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Theoretical studies on the antioxidant activity of pinobanksin and its ester derivatives: Effects of the chain length and solvent

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ABSTRACT

The effects of the ester group and solvent on the structure and antioxidant activity of pinobanksin were carried out using DFT calculation. First, the properties of the intramolecular hydrogen-bonds in the investigated compounds were studied. Second, the antioxidant capacities of the investigated compounds were analyzed by HAT, SET-PT and SPLET mechanisms from thermodynamic point. The conclusions are: (1) HAT mechanism is most favorable in the gas and CCl_4 phases, while SPLET mechanism is more favored in the CH_3CN and H_2O phases. In the $CHCl_3$ phase, the thermodynamically preferred mechanism is HAT for the 3 − OH and 5 − OH groups. While, HAT and SPLET mechanisms may run simultaneously for the 7 − OH group. (2) Replacing the 3 − OH group by ester group with different alkyl chains does not change much of the antioxidant activity of pinobanksin. (3) Besides, the 7 − OH group contributes mainly to the antioxidant activities of the investigated compounds.

1. Introduction

Free radicals formed in the body have the tendency to react with biomolecules such as nucleic acids, lipids and proteins (Dizdaroglu, Jaruga, Birincioglu, & Rodriguez, 2002; Fang, Yang, & Wu, 2002). For example, they can initiate a chain reaction that can damage DNA, causing some diseases such as cardiovascular diseases, cancer, cataracts and aging (Dizdaroglu et al., 2002). Antioxidants can protect biomolecules from undergoing free radicals damage in low concentration (Fang et al., 2002; Kamkar, Javan, Asadi, & Kamalinejad, 2010). They are recognized as potential strategies for preventing acute central nervous system injuries, cardiovascular diseases and asthma (Gilgun-Sherki, Rosenbaum, Melamed, & Offen, 2002; Hahn et al., 2017; Kirkham & Rahman, 2006).

Flavonoids are plant secondary metabolites commonly found in natural foods such as fruits, vegetables, cereals, propolis, pollen and honey (Ross & Kasum, 2002). They are a group of polyphenols and have received tremendously scientific interest since the past decades due to their ability to interact quickly with free radicals formed in the body, thus protecting the biomolecules from the damage of the free radicals (Villano, Fernández-Pachón, Moyá, Troncoso, & García-Parrilla, 2007). They have been used as universal remedies for a wide range of diseases such as early aging, cardiovascular diseases, cancer and other degenerative diseases related with the free radicals (Knekt et al., 2002).

The free radical scavenging capacity of a flavonoid is decided by its antioxidant activity. In the past decades, with the development of computational methodologies, it becomes easier to estimate the antioxidant activity of a flavonoid from theoretical calculations with accuracy equivalent or greater than those obtained from experiments. Therefore, theoretical calculations could be used as cogent tools for predicting antioxidant activity of compounds and designing novel potential antioxidants. At present, several density functional theory (DFT) investigations have been considered as the most suitable computational methods to calculate the antioxidant properties of flavonoids due to the low cost, high precision and short time performing calculations on medium-sized and large molecules (Laskar, Sk, Roy, & Begum, 2010; Lengyel, Rimarčík, Vagánek, & Klein, 2013; Lu, Qiang, Li, Zhang, & Zhang, 2014; Nenadis & Sigalas, 2011; Nenadis & Tsimidou, 2012; Payán-Gómez, Flores-Holguín, Pérez-Hernández, Piñón-Miramontes, & Glossman-Mitnik, 2010; Vagánek, Rimarčík, Dropková, Lengyel, & Klein, 2014; Vargas-Sánchez, Mendoza-Wilson, Torrescano-Urrutia, & Sánchez-Escalante, 2015; Wang et al., 2015; Xue, Zheng, An, Dou, & Liu, 2014; Zheng et al., 2017). Many investigations have proven the successes of different DFT methods to disclose the relationship between the structure and chemical property with the antioxidant activity (Laskar et al., 2010; Payán-Gómez et al., 2010; Xue et al., 2014).

The antioxidant activities of flavonoids are largely influenced by their molecular structure, more precisely to the presence and number of

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hydroxyl groups, and the conjugation and resonance effects. Previous works are mainly focused on the structure-activity relationships related to the type and number of the hydroxyl groups on the aromatic ring (Lengyel et al., 2013; Lu et al., 2014; Nenadis & Sigalas, 2011; Nenadis & Tsimidou, 2012; Vagánek et al., 2014; Vargas-Sánchez et al., 2015; Wang et al., 2015; Xue et al., 2014; Zheng et al., 2017). However, studies on the contributions of structural characteristics such as the substituting groups and the carbon chain to the antioxidant capacities of flavonoids are rather limited. Apart from the structural effect, the surrounding environment is also able to affect the bond dissociation enthalpy (BDE), ionization potential (IP) and proton affinity (PA) which are closely related with the antioxidant activity of a flavonoid (Lu et al., 2014; Nenadis & Tsimidou, 2012; Vagánek et al., 2014; Wang et al., 2015; Xue et al., 2014; Zheng et al., 2017). Besides, it may also alter the thermodynamically preferred antioxidant site and antioxidant mechanism for a molecule (Lu et al., 2014; Nenadis & Tsimidou, 2012; Vagánek et al., 2014; Wang et al., 2015; Xue et al., 2014; Zheng et al., 2017). Pinobanksin (3,5,7-trihydroxy-2-phenyl-chroman-4-one) and pinobanksin-3-*O*-ester derivatives are widely distributed in honey and propolis. It is found that they are typical flavonoids ubiquitously present in different geographical and botanical propolis (Huang, Zhang, Wang, Li, & Hu, 2014). They exhibit antiproliferative activity on M12.C3.F6 cells through apoptosis induction (Alday et al., 2015). At present, to the best of our knowledge, no theoretical study regarding the antioxidant capability of pinobanksin-3-*O*-ester derivatives with different carbon chain has been carried out so far. Therefore, in this study, the object is to perform a detailed calculation of the substituting 3 − OH group by different ester groups on the molecular structure and antioxidant reactivity of pinobanksin using DFT calculations. Since the surrounding environment also largely influences the molecular structure and the antioxidant activities of flavonoids, the gas phase as well as four solvent phases are also conducted in this work. The four solvents are carbon tetrachloride (CCl_4), chloroform ($CHCl_3$), acetonitrile (CH_3CN) and water (H_2O) having the dielectric constants of 2.24, 4.81, 36.6 and 80.1 respectively.

2. Computational details

All of the DFT calculations were carried out using the Gaussian 09 program suite (Frisch et al., 2009). For the investigated compounds, the geometry, distribution and energy of the frontier orbitals as well as the spin density of the radicals were obtained using the M062X/6-31G* method. The absence of imaginary frequency was used to confirm that the optimized structure was a local minimum. Single point energy calculations were performed at the M062X/6-311 + G** level of theory using the geometries optimized by M062X/6-31G* method. The solvent effect was performed using the SMD continuum solvent model. Atoms in molecules (AIM) (Bader, 1994) analysis was carried out using the M062X/6-311 + G** method to better understand the nature of the intramolecular hydrogen-bond in pinobanksin and pinobanksin-3-*O*-ester derivatives.

2.1. AIM analysis

In the AIM analysis, the search of bond critical point (BCP) and the detail topological analysis were performed by Multiwfn 3.3.8 suite (Lu & Chen, 2012). At the BCP, some topological parameters: the electron density (ρ_{BCP}), the Laplacian of electron density ($\nabla^2\rho_{BCP}$), the Lagrangian kinetic energy (G_{BCP}), the potential electron density (V_{BCP}) and the energy density (H_{BCP}) were used to describe the properties of the intramolecular hydrogen-bonding interaction. The hydrogen-bond energy (E_{HB}) is calculated by the method devised by Espinosa, Molins, and Lecomte (1998). The calculated equation is as follow:

$$E_{HB} = 1/2V_{BCP} \quad (1)$$

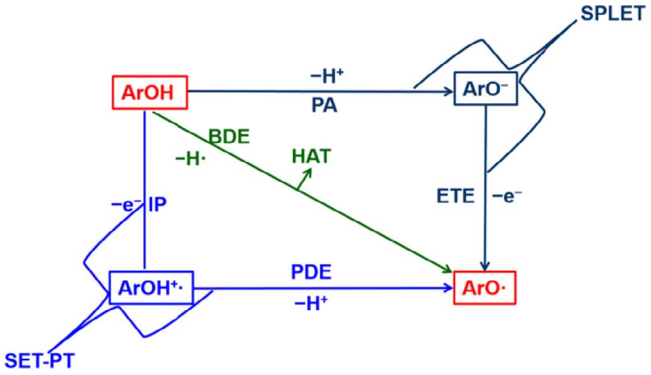

Fig. 1. Mechanisms of antioxidant action.

2.2. Antioxidant mechanism

According from the literature, the antioxidant action of flavonoids (ArOH) is mainly through three antioxidant mechanisms as shown in Fig. 1. They are the hydrogen atom transfer (HAT), single electron transfer followed by proton transfer (SET-PT) and sequential proton loss electron transfer (SPLET) (Leopoldini, Russo, & Toscano, 2011; Stepanić, Trošelj, Lučić, Marković, & Amić, 2013; Wright, Johnson, & DiLabio, 2001). The thermochemistry of the reactions may be a competitive antioxidant process as the reactivity is driven by kinetics. In this work, we mainly focused on the thermodynamics of the reactions as most of the works that concern the antioxidant activity of the flavonoids have done.

HAT is a single step mechanism in which hydrogen atoms break from the flavonoid hydroxyl groups to the free radicals by homolytic cleavage of the O—H bond. From the thermodynamic point of view, the capacity of this mechanism is driven by the BDE. SET-PT and SPLET are two steps mechanisms. In the SET-PT mechanism, electron abstraction from ArOH is followed by proton transfer. This mechanism is governed by IP and proton dissociation enthalpy (PDE). In the SPLET mechanism, proton abstraction from ArOH is followed by electron transfer. This mechanism is governed by PA and electron transfer enthalpy (ETE) of ArO^-.

The calculated equations for BDE, IP, PDE, PA and ETE are as follows:

$$BDE = H(ArO^{\cdot}) + H(H^{\cdot}) - H(ArOH) \quad (2)$$

$$IP = H(ArOH^{+\cdot}) + H(e^-) - H(ArOH) \quad (3)$$

$$PDE = H(ArO^{\cdot}) + H(H^+) - H(ArOH^{+\cdot}) \quad (4)$$

$$PA = H(ArO^-) + H(H^+) - H(ArOH) \quad (5)$$

$$ETE = H(ArO^{\cdot}) + H(e^-) - H(ArO^-) \quad (6)$$

In Eqs. (2)–(6), $ArO^{\cdot}$, $ArOH^{+\cdot}$ and ArO^- represent for flavonoid radical, cation radical and anion respectively.

The gas-phase $H(H^+)$ and $H(e-)$, the solvent-phase $H(H^+)$ and $H(e-)$ and the solvent-phase $H(H^{\cdot})$ were obtained from the works by Bartmess (1994), Rimarčík, Lukeš, Klein, and Ilčin (2010) and Parker (1992) respectively.

3. Results and discussion

3.1. Conformation analysis

The investigated compounds are pinobanksin and pinobanksin-3-*O*-ester derivatives with different alkyl chains. They are pinobanksin-3-*O*-acetate (3-acetyloxy-5,7-dihydroxy-2-phenyl-chroman-4-one), pinobanksin-3-*O*-propanoate (3-propionyloxy-5,7-dihydroxy-2-phenyl-chroman-4-one), pinobanksin-3-*O*-butyrate (3-butyryloxy-5,7-dihydroxy-2-phenyl-chroman-4-one), pinobanksin-3-*O*-pentanoate (3-