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Substitution effect on a hydroxylated chalcone: Conformational, topological and theoretical studies

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ABSTRACT

The effect of substituents on two hydroxylated chalcones was studied in this work. The first chalcone, with a dimethylamine group (HY-DAC) and the second, with three methoxy groups (HY-TRI) were synthesized and crystallized from ethanol on centrosymmetric space group $P2_1/c$. The geometric parameters and supramolecular arrangement for both structures obtained from single crystal X-ray diffraction data were analyzed. The intermolecular interactions were investigated by Hirshfeld surfaces with their respective 2D plot for quantification of each type of contact. Additionally, the observed interactions were characterized by QTAIM analysis, and DFT calculations were applied for theoretical vibrational spectra, localization and quantification of frontier orbitals and potential electrostatic map. The flatness of both structures was affected by the substituents, which led to different monoclinic crystalline packing. The calculated harmonic vibrational frequencies and homo-lumo gap confirmed the stability of the structures, while intermolecular interactions were confirmed by potential electrostatic map and QTAIM analysis.

1. Introduction

Chalcones have attracted much attention in the scientific community due to their multifunctional basic skeleton. Basically, they are formed by an olefin portion and a carbonyl group that bind two substituted aromatic rings, providing a delocalized π system [1–4]. The broad features of these compounds, such as materials applied to environmental science [5–9] and biological activities [3,10–17], are results of their natural origin which allows for a wide range of chemical compositions derived from this basic skeleton. Furthermore, the understanding of the structure-activity relationship has motivated the synthetic production of chalcones that possess the desired chemical, physical and biological properties [18].

As a result, hydroxylated chalcones have been thoroughly studied, and many results show desirable properties related to this group [19–21]. As environmental agents, these chalcones would act as defense against UV radiation and as protection against oxidative stress. Furthermore, these compounds could be involved in various physiological processes such as defense against bioaggressors, redox homeostasis and dissipation of excess excitation energy [22]. As biological agents, Hofmann et al. [23] state that a minimum of three hydroxyl groups was a requirement of effective xanthine oxidase inhibition. In addition, two hydroxyl groups at neighboring positions on at least one phenyl ring were responsible for effective radical scavenging, which makes hydroxylated chalcones interesting candidates as possible agents for the treatment of hyperuricemia. A QSAR study made by Silva et al. [24] shows that the presence of a hydroxyl group in *ortho* position increased activities against *S. mutans*, while its absence or OH in *meta* position decreased the activity.

However, unlike previous studies that assessed the effect of the chemical composition on the biological activities, we propose a comparative structural study of two hydroxylated chalcones in order to relate the chemical, physical and biological properties of these compounds to structural factors, such as flatness, bond angles and intermolecular interactions. The first, a dimethylamine-hydroxychalcone, is used as a ratiometric fluorescent probe for the detection of alkaline phosphatase (ALP), an indicator of several

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diseases, such as hepatitis, prostate cancer, osteoporosis and bone tumor [25–28]. The second chalcone is a trimethoxy-hydroxychalcone with chemical composition similar to the first, excepting only the substituents of the second ring, which enabled this study. We synthesized both chalcones and studied their structures from single crystal X-ray diffraction. In addition, we performed theoretical calculations in order to assess the vibrational frequencies, nucleophilic attack sites and chemical stability for both structures.

2. Methodology

2.1. Synthesis and crystallization

To a solution of aromatic aldehyde (2 mmol) and aromatic ketone (2 mmol) in 8.0 mL of ethanol, an amount of 1.0 mL of 24% sodium hydroxide in water at 10 °C was added. After stirring overnight at room temperature, the reaction medium was neutralized with 10% HCl. The solid was filtered and recrystallized from ethanol.

2.2. Crystallographic characterization

A single crystal of each compound was carefully selected under polarizing microscope in order to perform its structural analysis by X-ray diffraction. The crystals were collected at room temperature using a Bruker APEX II CCD diffractometer with graphite-monochromated MoKa radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods and refined by full-matrix least squares on F^2 using SHELXL2014 software [29]. HY-DAC crystallized in the monoclinic crystal system and space group P21/c [30] with the following unit cell metrics: a = 12.124 Å, b = 10.275 Å, c = 12.506 Å; $\alpha = 90°$, $\beta = 115.87°$, $\gamma = 90°$ and V = 1401.8 Å^3. HY-TRI also crystallized in the monoclinic crystal system and space group P21/c [30] with the following unit cell metrics: a = 12.687 Å, b = 8.586 Å, c = 15.349 Å; $\alpha = 90°$, $\beta = 107.99°$, $\gamma = 90°$ and V = 1549.9 Å^3. In both structures, H atoms connected to aromatic carbon atoms were placed at calculated positions and refined as riding, with C–H = 0.94 Å and Uiso(H) = 1.2Ueq(C). H atoms attached to N and O atoms, and CH_3 group, were located reliably on difference Fourier maps, and their positions were refined as riding on their parent atoms, with Uiso(H) = 1.2Ueq(N) and Uiso(H) = 1.5Ueq (C or O). Mercury [31] and Crystal Explorer 3.1 [32] were used to generate molecular representations, tables and pictures. The possible intermolecular interactions and hydrogen bond were checked by PARST software [33] and studied from the Hirshfeld surface. The crystallographic information files of $C_{17}H_{17}NO$ (HY-DAC) and $C_{18}H_{17}O_5$ (HY-TRI) molecule were deposited in the Cambridge Structural Database [34] under the codes CCDC 1507796 and 1507797, respectively.

2.3. Hirshfeld surface analysis

The potential intermolecular interactions of HY-DAC and HY-TRI were visualized and interpreted using Hirshfeld surface (HS) analysis. The idea for HS appeared from an attempt to define the space occupied by a molecule in a crystal intending to partition the crystal electron density into molecular fragments [35]. F. L. Hirshfeld defined a weight function for each atom in a molecule as

$$w_a(r) = \rho_a^{at}(\boldsymbol{r}) \Big/ \sum_{i\in molecule} \rho_i^{at}(\boldsymbol{r}) \tag{1}$$

where $\rho_i^{at}(r)$ are spherically averaged electron densities of the various atoms. Then, the electron density of an atomic fragment can be defined as

$$\rho_a(\boldsymbol{r}) = w_a(\boldsymbol{r})\rho^{mol}(\boldsymbol{r}) \tag{2}$$

where $\rho^{mol}(\boldsymbol{r})$ indicates the molecular electron density. Crystal Explorer 3.1 [32] software has been widely used to obtain several properties that can be viewed in HS. Among these properties we have the distance of atoms external (d_e) and internal (d_i), to the surface. This information can be represented in 3D or 2D histograms known as fingerprints. The Crystal Explorer 3.1[32] program normalizes these distances (d_{norm}) using the van der Waals radius of the appropriate internal and external atom of the surface [36].

$$d_{norm} = \left(d_i - r_i^{vdw}\right)\Big/ r_i^{vdw} + \left(d_e - r_e^{vdw}\right)\Big/ r_e^{vdw} \tag{3}$$

The graphical representation of d_{norm} allows us to identify a particular intermolecular interaction via a color coding system. Red and blue colors in the HS are associated with shorter and longer distances than van der Waals intermolecular contacts, respectively [37]. The surfaces were mapped for HY-DAC and HY-TRI as a function of d_e and d_i by Crystal Explorer 3.1 [32] software, and for the fingerprint we used the standard 0.6–2.8 Å view of d_e vs. d_i.

2.4. Computational procedure

The start geometries for HY-DAC and HY-TRI optimizations in gas phase were taken from X-ray data as described before. All computation procedures present in this work were carried out using the Gaussian09 [38] package of programs. The hybrid functional of Truhlar and Zhao, M06-2X [39], with 6–311 + g (d) basis set and B3LYP [40] exchange-correlation functionals with 6–311 g (d,p) [41,42] basis set were applied to calculate the geometric and electronic properties of the compounds. The M06-2X functional is a nonlocal functional parametrized for nonmetals with double the amount of nonlocal exchange [39]. This functional is recommended for noncovalent interaction such as C–H···O and C–H···π [43–45]. The optimizations of geometric parameters were carried out without constraint and to confirm if the optimized geometry found in local minimum analytic harmonic frequency calculations had been carried out using the same level of theory. With the support of potential energy distribution (PED) analysis in Veda 4 [46] software and the animation option of Gaussview [47], the assignments of the vibrational frequencies were made.

3. Results and discussion

3.1. Crystallographic structure

Our crystallographic data collected for (E)-3-(4-(dimethylamino)phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (HY-DAC) are very similar to those found by Zhiqiang Liu and coworkers [28], with monoclinic crystal system, $P2_1/c$ space group and unit cell parameters a = 12.124 Å, b = 10.275 Å, c = 12.506 Å and $\beta = 115.87°$, showing one molecule per asymmetric unit. Similarly, (E)-1-(2-hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (HY-TRI) also crystallized with a single molecule per asymmetric unit in a $P2_1/c$ space group and monoclinic crystal system, with metrics a = 12.687 Å, b = 8.586 Å, c = 15.394 Å and $\beta = 15.394°$, like those found by Hui Wu, Zhou Xua and Yong-Min Liang [48]. Complete data for HY-DAC and HY-TRI are shown in Table 1, followed by Ortep representations and an atom-numbering scheme for HY-DAC (Fig. 1a) and HY-TRI (Fig. 1b):

Excepting the substituted region, both structures are very similar in bond lengths and angles, as can be seen in Fig. 2a. Major