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Theoretical study of antioxidative ability and antioxidative mechanism of norathyriol in solution

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ABSTRACT

A quantum mechanical approach has been used to shed light on the antioxidative mechanism for scavenging ·OOH and ·OH radicals by norathyriol in the solution phase. Density functional theory (DFT) calculations at the B3LYP and UB3LYP/6-311+G(d,p) level are used to optimize norathyriol and its different radical forms. Analysis of the theoretical bond dissociation enthalpy (BDE) values for all OH sites of norathyriol in solution clearly shows the importance of the B-ring and the 6-OH and 7-OH groups in the antioxidant activity. We have also investigated the spin density of the radicals to determine the delocalization possibilities. The results of the calculations show that the oxidation of norathyriol by both the ·OOH and ·OH radical is an exothermic reaction. In all calculations solvent effects are considered using a polarized continuum model (PCM).

1. Introduction

Norathyriol, a metabolite of mangiferin found in mango, hypericum elegans, and tripterospermum lanceolatum, has received increasing interest attention since 1960 for its widespread use in biochemical field [1–6]. Ko et al. have examined the vasorelaxation of rat thoracic aorta caused by norathyriol isolated from Gentianaceae [3]; the inhibitory effect of norathyriol has been examined by Hsu et al. [4], Wang et al. [5]; and recently, the anti UV-induced skin cancer actions attributed to this compound have been reported by Li et al. [6]. Therefore, investigation of its fundamental chemical behavior is of great significance in elucidation of its pharmacological mechanisms and discovering and developing novel drugs.

Antioxidants are compounds that can prevent biological and chemical substances from oxidative damage by reactive oxygen species (ROS), such as the hydroxyl radical (·OH), the superoxide radical ($\cdot O_2^-$), singlet oxygen, and lipid peroxy-radicals [7]. Polyphenolic compounds, such as flavonoids, play an important biological role in plant pigmentation, nitrogen fixation, and chemical defense. They possess anti-cancer, anti-inflammatory, antibacterial, antiviral, and antiallergic properties that are a consequence of their antioxidant properties [8–11] and gained a tremendous interest as possible therapeutics against a wide variety of diseases, most of which involve radical damage. According to recent experimental and theoretical studies, the antimutagenic activity of phenolic compounds, particularly flavonoids such as rutin, is based on their scavenging capacity against the free radicals, such as ·OH, which can be expressed as $R\cdot + R'OH \rightarrow R'O\cdot + RH$, in order to be thermodynamically favorable for this reaction, the formed radical R′O· must be relatively stable [12,13].

Previous experimental and theoretical reports about antioxidant properties of polyphenolic compounds are mainly on the investigation of flavonoids, such as rutin [12–18]. Recently O–H bond dissociation enthalpies, ionization potentials, proton dissociation enthalpies, proton affinities and electron transfer enthalpies related to HAT, SET-PT and SPLET mechanisms in gas and solution-phases of some isoflavones and flavonoids were investigated by Lengyel et al. [12] and Vagánek et al. [13] However, as an important class of polyphenolic compounds, norathyriol, which consists of two benzene ring (A and B) condensed with a six-membered ring (C) (see Fig. 1), has gained not many interests. Furthermore, knowledge about the antioxidant properties of flavonoids is still limited and little report related to quantum mechanics for norathyriol and almost none about studies, essential to understand its mechanisms of radical scavenging and the relationship between structure and activity has been seen in the literature.

Therefore, the objective of this study is to investigate the antioxidant mechanism of norathyriol, including scavenging activities against the ·OOH and ·OH free radicals. In the present work,

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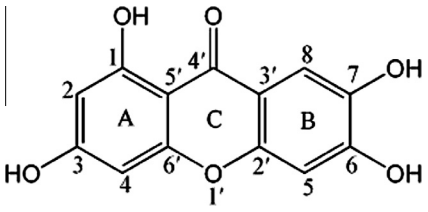

Fig. 1. Chemical structure of norathyriol.

density functional theory (DFT) has been employed to investigate the geometric structures of all reactants, transition states, intermediates, and products molecular orbitals, and the reaction mechanisms of ·OH and ·OOH radical with the norathyriol molecule in solution are clarified.

2. Computational details

2.1. Theoretical parameters: calculation of the bond-dissociation energy and spin distribution

Bond dissociation enthalpy (BDE), a quantum chemically determined suitable parameter for describing the abstraction of a hydrogen radical from an O–H bond, is the difference in total enthalpies between the flavonoid and its corresponding radical. The BDE can be calculated by $E_B = H_r + H_h - H_p$, where H_r is the enthalpy of the radical generated by H-abstraction, H_h is the enthalpy of the H-atom, and H_p is the enthalpy of the parent molecule. In the case of DFT method, which does not provide enthalpies directly, the total enthalpies of the species R·, $H(R)$, at the temperature T are usually estimated from the expression $H(R) = E_0 + ZPE + \Delta H_{trans} + \Delta H_{rot} + \Delta H_{vib} + RT$, where E_0 is the calculated total electronic energy, ZPE stands for zero-point energy, ΔH_{trans}, ΔH_{rot} and ΔH_{vib} are the translational, rotational and vibrational contributions to the enthalpy. Finally, RT represents PV-work term and is added to convert the energy to the enthalpy [12,13]. The computed value of H-atom enthalpy is −314.5 kcal/mol at $T = 298$ K.

Spin distributions, which is another important parameter of delocalization possibilities, is relevant to the antioxidant activity and are calculated for the different radicals of norathyriol. Afterward, the mechanism for the radical-scavenging reactions for norathyriol is discussed. The results of a previous study to obtain an accurate description of the BDE in phenolic compounds show the DFT method with 6-311+G (d,p) basis set [19] is sufficient to give an accurate description of the BDE [20–25]. Hence, we use this method for the continuation of our studies.

2.2. Molecular orbital calculation

All the calculations are performed with the Gaussian 03 program [26] on a Lenovo server. The hybrid B3LYP functional in conjunction with the 6-311+G(d,p) basis set are applied for the optimizations of all the stationary points. Harmonic vibrational frequencies are analyzed at the same level of optimization to characterize the nature of stationary points as true minima with no imaginary frequencies of transition states with only one imaginary frequency and to provide thermodynamic quantities such as thermal corrections to energy. To simulate the reaction in solution, solvent effects are estimated with the PCM model implemented in the Gaussian 03 to optimize structures, we have used the dielectric constants 78.39 at 298.15 K for H_2O [27–29]. In this continuum model, ΔE_0 are the zero-point energy (ZPE) corrected relative electronic energies. Corrections of the transition states between designated local minima have been confirmed by intrinsic reaction coordinate (IRC) calculations at the same level.

3. Results and discussion

3.1. Geometry optimization of norathyriol and energy properties

The planar conformer with C_s symmetry is the most abundant form of norathyriol in water solvent (Fig. 1). Hence, we used this conformer as a starting point and performed the geometry optimizations by considering the solvent effect using a polarized continuum model (PCM) at the B3LYP/6-311+G(d,p) level with no symmetry. Fig. 2 shows the optimized structure of norathyriol in water solvent.

A selection of calculated bond distances, bond angles, and dihedral angles are compiled in Table 1, from which we can see the internal hydrogen bonding on the H-1 atom and the conjugation effect is evident since the distance of O-1–H-1 is about 0.006 Å bigger than O-3–H-3 and the optimized structure retains C_s symmetry. It also shows that the ortho-dihydroxy structure in the B ring confers high stability to the radical species through H-bond formation.

The calculated gap energy value between the HOMO and LUMO of molecule ($\Delta E_{gap} = E_{LUMO} - E_{HOMO}$) of the norathyriol molecule is about 3.41 eV. It is well known that ΔE_{gap} is relevant to the reactivity of the molecular. The increase of ΔE_{gap} can make the molecular less stable and more reactive [30,31], which indicates that norathyriol should be a reactive molecule. The HOMO and LUMO distribution of norathyriol molecule is presented in Fig. 3.

3.2. BDE values of optimized norathyriol

Geometry optimizations on the radicals are performed by the UB3LYP/6-311+G(d,p) method in water solvent, starting from the optimized structure of the parent molecule after the H-atom was removed from the 1, 3, 6, and 7-OH positions. Table 2 shows the UB3LYP/6-311+G(d,p) calculated BDE values for the four radicals formed by H-abstraction on norathyriol. The results show the following BDE sequence for the OH groups: 7-OH < 6-OH < 3-OH < 1-OH. As expected, the BDE value for the 1-OH group has

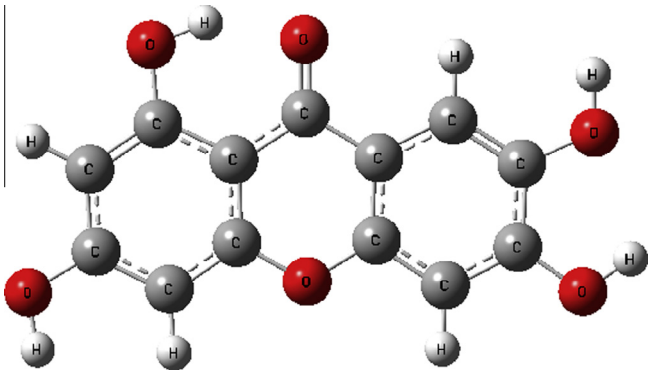

Fig. 2. Optimized structure of norathyriol in H_2O solvent at the B3LYP/6-311+G(d,p) level.

Table 1
Some structural details of the optimized structure of norathyriol at the B3LYP/6-311+G(d,p) level.

Bond distance (Å)		Bond angles (°)		Dihedral angles (°)	
O-1–H-1	0.99159	C-1–O-1–H-1	107.02	C-5′–C-1–O-1–H-1	180.00
O-3–H-3	0.98566	C-3–O-3–H-3	111.38	C-4–C-3–O-3–H-3	180.00
O-6–H-6	0.97894	C-6–O-6–H-6	111.73	C-5–C-6–O-6–H-6	180.00
O-7–H-7	0.98523	C-7–O-7–H-7	111.38	C-8–C-7–O-7–H-7	180.00