

Molecular Structure Design of Polyhydroxyl Antioxidants and Mechanism of Hydroxyl Radical Scavenging Reaction

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Abstract

Original Research Article

In this study, a variety of polyhydroxyl antioxidant molecules were designed and studied at the level of BHandHLYP/6-311++G(d,p) with the help of density functional theory, and the reaction of capturing hydroxyl radical was theoretically simulated. Based on the reaction thermodynamic and kinetic data obtained from the free radical scavenging reaction mechanism. The effect of hydroxyl number, position, conjugation and active site on reaction mechanism was discussed. The results show that the reactant **R3** has better kinetic and thermodynamic advantages in the simulation mechanism of hydroxyl radical scavenging. At 293K, the lowest relative Gibbs free energy of the transition state ΔG_{TS3-1} is 34.95 kJ·mol⁻¹, and the corresponding reaction enthalpy becomes -148.32 kJ·mol⁻¹, and **Path III-1** is the dominant Path. Temperature did not affect the reaction mechanism of the reaction.

Key words: polyhydroxyl antioxidant, structural design, hydroxyl radical scavenging reaction, mechanism study.

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1. INTRODUCTION

In the life science, free radical medicine believes that oxygen free radical is a highly active substance, its existence can cause peroxidation of the organism, but also DNA oxidative damage or cross-linking, leading to biological body lesions, so its excessive presence must be removed. Hydroxyl free radicals have high activity and are easy to attack cell membrane and mitochondrial membrane and react with unsaturated fatty acids in the membrane, resulting in enhanced lipid peroxidation. They are directly involved in and manufacturers of human diseases, aging and death. Hydroxyl free radicals can also trigger chain reactions, resulting in oxidative damage of organic materials [1].

The antioxidant activity of antioxidant molecules mainly shows that they can effectively block free radical chain reaction, thus reducing the generation of free radicals and scavenging free radicals [2]. Hydroxyl and amino antioxidants are mainly captured by free radicals, only hydroxyl group can exert antioxidant function in natural living organism [3]. Vitamin C molecule is the typical structure of multi-hydroxyl antioxidant, which has the ability of hydrogen supply, can effectively remove reactive oxygen free

radicals and be used as the body's exogenous scavenging oxygen free radical substances. As a natural free radical scavenger, vitamin C can directly or indirectly eliminate active free radicals, thus protecting the integrity of biofilm and improving the working ability of the body. At present, polyhydroxyl antioxidants have been shown to have high free radical scavenging ability in experimental operation [4-13] and theoretical simulation [14-18].

Based on the quantum chemistry theory and the structure of polyhydroxyl antioxidant vitamin C (**R4**), this project will design three polyhydroxyl antioxidant molecules and simulate their reaction mechanism with hydroxyl free radicals. By studying the molecular structure and remove hydroxyl radicals hydroxyl class antioxidant ability and structure-activity relationship between free radicals reaction path, to determine the clear biological in vivo or in vitro activity of free radicals (hydroxyl radicals) the advantages of the structure and reaction mechanism, to examine the hydroxyl number, conjugation, and active sites of this kind of radical scavenging reaction mechanism as well as the temperature influence. This study provides theoretical guidance and data support for the screening, synthesis and design of hydroxyl antioxidants and

related derivatives with high antioxidant activity. The obtained information will be fed back into quantum chemical calculation to guide the screening, synthesis, development and application [5,6] of novel antioxidants.

2 CALCULATION METHOD

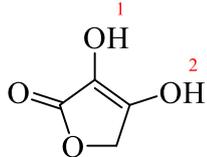
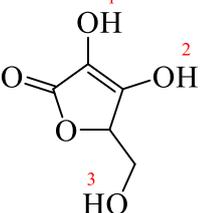
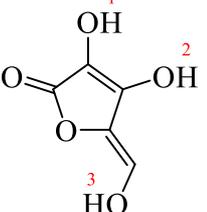
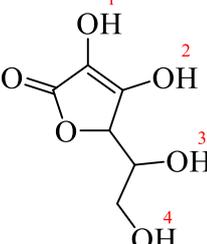
Density functional theory is used in the calculations in this study. The optimization and frequency of all stagnation points containing C, H and O atoms are performed at BHandLYP/6-311++G(d,p)[19-30] level. The optimization uses a non-restrictive calculation method without any symmetry constraints. The experimental conditions of geometric optimization and frequency calculation and simulation are gas phase, and the designed temperature is in the outdoor temperature range of Northeast China (263K ~ 303K). All calculations are completed by *Gaussian09* program [31].

3 Molecular structure design of polyhydroxyl antioxidant

In this study, the molecular structures of three polyhydroxyl antioxidants were designed based on vitamin C (**R4**), as shown in Table 1. The hydroxyl radical attacks the hydroxyl hydrogen atom (H1~H4) in the polyhydroxyl antioxidant (**R**), and through the transition states (**TS1-1** ~ **TS4-4**) to obtain the products (**P1-1** ~ **P4-4**) and H₂O, and finally structural multiple reaction paths (**Path I-1** ~ **Path IV-4**). The serial number of H atom marked on the **R** structure in the table corresponds to the attack position of hydroxyl radical, transition state (**TS**), reaction path (**Path**) and the name of the product radical (**P**). The reaction mechanism of hydroxyl radical scavenging by polyhydroxyl antioxidant (taking **R1** as an example) is shown in Figure 1.

Table-1: Structure of polyhydroxyl antioxidant (R) and name design of each stagnation point

$$R + \bullet OH \xrightarrow{TS} P + H_2O$$

Reactant	Path \ TS	Product
R1: 	Path I-1 \ TS1-1 Path I-2 \ TS1-2	P1-1 P1-2
R2: 	Path II-1 \ TS2-1 Path II-2 \ TS2-2 Path II-3 \ TS2-3	P2-1 P2-2 P2-3
R3: 	Path III-1 \ TS3-1 Path III-2 \ TS3-2 Path III-3 \ TS3-3	P3-1 P3-2 P3-3
R4: 	Path IV-1 \ TS4-1 Path IV-2 \ TS4-2 Path IV-3 \ TS4-3 Path IV-4 \ TS4-4	P4-1 P4-2 P4-3 P4-4

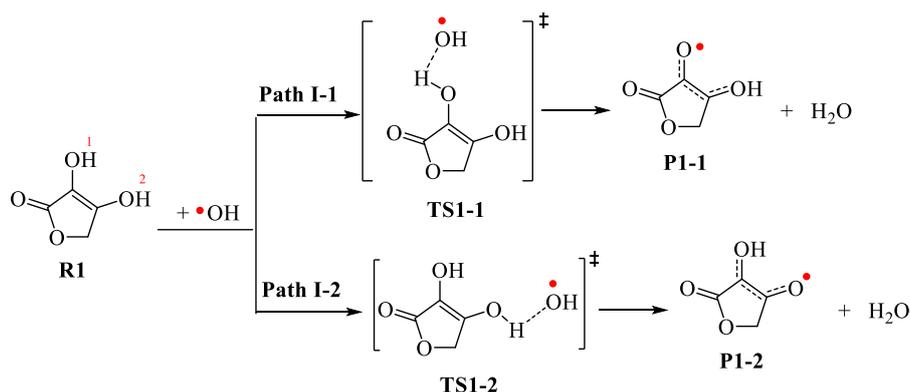


Fig-1: Mechanism of polyhydroxyl antioxidant (taking **R1 as an example) scavenging hydroxyl radical**

In Figure 1, **R1** polyhydroxyl antioxidant is taken as an example. When hydroxyl radical attacks H1 in **R1**, the transition state **TS1-1** is activated and the O—H bond breaks to generate oxygen radicals **P1-1** and H_2O , structural **Path I-1**. When hydroxyl group attacks H2 in **R1**, it passes through the activated transition state **TS1-2**, wherein the O—H bond breaks to generate oxygen radicals **P1-2** and H_2O , finally structural **Path I-2**. Similarly, hydroxyl groups attack H atom

mechanisms at different sites in **R2**, **R3**, and **R4** and form multiple reaction paths. The reaction barrier (ΔG_{TS} , 293K, $\text{kJ}\cdot\text{mol}^{-1}$) of hydroxyl radical scavenging by four polyhydroxyl antioxidants is shown in Figure 2.

4. RESULTS AND DISCUSSION

4.1 Effect of molecular structure of polyhydroxyl antioxidant on hydroxyl radical scavenging mechanism

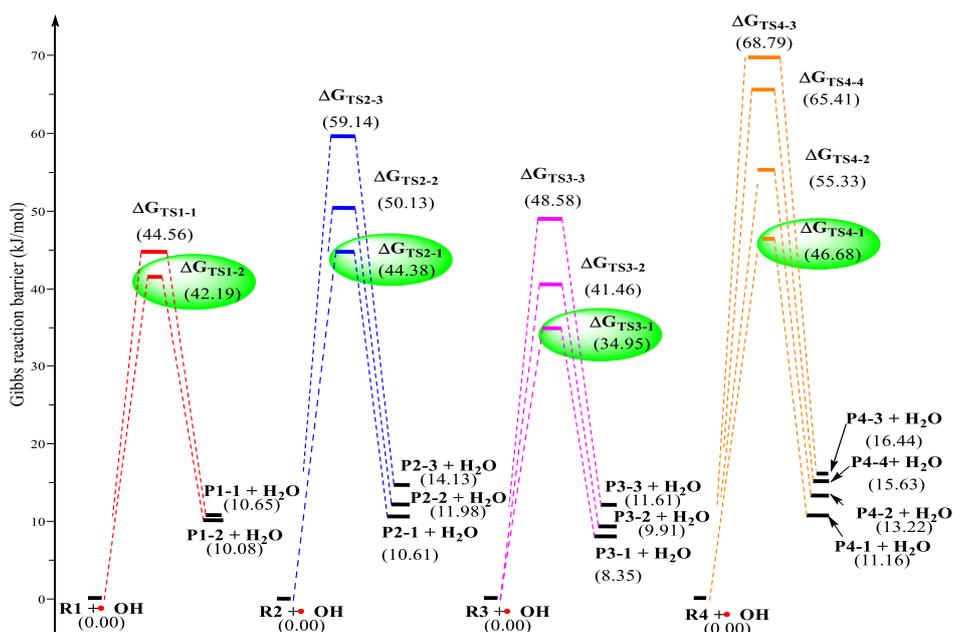


Fig-2: Hydroxyl radical scavenging potential barrier by polyhydroxyl antioxidants (ΔG , 293K, $\text{kJ}\cdot\text{mol}^{-1}$)

Considering the influences of enthalpy, entropy and temperature on the reaction paths, the relative Gibbs free energies of the activation transition states in the 12 reaction paths are described in Figure 2. As shown in this figure, H2 in hydroxyl attack **R1** is $2.37 \text{ kJ}\cdot\text{mol}^{-1}$ lower than H2 in hydroxyl attack H1, so **Path I-2** is the dominant Path for **R1** to clear hydroxyl radicals. Gibbs free energy change of this Path is also slightly lower than **Path I-1**, and the product is mainly **P1-2**. H1 in **R2** attacked by hydroxyl groups was $5.57 \text{ kJ}\cdot\text{mol}^{-1}$ and $14.76 \text{ kJ}\cdot\text{mol}^{-1}$ lower than H2 and H3, so

Path II-1 was the dominant Path for **R2** to clear hydroxyl radicals. The Gibbs free energy variation of the reaction is $1.37 \text{ kJ}\cdot\text{mol}^{-1}$ and $3.52 \text{ kJ}\cdot\text{mol}^{-1}$ lower than that of **Path II-2** and **Path II-3**, and **P2-1** is the main product. Hydroxyl radicals attack H1 in **R3** at $6.51 \text{ kJ}\cdot\text{mol}^{-1}$ and $13.63 \text{ kJ}\cdot\text{mol}^{-1}$ lower than H2 and H3, so **Path III-1** is the dominant pathway for **R3** to remove hydroxyl radicals. The Gibbs free energy variation of the reaction is $1.56 \text{ kJ}\cdot\text{mol}^{-1}$ and $3.26 \text{ kJ}\cdot\text{mol}^{-1}$ lower than that of **Path III-2** and **Path III-3**, and **P3-1** is the main product. The transition state Gibbs

free energy of H1 in **R4** attacked by hydroxyl radicals is 8.65 kJ·mol⁻¹, 22.11 kJ·mol⁻¹ and 18.73 kJ·mol⁻¹ lower than H2, H3 and H4. Therefore, **Path III-1** is the dominant pathway for **R4** to clear hydroxyl radicals. The Gibbs free energy variation of the reaction is 2.06

kJ·mol⁻¹, 5.28 kJ·mol⁻¹ and 4.47 kJ·mol⁻¹ lower than that of **Path IV-2**, **Path IV-3** and **Path IV-4**, and the product is mainly **P4-1**.

4.2 Effect of temperature on hydroxyl radical scavenging by polyhydroxyl antioxidant

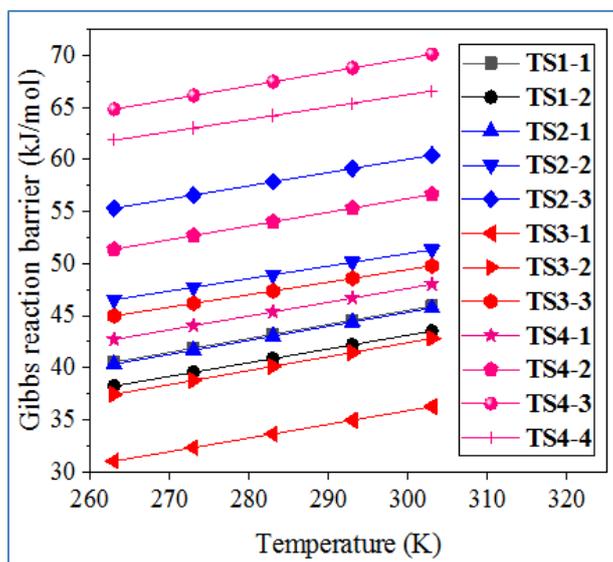


Fig-3: Gibbs free energy of transition state of hydroxyl radical scavenging reaction by polyhydroxyl antioxidant at different temperatures (ΔG_{TS} , kJ·mol⁻¹)

Figure 3 describes the Gibbs free energy of transition state of hydroxyl radical scavenging reaction by polyhydroxyl antioxidant at different temperatures of 263K ~ 303K. As can be seen from the figure, the activated Gibbs free energy of each transition state increases with the temperature, and the amplitude of increase is basically the same. Not only did the dominant pathway of hydroxyl radical scavenging reaction of each antioxidant not change, but also the relative level of Gibbs free energy of transition state activation of different antioxidant dominant pathway did not change. It can be seen that temperature change

has no effect on hydroxyl radical scavenging reaction mechanism of polyhydroxyl antioxidant.

Figure 4 depicts the enthalpies of hydroxyl radical scavenging by polyhydroxyl antioxidants at different temperatures of 263K ~ 303K. It can be seen from the figure that negative enthalpy (-29.58 kJ·mol⁻¹ ~ -150.50 kJ·mol⁻¹) of each reaction path is a favorable direction of thermodynamics. As the temperature increases, the enthalpy of each reaction path remains roughly constant. It can be seen that temperature change has little effect on the reaction enthalpy of hydroxyl radical scavenging by polyhydroxyl antioxidants.

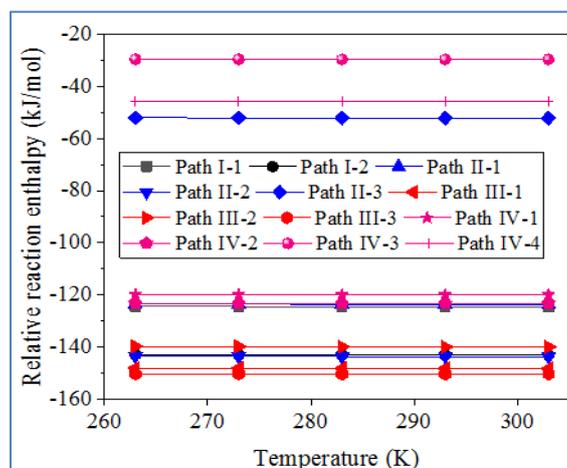


Fig-4: Enthalpies of hydroxyl radical scavenging by polyhydroxyl antioxidants at different temperatures ($\Delta_r H$, kJ·mol⁻¹)

5. CONCLUSION

In many hydroxyl class antioxidant molecule structure design and remove hydroxyl groups in the study of the mechanism of the reaction, this paper designs and simulates the reactant **R1** ~ **R4** and hydroxyl free radical reaction of multiple paths, and respectively from the point of view of kinetics and thermodynamics that the hydroxyl number, conjugation effect and electronic effect, space effect and the influence of temperature on the reaction mechanism, the conclusion is as follows.

(1) In the reactant **R1**, the dominant pathway attacked by hydroxyl radicals is H2, while in the reactant **R2** ~ **R4**, the dominant pathway attacked by hydroxyl radicals is H1.

(2) The reactant **R3** shows a good kinetic advantage in the simulation mechanism of hydroxyl radical scavenging. Within the temperature range of 263K~303K, the transition state of **Path III-1** varies from 31.02 kJ·mol⁻¹ to 36.26 kJ·mol⁻¹ relative to Gibbs free energy ΔG_{TS3-1} . **R3** has a low kinetic potential energy for scavenging hydroxyl radicals.

(3) From the perspective of thermodynamics, the reaction enthalpy data show that the $\Delta_r H$ of multiple reaction paths of **R1** ~ **R4** and hydroxyl radical are all less than 0, which is thermodynamic favorable direction. The enthalpy data of **R3** is more favorable in the reaction of hydroxyl radical scavenging, and $\Delta_r H$ values are all below -139 kJ·mol⁻¹.

(4) The effects of temperature on the mechanism of hydroxyl radical scavenging by polyhydroxyl antioxidants were investigated. It was found that the relative Gibbs free energy of the transition states increased with the increase of temperature, but the mechanism of the reaction did not change. It also shows that temperature has little effect on the enthalpy change of the reaction.

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