyl-1-picrylhydrazyl (DPPH) was used to verify the antioxidant activity of the compound. The reduction in DPPH was accompanied by absorbance decrease at 517 nm and the chalcone was estimated in the percentage of radical inhibition. The chalcone under study presented the best radical inhibition with a concentration of 200 mmol L^{-1}, with an inhibition percentage of 63.4%, being considered a good result when compared with quercetin, a compound that presents excellent antioxidant activity according to the literature [7, 8], which in this study showed an inhibition percentage of 97.5%.

Regarding the conformational study, two minimum energy structures were found (Fig. 2). The *s-cis* (b) conformer presented low energy and a population of 52.0% and the *s-cis* (a) presented a 35.0% population at equilibrium, with a ΔE= 0.23 kcal mol^{-1}, in relation to the lowest energy conformer.

However, the *s-cis* (b) conformer showed, through NBO calculations, greater stabilization energy, which can be explained by the ring B interaction with hydroxyl. While the *s-trans* (c) conformer showed a population of 6.4% (ΔE= 1.24 kcal mol^{-1}) and the *s-trans* (d) conformer 6.6% (ΔE= 1.22 kcal mol^{-1}). The greater stability of the *s-cis* conformer is due to its higher planarity, which allows a better electron delocalization involving the π and π* orbitals.

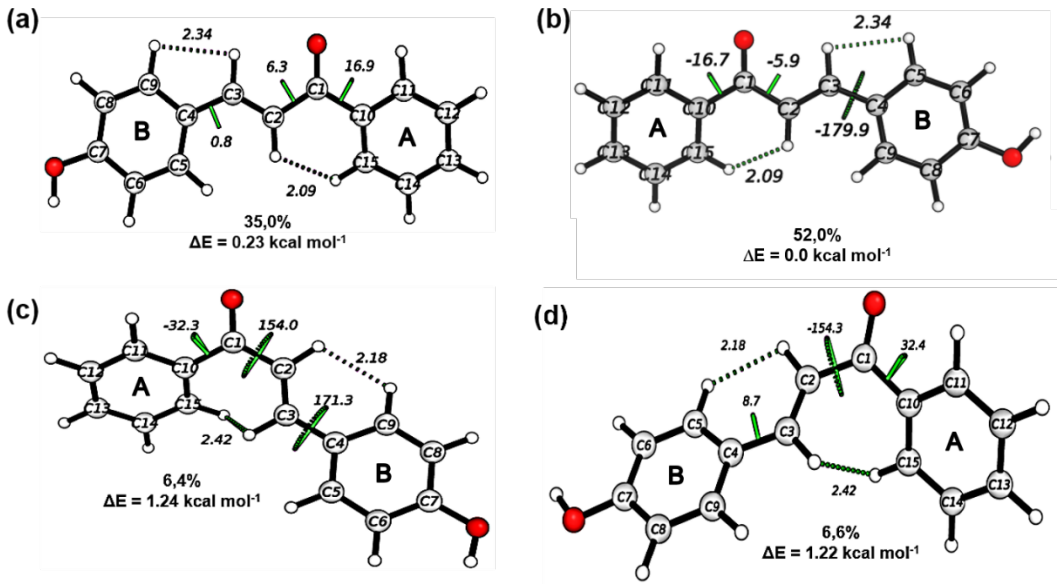

Fig. 2. Structures of *s-cis* (a and b) and *s-trans* (c and d) conformers of 4-hydroxychalcone conformational equilibrium calculated at M06-2X level.

Table 1 presents the energies of the π→π* orbital interactions grouped by the orbitals that are interacting. The *s-cis* (a) conformation presented greater stabilizing effect (510.37 kcal mol^{-1}) in relation to *trans* conformation (496.52 (c) and 499.71 (d) kcal mol^{-1}, respectively). Among the main orbital interactions that contribute to stability, the following stand out: the $\pi_{C2\text{-}C3}$ interaction, of vinyl bond with the $\pi^*_{C=O}$ interaction of carbonyl and their reciprocal interaction, with a contribution of 24.34 kcal mol^{-1} to the *s-cis* (a) conformer, and 20.85 (c) and 20.92 (d) kcal mol^{-1} to the *s-trans*. Another interaction that contributes significantly to the stabilization of the molecule is the $\pi_{Ring\text{-}A}$ interaction with $\pi^*_{C=O}$, with stabilization energy of 18.42 kcal mol^{-1} for *s-cis* (a) and 13.92 kcal mol^{-1} for *s-trans* conformers. This results from the largest dihedral angle between them, due to the repulsion that H_β has with H in ortho of ring A. This repulsion leaves the dihedral angle farther away from 0 or 180 degrees that would increase the overlap between π → π* orbitals. The *s-cis* (b) has the lower energy and the largest population but its stabilization energy is lower in relation to the *s-cis* (a) conformer. This can be explained by the fact that the difference in hydroxyl stereochemistry of aromatic Ring B, with the *s-cis* (a) conformer showing more electronic repulsions when compared to the *s-cis* (b) due to its position in relation to the hydrogens of aromatic carbons.

Table 1. Hyperconjugative interactions (kcal mol^{-1}) calculated at M06-2X/6-311G++(2d,2p) level.

Interactions*	Conformers			
	s-cis (a)	*s-cis (b)*	*s-trans (c)*	*s-trans (d)*
$\pi_{C=O} \rightarrow \pi^*_{C2\text{-}C3}$	3.86	3.86	5.49	5.51
$\pi_{C2\text{-}C3} \rightarrow \pi^*_{C=O}$	24.34	24.35	20.85	20.92
$\pi_{C=O} \rightarrow \pi^*_{Ring\text{-}A}$	4.70	4.70	3.68	3.67
$\pi_{Ring\text{-}A} \rightarrow \pi^*_{C=O}$	18.42	18.49	13.92	13.94
$\pi_{C2\text{-}C3} \rightarrow \pi^*_{Ring\text{-}B}$	11.87	12.14	12.03	11.88
$\pi_{Ring\text{-}B} \rightarrow \pi^*_{C2\text{-}C3}$	20.28	20.31	18.83	18.84
Within Ring A	168.11	168.05	169.68	169.69
Within Ring B	168.43	162.02	162.14	166.60
LP_{O16}	50.11	50.07	48.61	48.57
LP_{O28}	40.14	41.33	41.29	40.09
Σ_{TOTAL} (kcal mol^{-1})	**510.37**	**505.32**	**496.52**	**499.71**

3. Material and Methods

The synthesis of 4-hydroxychalcone was performed by the Claisen-Schmidt method, with basic homogeneous catalysis, using a sodium hydroxide solution. In a round bottom flask, 4-hydroxybenzaldehyde (0.01 mmol), acetophenone (0.01 mmol), 10 mL methanol and the catalyst were added. The reaction mixture was stirred at room temperature for a period of 24 hours, according to the methodology described by Yazdan et al. [3]. The ^{1}H NMR characterization was performed using Bruker 400MHz AVANCE III spectrometer, using approximately 20 mg of the compound in $CDCl_3$, with TMS as the internal reference and probe temperature maintained at around 25 °C. The IR analysis was performed using a

Shimadzu FTIR Prestige-21 spectrometer, with the samples being prepared in a potassium bromide tablet (KBr). The operating conditions of the equipment were 64 scans, 4 cm^{-1} resolution and the range analyzed was 400-4000 cm^{-1}.

The antioxidant activity was evaluated by the DPPH radical methodology, after a 30-minute reaction period according to the methodology described by Hamlaoui et al. [9], with different concentrations of chalcone and later comparison with a quercetin standard solution.

Conformational equilibrium was investigated through theoretical calculations using the Gaussian 09 [10] program for the optimization of structures and NBO 5.9 [11] for the analysis of stereo-electronic effects, at M06-2X/6-311G++(2d,2p) level.

4. Conclusions

With the procedure adopted, it was possible to obtain 4-hydroxychalcone, confirmed by ^1H NMR and FTIR spectroscopic analyses. Regarding the antioxidant activity, the chalcone under study presented a satisfactory result when compared to antioxidants already described in the literature. Theoretical calculations made it possible to verify the geometries involved in the conformational equilibrium, with the *s-cis* structure being the most stable, which is due to its greater planarity in relation to the *s-trans* conformer.

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References and Notes

[1] Patil, C. B.; Mahajan, S. K.; Katti, S. A. *J. Pharm. Sci. & Res.* **2009**, *3*, 11.

[2] Gaonkar, S. L.; Vignesh, U. N. *Res. Chem. Intermed.* **2017**, *43*, 6043. [Crossref]

[3] Yazdan, S. K.; Kumar, K. S.; Ratnabhushanam, B.; Padmavathi, J. V.; Kishore, G. K.; Mohan, K. *J. Appl. Chem.* **2014**, *3*, 601.

[4] Rozmer, Z.; Perjesi, P. *Phytochem. Rev*. **2016**, *15*, 87. [Crossref]

[5] Arshad, M. N.; Al-Dies, A. M.; Asiri A. M.; Khalid M.; Birinji A. S.; Al-Amry K. A.; Braga, A. A. C. *J. Mol. Struct.* **2017**, *1141*, 142. [Crossref]

[6] Pavia, D. L.; Lampman, G. M.; Kriz, G. S.; Vyvyan, J. R, *Introdução à Espectroscopia*, Cengage L, 2010.

[7] Boots, A. W.; Haenen, G. R. M. M.; Bast, A. *Eur. J. Pharmacol.* **2008**, *585*, 325. [Crossref]

[8] Lahsasni, S. A.; Al Korbi, F. H.; Aljaber, N. A. *Chem. Cent. J.* **2014**, *8*, 32. [Crossref]

[9] Hamlaoui, I.; Bencheraiet, R.; Bensegueni, R.; Bencharif, M. *J. Mol. Struct.* **2018,** *1156*, 385. [Crossref]

[10] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Minacci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J, 2010. Gaussian 09, Revision B.01. Gaussian, Inc., Wallingford CT.

[11] Glendening, E. D.; Badenhoop, J. K.; Reed, A. E.; Carpenter, J. E.; Bohmann, J. A.; Morales, C. M.; Weinhold, F. 2009. NBO 5.9. (Theoretical Chemistry Institute, University of Wisconsin, Madison, WI.

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