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ORIGINAL RESEARCH

# Reaction mechanism of ferulic acid scavenging OH and $NO_2$ radicals: a theoretical study

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## Abstract

As a derivative of cinnamic acid, ferulic acid (FA) is a bio-active ingredient of many foods and is considered to be a good natural antioxidant. A theoretical study on the reaction mechanism of FA scavenging two damaging radicals (·OH and $\cdot NO_2$) was investigated through the density functional theory (DFT) method. Two most possible reaction mechanisms, hydrogen atom transfer (HAT) and radical adduct formation (RAF), were studied. All possible reaction/attack sites were examined, and the corresponding pathways in both gaseous and aqueous medium were identified by thermodynamic and kinetic calculations. It was found that the most active site of FA scavenging ·OH is the –OH group in benzene ring by HAT mechanism. While, for scavenging $\cdot NO_2$, the RAF reaction on the C = C double bond is the dominant channel in the aqueous phase.

**Keywords** DFT · Antioxidant · Mechanism · Ferulic acid · Radical

## Introduction

Free radicals are species containing one or more unpaired electrons, which gives them a high reactivity. Free radicals were initially thought to be oxygen-centered radicals, defined as reactive oxygen species (ROS), but also include a subgroup of reactive nitrogen species (RNS), all of which are products of normal cell metabolism. The overproduction of ROS and RNS in vivo results in oxidative stress and nitrosative stress, which leads to the damage to cell macromolecules including lipids, proteins, and DNA, thus increases the risk of ischemic heart disease, Alzheimer's disease, ischemia–reperfusion injury, skin disease, kidney disease, and other diseases [1–4]. That is what prompted us to develop ways to control ROS and RNS in pathophysiological processes, and the antioxidant-based response is one of them. Both natural and synthetic antioxidants had been developed, while the toxicity found in the synthetic antioxidants led to a growing interest in cheap, non-toxic natural antioxidants [5–7].

Ferulic acid (4-hydroxy-3-methoxycinnamic acid, FA) is an important phenolic acid, which can be found in various natural plants such as whole grains, spinach, parsley, grapes, rhubarb, and cereal seeds [8]. FA has low toxicity and possesses a broad spectrum of biological and pharmacological properties, including anti-inflammatory, antibacterial, antiviral, antioxidant, antihypertension, antidiabetes, and anticancer effects [9–12]. One of the most important functions of phenolic acids, especially cinnamic acid derivatives, is their antioxidant activity, manifested in the ability to eliminate oxygen and free radicals (mainly superoxides, hydroxyl groups and hydroxyl peroxides). FA is considered to be a superior antioxidant, and its antioxidant properties have been confirmed by many experimental studies [13–16]. FA is more readily absorbed into the body than other phenolic acids and stays in the blood longer. The beneficial effects of FA on human health have been widely advocated, at least in part, because of its strong antioxidant activity [17, 18].

Therefore, the main objective of this work is to systematically study the reaction mechanism of FA with two typical ROS and RNS (·OH and $\cdot NO_2$), and to provide thermodynamic and kinetic details of all possible reaction pathways. It is hoped that the results of this study can provide some theoretical basis for the development of natural and high-activity scavengers against ROS and RNS.

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## Computational methods

Full geometry optimization and frequency calculations were performed at the M05-2X/6-311 g(d,p) functional and basis set, using the GAUSSIAN 09 computational package [19]. The M05-2X functional has been successfully used in the studies on thermochemistry, kinetics, and non-covalent interactions, especially for calculating the energies of reactions involving free radicals [20–25].

Unrestricted calculations were used for open shell systems. To determine the nature of all stationary points, vibrational frequencies were obtained, at the same time, the local minima and transition states (TS) were identified by the number of imaginary frequencies (0 or 1, respectively). Intrinsic reaction coordinate (IRC) calculations have also been carried out to confirm that all TSs properly connect reactions and products.

To mimic the aqueous media in the body, the solvent effects were introduced using the solvation model of the continuum solvation model based on solute electron density (SMD) which is recommended by Gaussian Manual to compute solvation energy [26]. At the level of M05-2X/6–311 + + G(d,p), all the reactant complexes and product complexes were optimized in aqueous solution by SMD model to evaluate the reaction Gibbs energies and reaction enthalpies. Due to the complexity and expensiveness of transition states optimization, the solvation effects of TS were estimated by the single point calculations on the basis of the optimized gas-phase geometries using SMD model. Both zero-point vibrational energies and thermal corrections at 298.15 K obtained at the M05-2X/6–311 + + G(d,p) level were used to correct electron energies of single point calculations.

Reaction enthalpy in solution was computed by the difference of enthalpy values between products and reactants optimized in the presence of SMD model. Relative Gibbs energy in solutions was computed using thermodynamic cycle and Hess' law which explicitly include solvation energy. For example, the thermodynamic cycle for the addition reaction between FA and ·OH is as follows:

$$\mathrm{FAgas} + \cdot\mathrm{OH}_{\mathrm{gas}} \xrightarrow{\triangle G_{\mathrm{gas}}} \cdot(\mathrm{FA}-\mathrm{OH})_{\mathrm{gas}} \uparrow -\mathrm{Gs(FA)} \uparrow - \triangle \mathrm{Gs}(\cdot\mathrm{OH}) \downarrow \mathrm{Gs} \cdot (\mathrm{FA}-\mathrm{OH})\mathrm{FA}_{\mathrm{solv}} + \cdot\mathrm{OH}_{\mathrm{solv}} \xrightarrow{\triangle G_{\mathrm{sol}}} \cdot(\mathrm{FA}-\mathrm{OH})_{\mathrm{solv}} \quad (1)$$

With this strategy, the Gibbs energy of reaction in solution ($\Delta G_{\mathrm{solv}}$) can be determined as the sum of the Gibbs energy of reaction in the gaseous phase ($\Delta G_{\mathrm{gas}}$) and the difference in solvation energies ($\Delta\Delta G_{\mathrm{s}}$):

$$\triangle G_{\mathrm{solv}} = \triangle G_{\mathrm{gas}} + \triangle \triangle G_{\mathrm{s}} \quad (2)$$

where $\Delta\Delta G_{\mathrm{s}}$ is calculated as:

$$\triangle \triangle G_{\mathrm{s}} = \triangle G_{\mathrm{s}} \cdot (\mathrm{SA}-\mathrm{OH}) - \triangle G_{\mathrm{s}}(\mathrm{SA}) - \triangle G_{\mathrm{s}}(\cdot\mathrm{OH}) \quad (3)$$

where $\Delta G_{\mathrm{s}}$ is the solvation energy. The reference state is 1 M in all cases. The solvent cage effect was included with Okuno's corrections, which take into account the free volume theory. These corrections agree well with those independently obtained by Ardura et al. [27, 28]. In this work, the expression used to correct the Gibbs energy as follows:

$$\triangle G_{\mathrm{sol}}^{\mathrm{FV}} \cong \triangle G_{\mathrm{sol}}^{0} - RT\left\{\ln\left[n10^{(2n-2)}\right] - (n-1)\right\} \quad (4)$$

where $n$ is the reaction molecularity. According to Eq. 7, the solvent cage effect causes a decrease of 2.54 kcal/mol in $\Delta G$ for a bi-molecular reaction at 298.15 K [29].

## Results and discussion

It is generally believed that the reaction between phenolic compound and radical (·R) takes place mainly through three mechanisms: direct H-transfer process from the antioxidant molecule (Eq. 5), radical adduct formation (Eq. 6) and single-electron transfer process (Eqs. 7a and 7b):

Hydrogen atom transfer (HAT):

$$\mathrm{FA} + \cdot\mathrm{R} \rightarrow \cdot\mathrm{FA}(-\mathrm{H}) + \mathrm{RH} \quad (5)$$

Radical adduct formation (RAF):

$$\mathrm{FA} + \cdot\mathrm{R} \rightarrow \cdot(\mathrm{FA}-\mathrm{R}) \quad (6)$$

Single-electron transfer (SET):

$$\mathrm{FA} + \cdot\mathrm{R} \rightarrow \cdot\mathrm{FA}(-\mathrm{H})^{+} + \mathrm{RH}^{-} \quad (7a)$$

$$\cdot\mathrm{FA}(-\mathrm{H})^{+} + \mathrm{RH}^{-} \rightarrow \cdot\mathrm{FA}(-\mathrm{H}) + \mathrm{RH} \quad (7b)$$

Based on the previous studies on the reaction mechanism of gallic acid, caffeic acid, erucic acid, and other phenolic compounds with radicals, the mechanism of SET is not obvious [30–33]. Therefore, the reaction mechanisms of HAT and RAF are included in this paper.

The optimized structure of FA as well as the atomic numbering scheme are shown in Fig. 1. As can be seen, the FA has a nearly planar structure with a dihedral angle of about 179.93° between the benzene ring and the carbonyl group. The planar structure of the FA implies that it is completely conjugated and results in electrons having a wide range of spin delocalization, which can explain its potential scavenging activity on radicals [34].

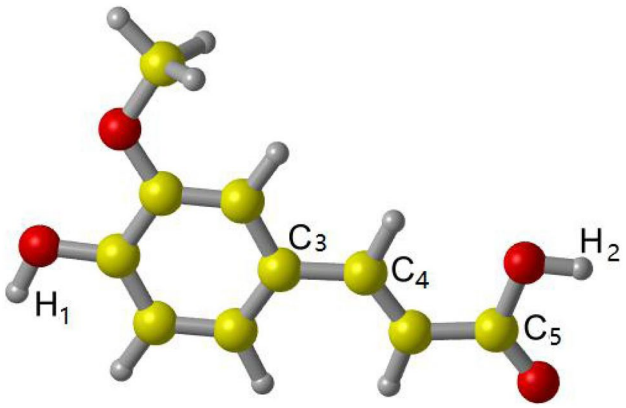


**Fig. 1** The optimized geometry of FA in the gaseous phase

## ·OH scavenging activity

To determine the activity of FA capturing ·OH, the reactions of two HAT channels (denoted as $O_{H1}$ and $O_{H2}$) as well as three RAF channels ( denoted as $O_{C3}$, $O_{C4}$, and $O_{C5}$) were studied. At the level of M05-2X/6–311 + G (d,p), all reactant complexes and product complexes of FA scavenging ·OH were optimized and the geometries are shown in Figs. 2 and 3, respectively. At the same level, the reaction Gibbs free energies ($\Delta G$) and reaction enthalpies ($\Delta H$) for all pathways in the gaseous phase and in the aqueous phase were obtained and listed in Table 1.

From Table 1, we can find that all pathways of FA scavenging ·OH are exothermic ($\Delta H < 0$), and except $O_{C5}$, all the other four pathways are exergonic ($\Delta G < 0$). Therefore, these four pathways ($O_{H1}$, $O_{H2}$, $O_{C3}$, and $O_{C4}$) are thermodynamic feasible in both the gaseous and aqueous phases. Among them, the HAT pathway $O_{H1}$ is the most exothermic and exergonic reaction, indicating that it is the most thermodynamically advantageous pathway in both the gaseous and aqueous phases. In the aqueous phase, the absolute value of $\Delta_{Gsolv}$ of two HAT pathways is greater than that of three RAF pathways, suggesting that all HAT reactions can release more energy. So we infer that, from the thermodynamic point of view, both HAT and RAF mechanisms are feasible for FA capturing ·OH in vivo, but the HAT mechanism is more advantageous.

At the M05-2X/6-311G (d, p) level, the TSs of all pathways for FA capturing ·OH is identified and shown in Fig. 4, and the activation energy barriers ($\Delta G^{\neq}$) in both the gaseous and aqueous phases are calculated and listed in Table 2.

For the 5 reactions of FA with ·OH, the activation energy barrier of the pathway $O_{H1}$ is lowest wherever in the gaseous phase or in the aqueous phase. Therefore, the HAT reaction $O_{H1}$ is the major pathway of FA scavenging ·OH. This result is consistent with the thermodynamic result discussed above. Therefore, from the thermodynamics and kinetics point of view, $O_{H1}$ is the most dominant pathway in all reactions of FA with ·OH, and the HAT is the dominant mechanism of two feasible mechanism. In addition, the pathway $O_{C4}$ has the lowest activation energy barrier in all RAF reactions, so it is a more dynamically advantageous pathway for the RAF mechanism.

## ·$NO_2$ scavenging activity

For the reaction of FA with ·$NO_2$, the active site is the same as for capturing ·OH. So similarly, two HAT pathways ($N_{H1}$ and $N_{H2}$) and three RAF pathways ($N_{C3}$, $N_{C4}$, and $N_{C5}$) have been studied.

At the level of M05-2X/6–311 + G (d,p), all reactant complexes and product complexes of FA scavenging ·$NO_2$ are optimized, and the geometries are shown in Figs. 5 and 6, respectively. At the same level, the reaction Gibbs free energies ($\Delta G$) and reaction enthalpies ($\Delta H$) for all pathways in the gaseous phase and in the aqueous phase are obtained and listed in Table 3.

As can be seen from Table 3, only the pathway $N_{C4}$ is exothermic reaction in the gaseous phase, indicating that it is thermodynamically difficult for FA capturing ·$NO_2$ in the gaseous phase. While in the aqueous phase, the pathways $N_{H1}$ and $N_{C4}$ are exothermic reaction, and the pathway $N_{H1}$ is an exergonic reaction. Therefore, the HAT pathway $N_{H1}$

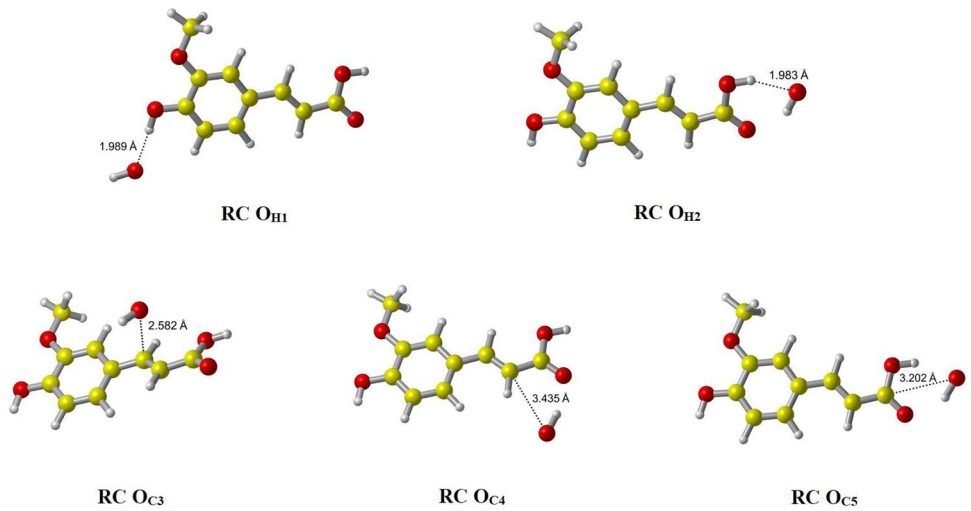


**Fig. 2** The optimized geometries of reactant complexes for the reactions of SA with ·OH

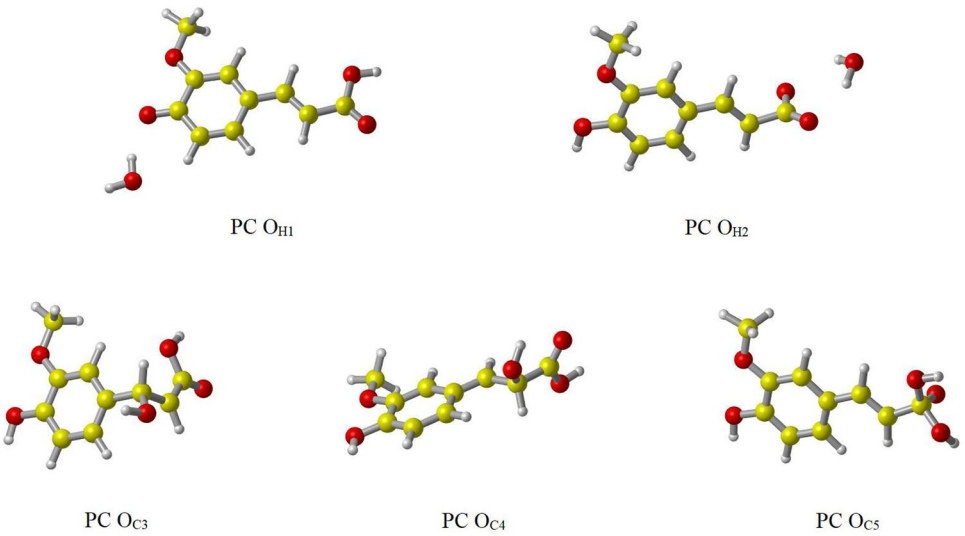


**Fig. 3** The optimized geometries of product complexes for the reactions of SA with ·OH

**Table 1** The reaction enthalpies ($\Delta H$) and Gibbs energies ($\Delta G$) at 298 K for reactions of FA with ·OH in the gaseous phase and in the aqueous phase (in kcal/mol)

| FA + •OH | $\Delta H_{gas}$ | $\Delta G_{gas}$ | $\Delta H_{solv}$ | $\Delta G_{solv}$* |
|---|---|---|---|---|
| $O_{H1}$ | −34.87 | −34.23 | −37.75 | −41.30 |
| $O_{H2}$ | −3.09 | −3.50 | −23.26 | −26.54 |
| $O_{C3}$ | −31.91 | −20.27 | −30.14 | −22.57 |
| $O_{C4}$ | −33.18 | −21.32 | −32.35 | −24.28 |
| $O_{C5}$ | −4.06 | 7.84 | −7.21 | 0.81 |

*The values of $\Delta G_{solv}$ have included the correction of solvent cage effect (−2.54 kcal/mol)

**Table 2** The activation energy barrier ($\Delta G^{\neq}$) for FA scavenging ·OH in the gaseous phase and in the aqueous phase, at 298 K (in kcal/mol)

| FA + •OH | $\Delta G^{\neq}_{gas}$ | $\Delta G^{\neq}_{solv}$ |
|---|---|---|
| $O_{H1}$ | 7.08 | 2.08 |
| $O_{H2}$ | 13.41 | 7.92 |
| $O_{C3}$ | 9.14 | 8.94 |
| $O_{C4}$ | 8.27 | 7.50 |
| $O_{C5}$ | 22.84 | 37.72 |

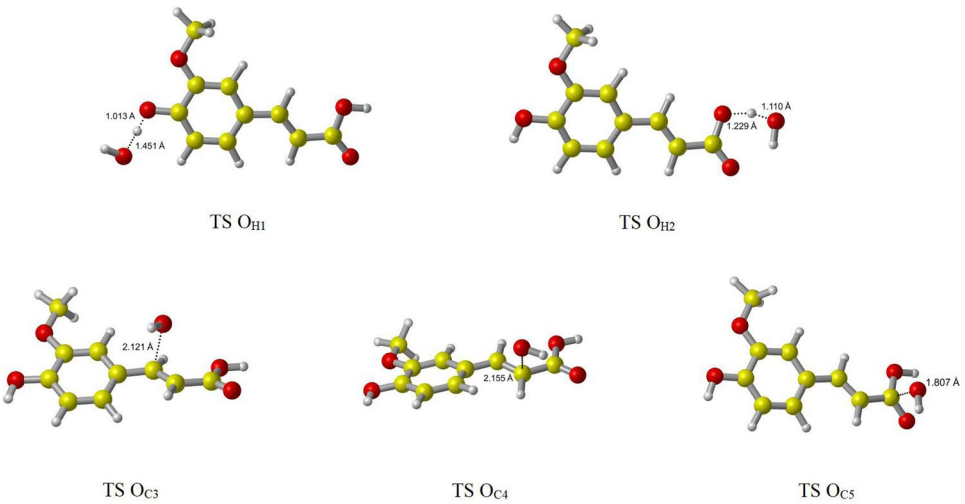


**Fig. 4** The transition state geometries for the reactions of FA with ·OH

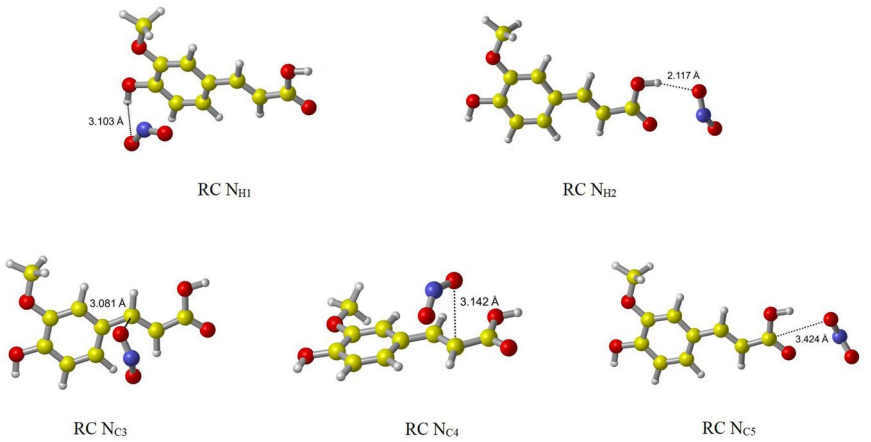


**Fig. 5** The optimized geometries of reactant complexes for the reactions of FA with $\cdot NO_2$

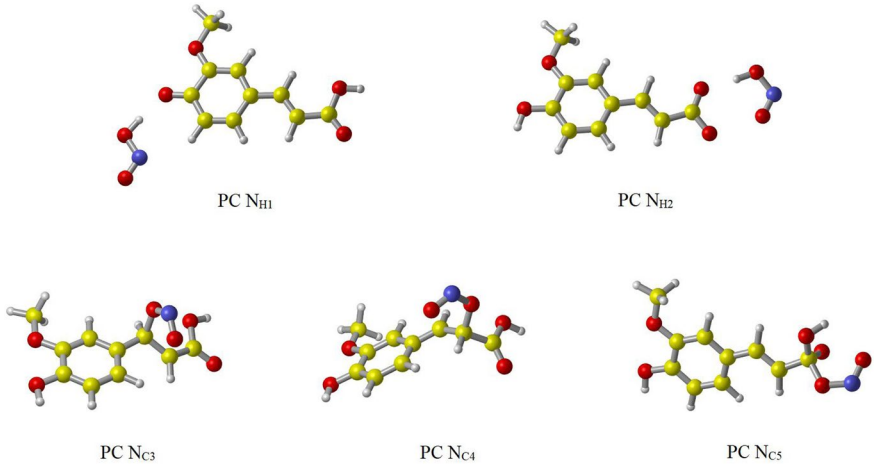


**Fig. 6** The optimized geometries of product complexes for the reactions of FA with $\cdot NO_2$

**Table 3** The reaction reaction enthalpies ($\Delta H$) and Gibbs energies ($\Delta G$) at 298 K for reactions of FA with $\cdot NO_2$ in the gaseous phase and in the aqueous phase (in kcal/mol)

| FA + •$NO_2$ | $\Delta H_{gas}$ | $\Delta G_{gas}$ | $\Delta H_{solv}$ | $\Delta G_{solv}$* |
|---|---|---|---|---|
| $N_{H1}$ | 3.21 | 4.10 | −2.51 | −5.79 |
| $N_{H2}$ | 34.98 | 34.82 | 11.98 | 8.97 |
| $N_{C3}$ | 6.50 | 20.03 | 2.76 | 12.18 |
| $N_{C4}$ | −0.53 | 13.70 | −3.08 | 7.35 |
| $N_{C5}$ | 41.49 | 54.69 | −3.73 | 3.95 |

*The values of $\Delta G_{solv}$ have included the correction of solvent cage effect (−2.54 kcal/mol)

**Table 4** The activation energy barrier ($\Delta G^{\neq}$) for FA scavenging $\cdot NO_2$ in the gaseous phase and in the aqueous phase, at 298 K (in kcal/mol)

| FA + •$NO_2$ | $\Delta G^{\neq}_{gas}$ | $\Delta G^{\neq}_{solv}$ |
|---|---|---|
| $N_{H1}$ | 24.48 | 32.65 |
| $N_{H2}$ | 38.48 | 41.80 |
| $N_{C3}$ | 27.21 | 21.90 |
| $N_{C4}$ | 25.30 | 20.18 |
| $N_{C5}$ | 49.85 | 50.09 |

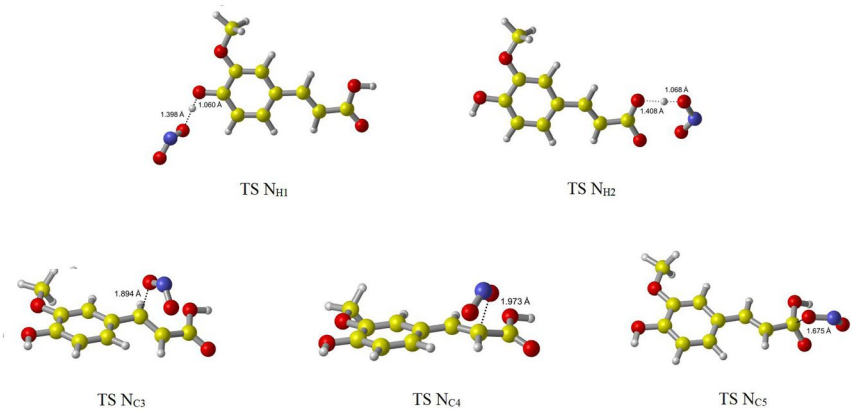


**Fig. 7** The transition state geometries for the reactions of FA with $\cdot NO_2$

and the RAF pathway $N_{C4}$ are thermodynamically feasible for FA to remove $\cdot NO_2$ in the aqueous phase.

At the M05-2X/6-311G(d, p) level, the TSs of all pathways for FA capturing $\cdot NO_2$ are identified and shown in Fig. 7, the activation energy barriers ($\Delta G^{\neq}$) in both the gaseous and aqueous phases are calculated and listed in Table 4.

From Table 4, we can find that the HAT pathway $N_{H1}$ has the lowest activation energy barrier of all gaseous-phase reactions, so it is the major pathway of FA scavenging $\cdot NO_2$ in the gaseous phase. In the aqueous phase, the pathway $N_{C4}$ has the lowest activation energy barrier of any reaction. According to the previous discussion, the pathway $N_{C4}$ is thermodynamically feasible, so it can be inferred that the RAF pathway $N_{C4}$ is the most advantageous pathway for FA capturing $\cdot NO_2$ in vivo.

## Conclusions

In this paper, a theoretical calculation was carried out to investigate the activity of ferulic acid in scavenging the damaging radicals ·OH and $\cdot NO_2$.

For FA scavenging ·OH, both HAT and RAF mechanisms are very feasible thermodynamically and kinetically. In the gaseous phase and in the aqueous phase, the most active site is H1 site in the benzene ring. The RAF mechanism is weaker than HAT, and the activities of the pathway $O_{C4}$ is better than other two RAF pathways.

For FA scavenging $\cdot NO_2$, the reactions $N_{H1}$ and $N_{C4}$ in the aqueous phase are thermodynamically feasible. The RAF reaction from site C4 is the major channel in vivo, while the activity of the HAT reaction $N_{H1}$ is weaker.

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**Author contribution** Conceptualization: Y. L., P. S. Data curation: W. W., D. D. W. Formal analysis: Y. L., W. W. Investigation: Y. L., D. D. W., X. J. B. Methodology: H. Z., P. S. Resources: Y. L., P. S., W. W. Supervision: H. Z. Validation: D. D. W., X. J. B.

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**Availability of data and material** All relevant data are within the paper and its Supporting Information files.

## Declarations

**Ethics approval** Not applicable.

**Consent to participate** Not applicable.

**Consent for publication** Not applicable.

**Conflict of interest** The authors declare no competing interests.

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