

Theoretical investigation on the antioxidant activity of p-cresol and its derivatives: Effects of propenyl group and solvents

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Abstract. The effect of propenyl group on the antioxidant activity of p-cresol and its derivatives were investigated in gas and solvent phases by using density functional theory (DFT) method. Three accepted antioxidant mechanisms, including hydrogen atom transfer (HAT), single-electron transfer followed by proton transfer (SET-PT) and sequential proton loss electron transfer (SPLET), were considered to explore which mechanism p-cresol and its derivatives preferred to in different environments. The bond dissociation enthalpy (BDE), ionization potential (IP), proton dissociation enthalpy (PDE), proton affinity (PA) and electron transfer enthalpy (ETE), closely related to the above three antioxidant mechanisms, were calculated systematically. The obtained results indicate that the antioxidant process of studied compounds prefers to the SET-PT and SPLET mechanism in gas phase and polar solvents, respectively. Meaningfully, the introduction of the propenyl group into the molecular structure can reduce the PA values and then improve the antioxidant activity of the studied compounds, which can provide theoretical guidance for the synthesis of novel antioxidants in the experiment.

Keywords: Proton transfer; Substituent group; Solvent effects; Density functional theory

1. Introduction

Too much free radicals in vivo can cause damage to DNA, unsaturated fatty acids in biomembrane, protein and other biological macromolecules, thereby resulting in many diseases [1,2]. To mitigate the harm of free radicals to the human body, more and more researchers are devoting themselves to find and synthesize novel antioxidants with the advantages of efficient, cheap, low toxic or even non-toxic [3-5].

Cresols have three isomers, which are named o-cresol, m-cresol and p-cresol, respectively. Each monomer of cresol is an important intermediate to synthesize antioxidants, preservatives, disinfectants and so on [6,7]. P-cresol is an important organic chemical raw material. A series of derivatives can be obtained by further processing with p-cresol as starting material, in which an extensive family of antioxidants can be derived through coupling reaction based on p-cresol, such as butylated hydroxytoluene (BHT), and these antioxidants receive a great deal of attention because of their relatively low toxicity [8,9]. Recently, Marteau et al. [10] designed and synthesized a series of novel antioxidants by introducing the propenyl group into the structure of p-cresol and its derivatives. The chemical structures of p-cresol and its derivatives, named as P, 1P, 1PP, 5P and 6P respectively, are shown in **Figure 1**. The results indicated the antioxidant activities of p-cresol and its derivatives were gradually enhanced along with the increased number of propenyl group in p-cresol. Why did the introduction of propenyl group can enhance the antioxidant activities of p-cresol and its

derivatives?

In this work, the relationship between the structures and antioxidant activities of p-cresol and its derivatives were investigated by using DFT method. Besides the influence of structure, the surrounding environment will also affect the parameters containing bond dissociation enthalpy (BDE), ionization potential (IP) and proton affinity (PA), which are connected with the antioxidant activities of phenolic compounds [11-13]. So the gas and three solvents including toluene, methanol and water were taken into accounts in this work. The parameters related to three antioxidant mechanisms, including hydroxyl BDE, IP, PDE, PA and ETE, were calculated to evaluate the antioxidant activities of p-cresol and its derivatives.

All the calculations in this work were completed by using Gaussian program suite [14]. The geometric configurations of the investigated compounds were optimized in the framework

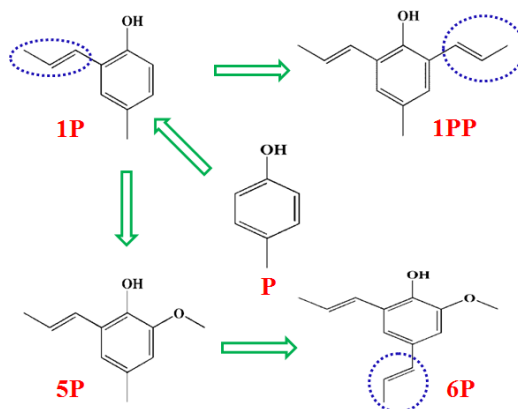


Figure 1: Chemical structures of the investigated compounds.

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of DFT [15-17], with B3LYP [18-23] functional at 6-31G(d,p) basis set. For the sake of the following discussion, we have numbered the atoms in the compound 1PP. Three solvents, containing toluene, methanol and water with the dielectric constants of 2.38, 32.63 and 78.39, respectively, were considered to investigate the effect of solvent polarity on the antioxidant activities of p-cresol and its derivatives. The calculations in the solvent phases were adopted the integral equation formalism polarized continuum model (IEFPCM) [24-26]. The radical and ionic structures for the investigated compounds were optimized using DFT method with UB3LYP functional at 6-311++G(d,p). The BDE, IP, PDE, PA and ETE, which closely related to the above three antioxidant mechanisms, were calculated according to the equations in the literatures [11,27,28]. The enthalpies of hydrogen atom (H^{\cdot}), proton (H^+) and electron (e^-) in gas and solvent phases at the same method employed the values in the work of Rimarčík et al. [29].

As one of the theoretical parameters to characterize the rate of hydrogen abstraction reaction, the BDE value represents the order of difficulty of hydrogen abstraction from phenolic hydroxyl. The smaller the BDE value is, the easier hydrogen abstraction reaction occurs [30]. In view of this, the BDE values of p-cresol and its derivatives in gas and solvent phases were calculated and summarized in **Table 1**. As listed in **Table 1**, the BDE values of P, 1P and 1PP show the common tendency in the same environment: $1PP < 1P < P$, implying that the antioxidant activity gradually increases from P to 1P and 1PP, in agreement with the experimental results [10]. For

instance, the BDE values of P, 1P and 1PP in gas phase are 392.9 kcal/mol, 389.9 kcal/mol and 385.7 kcal/mol, respectively. When a methoxyl group is introduced into the structure of 1P forming the compound 5P, the BDE values of 5P in the different environments are all greater than that of 1P, which is due to the formation of intramolecular hydrogen bond between the hydrogen atom of phenolic hydroxyl and the oxygen atom of methoxyl group. Compared the BDE values of 5P with that of 6P in the different environments, we can find the BDE values of 6P are all lower than that of 5P. Those results indicate that increasing number of propenyl group in p-cresol is beneficial to enhancing the antioxidant activity of p-cresol in theory.

Moreover, with the increasing polarity of solvent (from toluene to water), the BDE values of the studied compounds decrease gradually except for that of 1PP showing the trend of first increase and then decrease. By comparing the BDE values of p-cresol and its derivatives in the investigated environments, we can find that the lowest BDE values for p-cresol and its derivatives all are in the water phase, which suggests that the antioxidant ability of p-cresol and its derivatives are the strongest in water phase.

The SET-PT and SPLET mechanisms are of importance in solvent media, so we have taken the two mechanisms into account in this work [31]. The calculated IP and PDE values of p-cresol and its derivatives in gas and solvent phases are listed in **Table 2**. As listed in **Table 2**, it can be found that the IP values of P, 1P and 1PP all are following the same order in the investigated environments: $1PP < 1P < P$, which indicates that increasing the number of propenyl group in p-cresol can improve the single electron donating ability of p-cresol. Moreover, the IP values of 5P are lower than that of 1P in the studied environments except in water phase, implying that introducing the methoxyl group into the structure of 1P can enhance the single electron donating ability of 1P. Compared the IP values of 5P with that of 6P in the studied environments, we can find that the IP values of 6P all are lower than that of

Table 1. Calculated bond dissociation enthalpy (BDE) values of investigated compounds in gas and solvent phases.

BDE (kcal/mol)	Gas	Toluene	Methanol	Water
P-OH	392.9	394.4	394.2	392.1
1P-OH	389.9	390.8	390.8	388.1
1PP-OH	385.7	387.3	387.4	385.2
5P-OH	390.5	391.2	389.3	389.2
6P-OH	388.7	389.3	387.3	387.2

Table 2. Calculated ionization potential (IP) and proton dissociation enthalpy (PDE) values of investigated compounds in gas and solvent phases.

	IP (kcal/mol)				PDE (kcal/mol)			
	Gas	Toluene	Methanol	Water	Gas	Toluene	Methanol	Water
P-OH	183.5	152.9	117.9	112.6	212.6	16.0	6.5	11.1
1P-OH	170.0	142.3	110.5	104.7	223.1	23.2	10.5	15.0
1PP-OH	165.2	140.3	109.2	104.0	223.7	21.6	8.4	12.8
5P-OH	165.0	139.5	108.3	125.1	228.7	26.2	11.2	38.7
6P-OH	158.5	134.7	104.0	120.9	233.4	29.2	13.4	40.9

Table 3. Calculated proton affinity (PA) and electron transfer enthalpy (ETE) values of investigated compounds in gas and solvent phases.

	PA (kcal/mol)				ETE (kcal/mol)			
	Gas	Toluene	Methanol	Water	Gas	Toluene	Methanol	Water
P-OH	347.9	95.1	46.1	48.8	48.2	73.8	78.3	74.8
1P-OH	343.7	93.5	46.3	47.9	49.4	71.9	74.7	71.8
1PP-OH	338.9	91.3	43.7	46.5	50.0	70.7	73.9	70.3
5P-OH	344.8	96.4	48.9	74.9	48.9	69.4	70.5	88.9
6P-OH	340.1	93.2	46.6	72.6	51.8	70.8	70.9	89.2