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Study of the molecular structure and chemical reactivity of pinocembrin by DFT calculations

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ABSTRACT

Pinocembrin flavonoid ($C_{15}H_{12}O_4$), 5,7-Dihidroxyflavanone, is one of the major chemical constituents of propolis extracts which is characterized by possessing antioxidant activity. However, the relationship between its structure and antioxidant properties are little known. The principal objective of this work was to study the molecular structure and chemical reactivity (electronic affinity, A; ionization potential, I; electronegativity, χ; hardness, η; electrophilicity, ω; Fukui indices) of pinocembrin employing the Density Functional Theory (DFT) method and different model chemistries, which include the PBEPBE, PBE1PBE, MPW1PW91, B3LYP and M05-2X functionals in combination with the 6-31G(d,p) and 6-31+G(d,p) basis set, in search of the most accurate results. This study indicate that different model chemistries were able to reproduce the molecular structure of pinocembrin compared with experimental reference data ($R > 0.99$). It is remarkable that M05-2X/6-31G(d,p) afford the best quality to simulate pinocembrin structure. Low values of chemical potential, obtained by different model chemistries, indicate that pinocembrin is capable to donate electrons and participle as an antioxidant compound, while the local reactivity analyzed through the Fukui indices showed that $C_{(4)}$ was the preferred sites for nucleophilic attack, and $O_{(4)}$ and $C_{(8)}$ sites participle in electrophilic and radical attack.

1. Introduction

Flavonoids are member of a class of natural compounds that has been subject of considerable scientific interest. Many studies have suggested that flavonoids exhibit biological activities, including antibacterial, antiviral, anti-inflammatory, anticarcinogenic and antioxidant activities. However, most interest has been devoted to their antioxidant activity [1,2]. The pinocembrin molecule ($C_{15}H_{12}O_4$) is a flavonoid known as 5,7-Dihidroxyflavanone, in nature is in its *S*-configuration. Previous studies demonstrated that pinocembrin is one of the major chemical constituents of Sonora propolis (>20%) and the antioxidant activity of this bee product is correlated with the presence of this compound, among others [3,4].

Flavonoids, such as pinocembrin, are characterized by possesses good ability to inhibit lipid peroxidation, associating this activity to certain structural features such as the presence of phenolic groups in the A ring of the molecule and the presence of the 4-keto group in ring C [5,6]. The therapeutic effect of pinocembrin on oxidative stress in the brain of rats [7,8] finding that treatment with pinocembrina reduced the compensatory increase of superoxide dismutase (SOD) and decreased levels of malondialdehyde (MDA). Numerous reports showed the crystal structure [9], and antioxidant activity of pinocembrin (*in vitro* and biological systems), which is associated with structural characteristics of the molecule.

Many computational investigations have been made citing the successes of different Density Functional Theory (DFT) methods compared to experimental methods, in computing the molecular structure and the intrinsic reactivity of phenolic compounds, which are very important in order to disclose the relationship between the structure and chemical properties with their antioxidant activity [10–12]. Comparisons of the performance and accurate calculations of different DFT methods such as model chemistries including gradient-corrected correlation (PBEPBE), hybrid (PBE1PBE, MPW1PW91 and B3LYP) and metahybrid functional (M05-2X), with its respective basis set, allow obtain such information to understand the antioxidant properties of pinocembrin [13,14]. Unfortunately, till now, no attempt has been made to analyze the application model chemistries for accurate calculations of structure and chemical reactivity of pinocembrin, which may allow to obtain the lack of information on the intrinsic reactivity of this molecule.

Therefore, in this study, the objective of this work is to (i) perform a detailed calculation of the molecular structure and chemical

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reactivity of pinocembrin flavonoid and (ii) assess the different DFT model chemistries to determine which provides satisfactory results of structural and chemical reactivity.

2. Theory and computational details

Molecular structure was designed with the program GAUSSVIEW 4.1. All calculations were performed employed the Density Functional Theory (DFT) method implemented in the GAUSSIAN 03W package [13]. Looking for more accurate model chemistry, we compare different functionals: gradient-corrected correlation (PBEPBE), hybrid (PBE1PBE, MPW1PW91 and B3LYP) and metahybrid functional (M05-2X) [14,15]. The 6-31G(d,p) basis set was used for the geometry and vibrational frequencies determination of the pinocembrin parent molecule and its radicals, anions and radical cations. From these calculations were derived some structural parameters such as bond distances, bond angles, dihedral angles, as well as some reactivity properties including total energy an thermochemical properties. Other structural parameters as shielding constants and chemical shifts by ^{13}C NMR, besides others reactivity properties among these chemical potential and Fukui indices were calculated.

The reactivity properties (i.e. total energies in neutral and ionized molecule, electronic affinity, ionization potential, hardness, electronegativity and electrophilicity [chemical potential properties], Fukui indices, and shielding constants by ^{13}C NMR spectroscopy) were calculated with the 6-31+G(d,p) basis set. Shielding constants (δ) calculation was obtained by the method GIAO [16]. All calculations were performed in gas-phase (at 298 K) with the purpose of obtaining the intrinsic properties of pinocembrina (i.e., free of any interaction).

The chemical potential (μ) according to the Density Functional Theory [17,18], is defined as the escaping tendency of electron from equilibrium:

$$\mu = (\partial E^2/\partial N^2)_{v(r)} = -\chi; \mu = -1/2(I + A) \quad (1)$$

where χ is the electronegativity.

Hardness has been defined as the resistance to charger transfer:

$$\eta = (\partial^2 E/\partial N^2)_{v(r)} \quad (2)$$

These equations are related with the electronegativity (χ), describes the ability of a molecule to attract electrons towards itself in a covalent bond; and the global hardness, measure the resistance towards the deformation or polarization of the electron cloud of the atoms, ions or molecules under small perturbation of chemical reaction, through the following relation:

$$\chi = \frac{(I + A)}{2} \quad (3)$$

$$\eta = \frac{1}{2}(I - A) \quad (4)$$

where

$$I = E(+) - E(0) \quad (5)$$

$$A = E(0) - E(-1) \quad (6)$$

The electrophilicity index (ω), measures the capacity of chemical species to accept electrons, was calculated using the electronic chemical potential and the chemical hardness:

$$\omega = \mu^2/2\eta \quad (7)$$

The condensed Fukui functions were computed by taking the finite difference approximations from population analysis of atoms in molecules, depending on the direction of electron transfer, through the following formulas [19]:

$$fk^+ = qk(N + 1) - qk(N) \quad \text{[for nucleophilic attack]} \quad (8)$$

$$fk^- = qk(N) - qk(N - 1) \quad \text{[for electrophilic attack]} \quad (9)$$

$$fk^0 = [qk(N + 1) - qk(N - 1)]/2 \quad \text{[for radical attack]} \quad (10)$$

where qk is the gross charge of atom k in the molecule.

3. Results and discussion

3.1. Structural properties

The representation of the molecular structure of pinocembrin molecule with its labeling and atomic numbering is shown in Fig. 1, which can be seen that structural conformation is not planar, with a torsional angle between ring B and C [$O_{(1)}$–$C_{(2)}$–$C'_{(1)}$–$C'_{(2)}$] is −32.0°. Bond interatomic distances (Å) computationally obtained are depicted in Fig. 2 and Table 1. The results were compared with experimental data of X-ray crystallography for pinocembrina [9], finding good correlation between computational and experimental bond distances and thus low standard deviations. The geometric parameters which analyzed in this work are of importance to have information about the conformation of the molecule. In the molecular structure of pinocembrina, the standard deviation (D.S) for the comparison of the calculated versus the experimental results are 0.0362 for the PBEPBE/6-31G(d,p), 0.0360 for the PBE1PBE/6-31G(d,p), 0.0363 for the MPW1PW91/6-31G(d,p), 0.0369 for the B3LYP/6-31G(d,p) and 0.0369 for the M05-2X/6-31G(d,p) model chemistry, in all cases for the interatomic bond distances. These results indicate that the calculated bond distances with DFT model chemistries are very similar to the crystal structure of pinocembrin. In agreement with our results [20] reported that M052-X/6-31+G(d,p) model chemistry successfully reproduces the molecular structure of flavonoids (quercetin).

The chemical shift (σ) obtained by ^{13}C NMR spectrometries for pinocembrina molecule are shown in Table 2, shows a typical example of the correlation between the spectral data of experimental ^{13}C NMR [21,22] and computational methods. Result showed that in both cases a linear trend with R values greater than 0.9900. The model chemistry M05-2X/6-31+G(d,p) presented the highest correlation ($R = 0.9958$). These results confirm that the computational determination of ^{13}C NMR spectral data was very close to the experimental data, which indicate that M05-2X method it is a good tool for studies related to the determination of neutral structure molecules of phenolic compounds such as flavonoids [12,14]. In agree with Espinoza-Hicks et al. [23] hybrid (PBE1PBE) and metahybrid (M05-2X) functionals can be used for calculation ^{13}C NMR spectra of chalcones.

In DFT methods, the exchange–correlation energy is the main issue among all of the approximations, therefore, the accuracy of each model chemistry is depended directly by the approximate nature of the exchange–correlation energy functional. PBEPBE is classified to the generalized gradient-corrected correlation (GCA) which represents a significant improvement over the LSDA method (local density approximation). LSD method assumes that the exchange–correlation energy at any point in space and can given by the electron density of a homogeneous electron gas of the same density [24]. However, PBEPBE accuracy is still not enough for a correct description of many chemical aspects. PBE1PBE, MPW1PW91 and B3LYP are classified as Hybrid-DFT functional, which combines the exchange–correlation of 25%, 25% and 20% of Hartree–Fock (HF, or exact) exchange, respectively. These functional are characterized by obtain accurate molecular structures,